WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)
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World Health Organization
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Introduction

Background
The results from the recent WHO/TRM Global Survey on National Policy on Traditional and Complementary/Alternative Medicine and on Regulation of Herbal Medicines in 2003 show that the European herbal medicines market is growing steadily. For example, between 1999 and 2001, herbal medicines sales increased by 22% in the Czech Republic, doubled in Turkmenistan, and increased by 170% in Bulgaria.

Currently, the European market is considered to be the world’s largest single commercial market for medicinal plants and herbal medicines. European countries are not just importers, but also producers of a large variety of medicinal plants and herbal medicines. European consumers, for example, in France, Germany, Italy, Sweden, Switzerland and the UK often use herbal medicines to complement treatment with conventional medicines.

In the Newly Independent States (NIS) and Countries of Central and Eastern Europe (CCEE), consumers likewise often favour herbal products, but for a different reason. Difficult economic conditions often limit access to the rather expensive conventional medicines that are available, with the result that they seek out less expensive alternative medicines such as herbal products.

Many European Union countries already have well-established national policies and programmes for regulating and monitoring herbal medicines. Many NIS and CCEE Member States are now similarly striving to develop and implement national policies and programmes to regulate herbal medicines.

Difficulties and needs in the field of herbal medicines in NIS countries
In some NIS and CCEE countries a number of medicinal plants are grown and not only consumed domestically, but also exported to other countries. Indeed, exporting medicinal plants is a principal source of income for some NIS and CCEE countries. Many NIS and CCEE governments are therefore keen to ensure quality control of medicinal plants and me-
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dicinal plant materials, so as to maintain and increase the credibility of their products on the international market. However, they often lack technical expertise, skills and knowledge in this area, as well as resources for conducting research and establishing national standards and quality assurance measures for medicinal plants and herbal medicines.

According to the information collected during WHO’s recent global survey on traditional medicine:
- nine NIS countries would like WHO to facilitate information sharing between Member States on regulatory issues;
- ten NIS countries would like WHO to provide general guidance on research and evaluation of traditional medicine;
- additional requests included requests for support for national capacity building in establishing national regulation of herbal medicines, and provision via databases of information on herbal medicines.

Some NIS and CCEE countries have developed their own national monographs on herbal medicines, either within national pharmacopoeias or national formularies. These countries include Armenia, Kyrgyzstan, Romania, Slovakia and Uzbekistan. However, since most NIS lack research data and funds, they have been unable to develop their own national monographs.

At the WHO regulatory training workshop for Europe in September 2003, many of the NIS participating national drug regulatory authorities requested assistance from WHO in developing monographs on medicinal plants commonly used in the NIS.

The objectives of development of the monographs for NIS countries

Since 1999, WHO has published four volumes of the WHO monographs on selected medicinal plants, that include 116 monographs. All of these volumes are now available on the WHO website (http://www.who.int/medicines).

Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role. For example, in the recent WHO global survey on national policy and regulation of herbal medicines, of the 34 countries reporting that they do not have their own national monographs and use other monographs, 13 use the WHO monographs as an authoritative reference. Moreover, the format of the WHO monographs continues to be commonly used for developing national monographs. In the same survey, of the 46 countries that have already developed national
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monographs on herbal medicines, several countries reported having used
the WHO format as a basis.

In order to meet demands of NIS countries to regulate herbal medi-
cines and to ensure safety, efficacy and quality of herbal medicines, WHO
has provided technical guidance and worked with the national health au-
thorities of interested NIS and CCEE to develop monographs on com-
monly-used medicinal plants in the NIS.

The NIS monographs include comprehensive scientific information
on the safety, efficacy and quality of medicinal plants. The format of the
NIS monographs is the same as of the WHO monographs on medicinal
plants. Each monograph follows a standard format, with information
presented in two parts, followed by a reference list. The first part presents
pharmacopoeial summaries for quality assurance, while the second part
includes sections on medicinal uses, pharmacology, safety issues and dos-
age forms.

Through the participation in the development of the monographs, the
objectives are to:

• assist national authorities and experts in NIS and CCEE countries
to learn how to develop official monographs on medicinal plants;
• facilitate the national regulatory authorities to build their national
capacity in establishing national quality specifications and stan-
dards for herbal medicines, national formularies on herbal medi-
cines, as well as quality assurance and control measures for herbal
medicines in NIS and CCEE countries;
• promote research on herbal medicines and networking of re-
searchers on herbal medicines within and outside the NIS and
CCEE;
• establish a network among the NIS and CCEE to facilitate sharing
of information and experience in regulation, research and use of
herbal medicines.

Process of the development of the monographs

for NIS countries

Firstly WHO worked with the national health authorities and experts of
NIS and CCEE countries to establish a working group on development
of the monographs. Then they developed a list of monographs on com-
monly-used medicinal plants in the NIS. The list was finalized by a Work-
ing group meeting. It was agreed that there would be a total of 30 to
35 monographs, which would be developed through two mechanisms:

• development of new monographs;
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- adoption of existing relevant monographs from the four volumes of WHO monographs on selected medicinal plants and translation into Russian.

Then WHO coordinated collection of relevant research information – not only with the national health authorities and experts of NIS and CCEE countries, but also together with WHO Collaborating Centres for traditional medicine and other research institutions and nongovernmental organizations (NGOs). The experts from NIS and CCEE countries drafted the new monographs, based on the standard format, simultaneously in English and Russian. The draft monographs have been widely circulated to 256 experts and national regulatory authorities in 99 countries, as well as NGOs, for their comments and opinions.

Then, draft new monographs were reviewed and finalized by a WHO Consultation. The participants included the national health authorities and experts of NIS and CCEE countries, as well as experts from WHO Collaborating Centres for traditional medicine and other research institutions and NGOs. Following extensive discussion, 13 of 14 new monographs were approved by the WHO Consultation.

In order to ensure the quality of the monographs, the final version has been reviewed by the experts from the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, IL, USA.

Use of the monographs
The monographs may serve as an authoritative source of information for national drug regulatory authorities, since they have been fully involved in the development of the monographs. However, it should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO’s official endorsement or approval and also not intended to replace any national monographs or national pharmacopoeia of medicinal plants. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.

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These WHO monographs are not pharmacopoeial monographs. Their purpose is to provide scientific information on the safety, efficacy and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in WHO’s Member States; to provide models to assist WHO’s Member States in developing their own monographs or formularies for these and other herbal medicines; and to facilitate information exchange among WHO’s Member States.

The format used for this volume essentially follows that of volumes 2, 3 and 4 of *WHO monographs on selected medicinal plants*.

The *Definition* provides the Latin binomial name, the most important criterion in quality assurance. Latin binomial synonyms and vernacular names, listed in *Synonyms* and *Selected vernacular names* respectively, are names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International Code of Botanical Nomenclature. The vernacular names comprise an alphabetical list of selected names from individual countries worldwide, in particular from areas where the medicinal plant is in common use. They refer to the medicinal plant itself not the medicinal plant part, which is identical to the monograph name. The lists are not complete, but reflect the names of the concerned medicinal plant appearing in the official monographs and reference books consulted and those in the Natural Products Alert (NAPRALERT) database (a database of literature from around the world on ethnomedical, biological and chemical information on medicinal plants, fungi and marine organisms, located at the WHO Collaborating Centre for Traditional Medicine at the University of Illinois at Chicago, Chicago, IL, USA). While every effort has been made to delete names referring to the medicinal plant part, the relevant section of each monograph may still include these.

*Geographical distribution* is not normally found in official compendia, but is included here to provide additional quality assurance information. The detailed botanical description under Description is intended for qual-
ity assurance at the stages of production and collection; the description of
the crude drug material under Plant material of interest is for the same
purpose at the manufacturing and commerce stages.

General identity tests, Purity tests and Chemical assays are all normal
compendial components included under those headings in these mono-
graphs. Where purity tests do not specify accepted limits, those limits
should be set in accordance with national requirements by the appropriate
authorities of Member States.

Each medicinal plant and the specific plant part used as crude drug
material contain active or major chemical constituents with a character-
istic profile that can be used for chemical quality control and quality
assurance. These constituents are described in the Major chemical con-
stituents.

Descriptions included in Medicinal uses should not be taken as imply-
ing WHO’s official endorsement or approval for such uses. They merely
represent the systematic collection of scientific information available at
the time of preparation, for information exchange.

The first category, Uses supported by clinical data, includes medical
indications that are well established in some countries and have been vali-
dated by clinical studies documented in the scientific literature. Clinical
trials may be controlled, randomized, double-blind studies, open trials,
cohort studies or well documented observations on therapeutic applica-
tions.

The second category, Uses described in pharmacopoeias and well estab-
lished documents, includes medicinal uses that are well established in
many countries and are included in official pharmacopoeias or govern-
mental monographs. Uses having a pharmacologically plausible basis are
also included, as well as information resulting from clinical studies that
clearly need to be repeated because of conflicting results.

The third category, Uses described in traditional medicine, refers to
indications described in unofficial pharmacopoeias and other literature,
and to traditional uses. Their appropriateness could not be assessed, be-
cause sufficient data to support the claims could not be found in the lit-
erature. Traditional uses that address severe pathologies, such as cancer,
AIDS, hepatitis, etc., as they relate to these modern biomedical terms,
should only be included under the third heading if pharmacological data
or robust ethnopharmacological/ethnobotanical reports are available to
support the claims.
The Experimental pharmacology section includes only the results of investigations that prove or disprove the cited medicinal uses. Brief details of the best-performed studies have been included in this section. Other published experimental data that are not associated with the medicinal uses have not been included, to avoid confusion.

The details included in the References have been checked against the original sources wherever possible. For references in languages other than English, except for those in Chinese and Japanese, the title is given in the original language, except in cases where an English summary is available.
Bulbus Allii Sativi*

Definition
Bulbus Allii Sativi consists of the fresh or dried bulbs of Allium sativum L. (Liliaceae) (1, 2).

Synonyms
Porvium sativum Rehb. (1, 3).

Selected vernacular names
It is most commonly known as “garlic”. Ail, ail commun, ajo, akashneem, allium, alubosa elewe, ayo-ish, ayu, banlasun, camphor of the poor, dai tóan, dasuan, dawang, dra thiam, foom, Gartenlauch, hom khao, hom kúa, hom thiam, hua thiam, kesumphin, kitunguu-sumu, Knoblauch, kra thiam, krathiam, krathiam cheen, krathiam khao, l’ail, lahsun, lai, lashun, lasan, lasun, lasuna, Lauch, lay, layi, lehsun, lesun, lobha, majo, naharu, nectar of the gods, ninniku, pa-se-waa, poor man’s treacle, rason, raosnam, rasun, rustic treacles, seer, skordo, sluôn, stinking rose, sudulunu, ta-suam, ta-suan, tafanuwa, tellagada, tellagaddalu, thiam, toi thum, tum, umbi bawang putih, vallaippundu, velluli, vellulli (1–13).

Description
A perennial, erect bulbous herb, 30–60 cm tall, strong smelling when crushed. The underground portion consists of a compound bulb with numerous fibrous rootlets; the bulb gives rise above ground to a number of narrow, keeled, grasslike leaves. The leaf blade is linear, flat, solid, 1.0–2.5 cm wide, 30–60 cm long, and has an acute apex. Leaf sheaths form a pseudostem. Inflorescences are umbellate; scape smooth, round, solid, and coiled at first, subtended by membraneous, long-beaked spathe, splitting on one side and remaining attached to umbel. Small bulbils are produced in inflorescences; flowers are variable in number and sometimes absent, seldom open and may wither in bud. Flowers are on slender

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.
pedicels; consisting of perianth of 6 segments, about 4–6 mm long, pinkish; stamens 6, anthers exserted; ovary superior, 3-locular. Fruit is a small loculicidal capsule. Seeds are seldom if ever produced (8, 9).

Plant material of interest: fresh or dried bulbs

**General appearance**
Bulbus Allii Sativi consists of several outer layers of thin sheathing protective leaves which surround an inner sheath. The latter enclose the swollen storage leaves called “couples”. Typically, the bulb possesses a dozen sterile sheathing leaves within which are 6–8 cloves bearing buds making a total of 10–20 cloves and 20–40 well-developed but short and embedded roots. The cloves are asymmetric in shape, except for those near the centre (1).

**Organoleptic properties**
Odour strong, characteristic alliaceous (1, 6, 8); taste very persistently pungent and acrid (1, 6, 8).

**Microscopic characteristics**
The bulbs show a number of concentric bulblets; each is 5–10 mm in diameter and consists of an outer scale, an epidermis enclosing a mesophyll free from chlorophyll, a ground tissue and a layer of lower epidermal cells. Dry scales consist of 2 or 3 layers of rectangular cells having end walls with a broadly angular slant. These cells contain many rhomboid crystals of calcium oxalate. The upper epidermal cells next to the dry scale layer consist of a single layer of rectangular to cubical cells next to which are several layers of large parenchymatous cells. Among these cells are interspaced many vascular bundles, each of which consists of xylem and phloem arranged alternately. Lower epidermis consists of cubical cells which are much smaller than the upper epidermal cells. The same arrangement of tissues is met within different bulblets, 2 or 3 of which are arranged concentrically (1, 6).

**Powdered plant material**
Pale buff to greyish or purplish white, with characteristic aromatic alliaceous odour and taste. It is characterized by the presence of sclereids of the epidermis of protective leaves, thin epidermis of storage cells, latex tubes, swollen parenchyma cells with granular contents, and lignified narrow spiral and annular vessels (1).
Geographical distribution
Bulbus Allii Sativi is probably indigenous to Asia (1, 7), but it is commercially cultivated in most countries.

General identity tests
Macroscopic and microscopic examinations and microchemical analysis are used to identify organic sulfur compounds (1), thin-layer chromatographic analysis to determine the presence of alliin (14).

Purity tests

Microbiology
The test for Salmonella spp. in Bulbus Allii Sativi products should be negative. The maximum acceptable limits of other microorganisms are as follows (2, 15, 16). Preparations for internal use: aerobic bacteria—not more than $10^5$/g or ml; fungi—not more than $10^4$/g or ml; enterobacteria and certain Gram-negative bacteria—not more than $10^3$/g or ml; Escherichia coli—0/g or ml.

Total ash
Not more than 5.0% (2).

Acid-insoluble ash
Not more than 1.0% (4).

Water-soluble extractive
Not less than 5.0% (4).

Alcohol-soluble extractive
Not less than 4.0% (4).

Moisture
Not more than 7% (2).

Pesticide residues
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Bulbus Allii Sativi is not more than 0.05 mg/kg (2). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (15) and guidelines for predicting dietary intake of pesticide residues (17).
Heavy metals
Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (15).

Radioactive residues
For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (15).

Other purity tests
Chemical tests and tests for foreign organic matter to be established in accordance with national requirements.

Chemical assays
Qualitative and quantitative assay for sulfur constituents (alliin, allicin etc.) content by means of high-performance liquid chromatography (18–22) or gas chromatography–mass spectroscopy (23) methods.

Major chemical constituents
The most important chemical constituents reported from Bulbus Allii Sativi are the sulfur compounds (7, 9, 24, 25). It has been estimated that cysteine sulfoxides (e.g. alliin [1]) and the non-volatile γ-glutamylcysteine peptides make up more than 82% of the total sulfur content of garlic (25).

The thiosulfimates (e.g. allicin [2]), ajoenes (e.g. E-ajoene [3], Z-ajoene [4]), vinylidithiins (e.g. 2-vinyl-(4H)-1,3-dithiin [5], 3-vinyl-(4H)-1,2-dithiin [6]), and sulfides (e.g. diallyl disulfide [7], diallyl trisulfide [8]), however, are not naturally occurring compounds. Rather, they are degradation products from the naturally occurring cysteine sulfoxide, alliin [1]. When the garlic bulb is crushed, minced, or otherwise processed, alliin is released from compartments and interacts with the enzyme alliinase in adjacent vacuoles. Hydrolysis and immediate condensation of the reactive intermediate (allylsulfenic acid) forms allicin [2]. One milligram of alliin is considered to be equivalent to 0.45 mg of allicin (26). Allicin itself is an unstable product and will undergo additional reactions to form other derivatives (e.g. products [3]–[8]), depending on environmental and processing conditions (24–26). Extraction of garlic cloves with ethanol at <0 °C gave alliin [1]; extraction with ethanol and water at 25 °C led to allicin [2] and no alliin; and steam distillation (100 °C) converted the alliin totally to diallyl sulfides [7], [8] (24, 25). Sulfur chemical profiles of Bulbus Allii Sativi products reflected the processing procedure: bulb, mainly
alliin, allicin; dry powder, mainly alliin, allicin; volatile oil, almost entirely diallyl sulfide, diallyl disulfide, diallyl trisulfide, and diallyl tetrasulfide; oil macerate, mainly 2-vinyl-[4H]-1,3-dithiin, 3-vinyl-[4H]-1,3-dithiin, E-ajoene, and Z-ajoene (18–22, 24). The content of alliin was also affected by processing treatment: whole garlic cloves (fresh) contained 0.25–1.15% alliin, while material carefully dried under mild conditions contained 0.7–1.7% alliin (18–21).

Gamma-glutamylcysteine peptides are not acted on by alliinase. On prolonged storage or during germination, these peptides are acted on by γ-glutamyl transpeptidase to form thiosulfimates (25).

**Dosage forms**

Fresh bulbs, dried powder, volatile oil, oil macerates, juice, aqueous or alcoholic extracts, aged garlic extracts (minced garlic that is incubated in aqueous alcohol (15–20%) for 20 months, then concentrated), and odourless garlic products (garlic products in which the allinase has been inactivated by cooking; or in which chlorophyll has been added as a deodorant; or aged garlic preparations that have low concentrations of water-soluble sulfur compounds) (18, 24).

The juice is the most unstable dosage form. Alliin and allicin decompose rapidly, and those products must be used promptly (18).

Dried Bulbus Allii Sativi products should be stored in well-closed containers, protected from light, moisture, and elevated temperature.

**Medicinal uses**

*Uses supported by clinical data*

As an adjuvant to dietetic management in the treatment of hyperlipidaemia, and in the prevention of atherosclerotic (age-dependent) vascular changes (5, 27–31). The drug may be useful in the treatment of mild hypertension (11, 28).
Uses described in pharmacopoeias and in traditional systems of medicine
The treatment of respiratory and urinary tract infections, ringworm and rheumatic conditions (1, 4, 7, 9, 11). The herb has been used as a carminative in the treatment of dyspepsia (32).

Uses described in folk medicine, not supported by experimental or clinical data
As an aphrodisiac, antipyretic, diuretic, emmenagogue, expectorant, and sedative, to treat asthma and bronchitis, and to promote hair growth (6, 9, 13).

Pharmacology

Experimental pharmacology
Bulbus Allii Sativi has a broad range of antibacterial and antifungal activity (13). The essential oil, water, and ethanol extracts, and the juice inhibit the in vitro growth of Bacillus species, Staphylococcus aureus, Shigella sonnei, Erwinia carotovora, Mycobacterium tuberculosis, Escherichia coli, Pasteurella multocida, Proteus species, Streptococcus faecalis, Pseudomonas aeruginosa, Candida species, Cryptococcus species, Rhodotorula rubra, Torulopsis species, Trichosporon pullulans, and Aspergillus niger (33–40). Its antimicrobial activity has been attributed to allicin, one of the active constituents of the drug (41). However, allicin is a relatively unstable and highly reactive compound (37, 42) and may not have antibacterial activity in vivo. Ajoene and diallyl trisulfide also have antibacterial and antifungal activities (43). Garlic has been used in the treatment of roundworm (Ascaris strongyloides) and hookworm (Ancylostoma caninum and Necator americanus) (44, 45). Allicin appears to be the active anthelmintic constituent, and diallyl disulfide was not effective (46).

Fresh garlic, garlic juice, aged garlic extracts, or the volatile oil all lowered cholesterol and plasma lipids, lipid metabolism, and atherogenesis both in vitro and in vivo (18, 43, 47–64). In vitro studies with isolated primary rat hepatocytes and human HepG2 cells have shown that watersoluble garlic extracts inhibited cholesterol biosynthesis in a dose-dependent manner (48–50). Antihypercholesterolaemic and antihyperlipidaemic effects were observed in various animal models (rat, rabbit, chicken, pig) after oral (in feed) or intragastric administration of minced garlic bulbs; water, ethanol, petroleum ether, or methanol extracts; the essential oil; aged garlic extracts and the fixed oil (51–64). Oral administration of allicin to rats during a 2-month period lowered serum and liver levels of total lipids, phospholipids, triglycerides, and total cholesterol (65). Total plasma lipids and cholesterol in rats were reduced after intraperitoneal...
injection of a mixture of diallyl disulfide and diallyl trisulfide (66). The mechanism of garlic’s antihypercholesterolaemic and antihyperlipidaemic activity appears to involve the inhibition of hepatic hydroxymethylglutaryl-CoA (HMG-CoA) reductase and remodelling of plasma lipoproteins and cell membranes (67). At low concentrations (<0.5 mg/ml), garlic extracts inhibited the activity of hepatic HMG-CoA reductase, but at higher concentrations (>0.5 mg/ml) cholesterol biosynthesis was inhibited in the later stages of the biosynthetic pathway (68). Alliin was not effective, but allicin and ajoene both inhibited HMG-CoA reductase in vitro ($IC_{50} = 7$ and 9 mmol/l respectively) (49). Because both allicin and ajoene are converted to allyl mercaptan in the blood and never reach the liver to affect cholesterol biosynthesis, this mechanism may not be applicable in vivo. In addition to allicin and ajoene, allyl mercaptan (50 mmol/l) and diallyl disulfide (5 mmol/l) enhanced palmitate-induced inhibition of cholesterol biosynthesis in vitro (50). It should be noted that water extracts of garlic probably do not contain any of these compounds; therefore other constituents of garlic, such as nicotinic acid and adenosine, which also inhibit HMG-CoA reductase activity and cholesterol biosynthesis, may be involved (69, 70).

The antihypertensive activity of garlic has been demonstrated in vivo. Oral or intragastric administration of minced garlic bulbs, or alcohol or water extracts of the drug, lowered blood pressure in dogs, guinea-pigs, rabbits, and rats (52, 71–73). The drug appeared to decrease vascular resistance by directly relaxing smooth muscle (74). The drug appears to change the physical state functions of the membrane potentials of vascular smooth muscle cells. Both aqueous garlic and ajoene induced membrane hyperpolarization in the cells of isolated vessel strips. The potassium channels opened frequently causing hyperpolarization, which resulted in vasodilation because the calcium channels were closed (75, 76). The compounds that produce the hypotensive activity of the drug are uncertain. Allicin does not appear to be involved (43), and adenosine has been postulated as being associated with the activity of the drug. Adenosine enlarges the peripheral blood vessels, allowing the blood pressure to decrease, and is also involved in the regulation of blood flow in the coronary arteries; however, adenosine is not active when administered orally. Bulbus Allii Sativi may increase production of nitric oxide, which is associated with a decrease in blood pressure. In vitro studies using water or alcohol extracts of garlic or garlic powder activated nitric-oxide synthase (77), and these results have been confirmed by in vivo studies (78).

Aqueous garlic extracts and garlic oil have been shown in vivo to alter the plasma fibrinogen level, coagulation time, and fibrinolytic activity
(43). Serum fibrinolytic activity increased after administration of dry garlic or garlic extracts to animals that were artificially rendered arteriosclerotic (79, 80). Although adenosine was thought to be the active constituent, it did not affect whole blood (43).

Garlic inhibited platelet aggregation in both in vitro and in vivo studies. A water, chloroform, or methanol extract of the drug inhibited collagen-, ADP-, arachidonic acid-, epinephrine-, and thrombin-induced platelet aggregation in vitro (81–87). Prolonged administration (intragastric, 3 months) of the essential oil or a chloroform extract of Bulbus Allii Sativi inhibited platelet aggregation in rabbits (88–90). Adenosine, alliin, allicin, and the transformation products of allicin, the ajoenes; the vinyldithiins; and the dialkyloligosulphides are responsible for inhibition of platelet adhesion and aggregation (4, 42, 91–93). In addition methyl allyl trisulphide, a minor constituent of garlic oil, inhibited platelet aggregation at least 10 times as effectively than allicin (94). Inhibition of the arachidonic acid cascade appears to be one of the mechanisms by which the various constituents and their metabolites affect platelet aggregation. Inhibition of platelet cyclic AMP phosphodiesterase may also be involved (91).

Ajoene, one of the transformation products of allicin, inhibited in vitro platelet aggregation induced by the platelet stimulators—ADP, arachidonic acid, calcium ionophore A23187, collagen, epinephrine, platelet activating factor, and thrombin (95, 96). Ajoene inhibited platelet aggregation in cows, dogs, guinea-pigs, horses, monkeys, pigs, rabbits, and rats (95, 96). The antiplatelet activity of ajoene is potentiated by prostacyclin, forskolin, indometacin, and dipyridamole (95). The mechanism of action involves the inhibition of the metabolism of arachidonic acid by both cyclooxygenase and lipoxygenase, thereby inhibiting the formation of thromboxane A2 and 12-hydroxyeicosatetraenoic acid (95). Two mechanisms have been suggested for ajoene’s antiplatelet activity. First, ajoene may interact with the primary agonist–receptor complex with the exposure of fibrinogen receptors through specific G-proteins involved in the signal transduction system on the platelet membrane (92). Or it may interact with a haemoprotein involved in platelet activation that modifies the binding of the protein to its ligands (96).

Hypoglycaemic effects of Bulbus Allii Sativi have been demonstrated in vivo. Oral administration of an aqueous, ethanol, petroleum ether, or chloroform extract, or the essential oil of garlic, lowered blood glucose levels in rabbits and rats (24, 97–104). However, three similar studies reported negative results (105–107). In one study, garlic bulbs administered orally (in feed) to normal or streptozotocin-diabetic mice reduced hyperphagia and polydipsia but had no effect on hyperglycaemia or hypoinsu-
Bulbus Allii Sativi

Allicin administered orally to alloxan-diabetic rats lowered blood glucose levels and increased insulin activity in a dose-dependent manner (24). Garlic extract's hypoglycaemic action appears to enhance insulin production, and allicin has been shown to protect insulin against inactivation (108).

Intragastric administration of an ethanol extract of Bulbus Allii Sativi decreased carrageenin-induced rat paw oedema at a dose of 100 mg/kg. The ant-inflammatory activity of the drug appears to be due to its anti-prostaglandin activity (109, 110).

A water or ethanol extract of the drug showed antispasmodic activity against acetylcholine, prostaglandin E2 and barium-induced contractions in guinea-pig small intestine and rat stomach (111). The juice of the drug relaxed smooth muscle of guinea-pig ileum, rabbit heart and jejunum, and rat colon and fundus (112, 113). The juice also inhibited norepinephrine-, acetylcholine- and histamine-induced contractions in guinea-pig and rat aorta, and in rabbit trachea (112, 113).

Clinical pharmacology

The efficacy of Bulbus Allii Sativi as a carminative has been demonstrated in human studies. A clinical study of 29 patients taking two tablets daily (~1000 mg/day) of a dried garlic preparation demonstrated that garlic relieved epigastric and abdominal distress, belching, flatulence, colic, and nausea, as compared with placebo (32). It was concluded that garlic sedated the stomach and intestines, and relaxed spasms, retarded hyperperistalsis, and dispersed gas (32).

A meta-analysis of the effect of Bulbus Allii Sativi on blood pressure reviewed a total of 11 randomized, controlled trials (published and unpublished) (113, 114). Each of the trials used dried garlic powder (tablets) at a dose of 600–900 mg daily (equivalent to 1.8–2.7 g/day fresh garlic). The median duration of the trials was 12 weeks. Eight of the trials with data from 415 subjects were included in the analysis; three trials were excluded owing to a lack of data. Only three of the trials specifically used hypertensive subjects, and many of the studies suffered from methodological flaws. Of the seven studies that compared garlic with placebo, three reported a decrease in systolic blood pressure, and four studies reported a decrease in diastolic blood pressure (115). The results of the meta-analysis led to the conclusion that garlic may have some clinical use-fulness in mild hypertension, but there is still insufficient evidence to recommend the drug as a routine clinical therapy for the treatment of hypertension (115).

A meta-analysis of the effects of Bulbus Allii Sativi on serum lipids and lipoproteins reviewed 25 randomized, controlled trials (published
and unpublished) (116) and selected 16 with data from 952 subjects to include in the analysis. Fourteen of the trials used a parallel group design, and the remaining two were cross-over studies. Two of the studies were conducted in an open-label fashion, two others were single-blind, and the remainder were double-blind. The total daily dose of garlic was 600–900 mg of dried garlic powder, or 10 g of raw garlic, or 18 mg of garlic oil, or aged garlic extracts (dosage not stated). The median duration of the therapy was 12 weeks. Overall, the subjects receiving garlic supplementation (powder or non-powder) showed a 12% reduction (average) in total cholesterol, and a 13% reduction (powder only) in serum triglycerides. Meta-analysis of the clinical studies confirmed the lipid-lowering action of garlic. However, the authors concluded that the overall quality of the clinical trials was poor and that favourable results of better-designed clinical studies should be available before garlic can be routinely recommended as a lipid-lowering agent. However, current available data support the hypothesis that garlic therapy is at least beneficial (116). Another metaanalysis of the controlled trials of garlic’s effects on total serum cholesterol reached similar conclusions (117). A systematic review of the lipid-lowering potential of a dried garlic powder preparation in eight studies with 500 subjects had similar findings (118). In seven of the eight studies reviewed, a daily dose of 600–900 mg of garlic powder reduced serum cholesterol and triglyceride levels by 5–20%. The review concluded that garlic powder preparations do have lipid-lowering potential (118).

An increase in fibrinolytic activity in the serum of patients suffering from atherosclerosis was observed after administration of aqueous garlic extracts, the essential oil, and garlic powder (119, 120). Clinical studies have demonstrated that garlic activates endogenous fibrinolysis, that the effect is detectable for several hours after administration of the drug, and that the effect increases as the drug is taken regularly for several months (43, 121). Investigations of the acute haemorheological (blood flow) effect of 600–1200 mg of dry garlic powder demonstrated that the drug decreased plasma viscosity, tissue plasminogen activator activity and the haematocrit level (118).

The effects of the drug on haemorheology in conjunctival vessels was determined in a randomized, placebo-controlled, double-blind, cross-over trial. Garlic powder (900 mg) significantly increased the mean diameter of the arterioles (by 4.2%) and venules (by 5.9%) as compared with controls (122). In another double-blind, placebo-controlled study, patients with stage II peripheral arterial occlusive disease were given a daily dose of 800 mg of garlic powder for 4 weeks (123, 124). Increased capil-
lary erythrocyte flow rate and decreased plasma viscosity and plasma fibrinogen levels were observed in the group treated with the drug (123, 124). Determinations of platelet aggregation ex vivo, after ingestion of garlic and garlic preparations by humans, suffer from methodological difficulties that may account for the negative results in some studies (24). In one study in patients with hypercholesterolaemia treated with a garlic–oil macerate for 3 months, platelet adhesion and aggregation decreased significantly (125). In a 3-year intervention study, 432 patients with myocardial infarction were treated with either an ether-extracted garlic oil (0.1 mg/kg/day, corresponding to 2 g fresh garlic daily) or a placebo (126). In the group treated with garlic, there were 35% fewer new heart attacks and 45% fewer deaths than in the control group. The serum lipid concentrations of the treated patients were also reduced (126).

The acute and chronic effects of garlic on fibrinolysis and platelet aggregation in 12 healthy patients in a randomized, double-blind, placebo-controlled cross-over study were investigated (30). A daily dose of 900 mg of garlic powder for 14 days significantly increased tissue plasminogen activator activity as compared with placebo (30). Furthermore, platelet aggregation induced by adenosine diphosphate and collagen was significantly inhibited 2 and 4 hours after garlic ingestion and remained lower for 7 to 14 days after treatment (30). Another randomized, double-blind, placebo-controlled study investigated the effects of garlic on platelet aggregation in 60 subjects with increased risk of juvenile ischaemic attack (29). Daily ingestion of 800 mg of powdered garlic for 4 weeks significantly decreased the percentage of circulating platelet aggregates and spontaneous platelet aggregation as compared with the placebo group (29).

Oral administration of garlic powder (800 mg/day) to 120 patients for 4 weeks in a double-blind, placebo-controlled study decreased the average blood glucose by 11.6% (30). Another study found no such activity after dosing noninsulin-dependent patients with 700 mg/day of a spray-dried garlic preparation for 1 month (127).

Contraindications

Bulbus Allii Sativi is contraindicated in patients with a known allergy to the drug. The level of safety for Bulbus Allii Sativi is reflected by its worldwide use as a seasoning in food.

Warnings

Consumption of large amounts of garlic may increase the risk of post-operative bleeding (128, 129).
Precautions

Drug interactions
Patients on warfarin therapy should be warned that garlic supplements may increase bleeding times. Blood clotting times have been reported to double in patients taking warfarin and garlic supplements (130).

Carcinogenesis, mutagenesis, impairment of fertility
Bulbus Allii Sativi is not mutagenic in vitro (Salmonella microsome reversion assay and Escherichia coli) (131, 132).

Pregnancy: non-teratogenic effects
There are no objections to the use of Bulbus Allii Sativi during pregnancy and lactation.

Nursing mothers
Excretion of the components of Bulbus Allii Sativi into breast milk and its effect on the newborn has not been established.

Other precautions
No general precautions have been reported, and no precautions have been reported concerning drug and laboratory test interactions, paediatric use, or teratogenic or non-teratogenic effects on pregnancy.

Adverse reactions
Bulbus Allii Sativi has been reported to evoke occasional allergic reactions such as contact dermatitis and asthmatic attacks after inhalation of the powdered drug (133). Those sensitive to garlic may also have a reaction to onion or tulip (133). Ingestion of fresh garlic bulbs, extracts, or oil on an empty stomach may occasionally cause heartburn, nausea, vomiting, and diarrhoea. Garlic odour from breath and skin may be perceptible (7). One case of spontaneous spinal epidural haematoma, which was associated with excessive ingestion of fresh garlic cloves, has been reported (134).

Posology
Unless otherwise prescribed, average daily dose is as follows (7): fresh garlic, 2–5 g; dried powder, 0.4–1.2 g; oil, 2–5 mg; extract, 300–1000 mg (as solid material). Other preparations should correspond to 4–12 mg of alliin or about 2–5 mg of allicin).

Bulbus Allii Sativi should be taken with food to prevent gastrointestinal upset.
References

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Radix Althaeae*

Definition
Radix Althaeae consists of the dried roots of Althaea officinalis L. (Malvaceae) (1–4).

Synonym
Malva officinalis L. (5).

Selected vernacular names
Altea, altee, althea, bardul khatmi, benefischi, bismalva-hibiscus, blanca malva, bon visclo, bourdon de St Jacques, Eibisch, Eibischwurzel, erva molle, guimauve, Heilwurz, hobbiza, Ibschwitz, kairi, khatmi, korzén prawóslazu, marshmallow, marshmallow root, malvaccioniu, malvavisco, marmolone, molotta, Moorish mallow, orvosiziliz gyökér, racine d’althée, racine de guimauve, Sammetpappel, sauvage, Schleimwurzel, suzmool, sweet weed, white mallow, wymote (3, 6–8).

Geographical distribution
Indigenous to western Asia and Europe, and is naturalized in the United States of America (9, 10). Roots are obtained from commercially cultivated plants that are at least 2 years old and harvested in the autumn (6, 10).

Description
A perennial herb with erect, woody stems, 60–120 cm high. Leaves alternate, ovate to slightly cordate, serrate, velvety, large, occasionally 3-lobed. Flowers pale pink, axillary, the calyx of each surrounded by a 6–9 cleft involucre. Fruit a set of cocci united into a ring (11).

Plant material of interest: dried roots

General appearance
Cylindrical or tapering, slightly twisted roots, up to 2 cm thick, with deep longitudinal furrows. Outer surface greyish-brown, bearing numerous

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
rootlet scars. Fracture externally fibrous, internally rugged and granular; section shows a thick, whitish bark with brownish periderm, separated by a well-marked, brownish cambium from the white xylem; stratified structure of the bark and radiate structure of xylem become more distinct when moist. Peeled root has greyish-white finely fibrous outer surface; cork and external cortical parenchyma absent (2).

Organoleptic properties

Odour: faint, aromatic; taste: mucilaginous (1).

Microscopic characteristics

Phloem with numerous long, thin-walled, non-lignified fibres arranged in tangential groups alternating with groups of sieve tissue, with a ground tissue of thin-walled parenchyma; xylem containing reticulate or scalariform thickening and bordered pits accompanied by lignified tracheids, a small amount of lignified parenchyma and occasional small groups of fibres with only the middle lamella lignified; xylem and phloem transversed by numerous non-lignified medullary rays, mostly uniseriate; majority of parenchyma cells of the phloem and medullary rays contain abundant small starch grains which are mostly simple, spherical to ovoid, occasionally 2–3 compound, with a well-marked circular or slit-shaped hilum; some of these parenchyma cells contain cluster crystals of calcium oxalate 20–40 µm in diameter, while others exist as idioblasts containing mucilage (1). 

Powdered plant material

Brownish-grey (unpeeled root) or whitish (peeled root). Fragments of colourless, mainly un lignified, thick-walled fibres with pointed or split ends; fragments of reticulate or scalariform thickening and bordered pits; cluster crystals of calcium oxalate about 20–35 µm, mostly 25–30 µm, in diameter; parenchyma cells containing mucilage; fragments of cork with thin-walled, tabular cells in the powdered material from the unpeeled root. Numerous starch grains, 3–25 µm in diameter, with occasionally a longitudinal hilum; starch grains mostly simple, a few being 2–4 compound (2).

General identity tests

Macroscopic and microscopic examinations (1, 2).

Purity tests

Microbiology

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (12).
**Foreign organic matter**
Not more than 2% of brown, deteriorated drug and not more than 2% of cork in the peeled root (2).

**Total ash**
Not more than 6% in the peeled root and not more than 8% in the un-peeled root (2).

**Acid-insoluble ash**
Not more than 3% in the peeled root (1).

**Water-soluble extractive**
Not less than 22% (1).

**Loss on drying**
Not more than 12% (2).

**Swelling index**
Not less than 10 (2).

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (2). For other pesticides, see the European pharmacopoeia (2), and the WHO guidelines on quality control methods for medicinal plants (12) and pesticide residues (13).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (12).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (12) for the analysis of radioactive isotopes.

**Other purity tests**
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

**Chemical assays**
Not less than 10% total mucilage in the peeled root as determined by gravimetric analysis (14).
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Major chemical constituents
The mucilage content ranges from 10 to 20% and consists of a mixture of acidic galacturonorhamnans, neutral glucans and neutral arabinogalactans (6, 8, 9, 15–17).

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and in traditional systems of medicine
As a demulcent for symptomatic treatment of dry irritable coughs and irritations of oral and pharyngeal mucosa and as an emollient for wounds and dry skin (8, 18–23). Also used in cough mixtures to mask the bitter or pungent taste of other drugs (16).

Uses described in folk medicine, not supported by experimental or clinical data
Treatment of asthma, cystitis, dysentery and irritations of the gastric mucosa (7).

Pharmacology
Experimental pharmacology
The demulcent effects of Radix Althaeae are due to its high content of polysaccharide hydrocolloids, which form a protective coating on the oral and pharyngeal mucosa, soothing local irritation and inflammation (24).

Anti-inflammatory activity
A polysaccharide fraction (500 µg/ml) isolated from a root extract had anti-complement activity in human serum in vitro (25). Aqueous extracts of the roots stimulated phagocytosis, and the release of oxygen radicals and leukotrienes from human neutrophils in vitro (26). The aqueous extract also induced the release of cytokines, interleukin-6 and tumour necrosis factor from human monocytes in vitro, thereby exhibiting anti-inflammatory and immunostimulant activity (26). Intraperitoneal administration of isolated mucilage polysaccharides to mice (10 mg/kg body weight) induced a 2.2-fold increase in the phagocytic activity of macrophages as measured by the colloidal carbon clearance test (27). However, intragastric administration of an 80% ethanol extract of the roots to rats (100 mg/kg body weight) did not inhibit carrageenan-induced footpad oedema (28).
Weak inhibition (17%) of mucociliary transport in isolated, ciliated epithelium of the frog oesophagus was demonstrated after treatment of the isolated tissues with 200 µl of an aqueous root macerate (6.4 g/140 ml) (29).

**Antitussive activity**
Intragastric administration of a polysaccharide fraction, isolated from an aqueous root extract, to cats (50 mg/kg body weight) suppressed the intensity and the frequency of coughs induced by mechanical irritation of laryngopharyngeal and tracheobronchial mucosa (30). The antitussive activity of this polysaccharide fraction (50 mg/kg body weight) was as effective as Syrupus Althaeae (1.0 g/kg body weight), and more effective than prenoxdiazine (30 mg/kg body weight) (30).

**Clinical pharmacology**
None.

**Contraindications**
No information available.

**Warnings**
No information available.

**Precautions**

**Drug interactions**
Simultaneous administration of Radix Althaeae may delay the absorption of other drugs (8).

**Other precautions**
No information available on general precautions or precautions concerning drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Radix Althaeae should not be administered during pregnancy or lactation or to children without medical supervision.

**Adverse reactions**
No information available.
**Dosage forms**

Peeled or unpeeled, broken, chopped or powdered crude drug (1, 2) and galenical preparations thereof. Store in a well-closed container, protected from light (2).

**Posology**

(Unless otherwise indicated)

For dry cough, oral or pharyngeal irritation: 0.5–3.0 g of crude drug as an aqueous, cold macerate (14, 19, 20, 31) or 2–8 ml of syrup (20, 22, 32), which may be repeated up to a daily dose of 15 g of crude drug. For gastric irritation: 3–5 g of crude drug as an aqueous, cold macerate up to three times daily (19, 20, 31).

**References**

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Radix Althaeae

Herba Bidentis

Definition
Herba Bidentis consists of the whole or cut dried aerial parts of *Bidens tripartita* L. (Asteraceae), collected at the time of mass budding, which marks the onset of the flowering phase (I).

Synonyms

Selected vernacular names
Bastard agrimony, bastard hemp, beggar-ticks, bident á feuilles tripartites, bident trifolié, bident tripartite, brønnsle, bur beggarsticks, bur marigold, căñamo acuático, càrligior, chamquisari, dentită, dokaebibaneul, Dreiteiligere Zweizahn, forbicina comune, gatalryukcho, guichimchae, guichimcho, guiwoocho, kolmistruse, langyecae, lang ba cao, lang pa ts’ao, longbacaocao, orkbila, paneuldaksari, papachim, purple-stem beggarticks, purplestem beggarticks, qinnab maiy, railway beggar’s tick, spanish needles, sticktights, strzalki, sunītis nokarenais, sunītis trejdaivu, sukeneviri, swamp beggar-ticks, ta-ukogi, tel maiy, three-lobe beggarticks, threllobe beggarticks, thsereda triohrazdelnaja, trifid bur-marigold, tripartite bur marigold, tuldokaebibaneul, tummarusokki, uczep dwuzebny, uczep trojdzielny, veerdelig tandzaad, water agrimony, water hemp, wolf’s grasp weed (2, 3–14).

Geographical distribution
Indigenous to damp and temperate regions near fresh water sources throughout Asia, Africa, Australia, Europe, North America and New Zealand. The plant is found in the damp regions of the Newly Independent States, such as in Northern Siberia and the southern part of the far east region (4, 5, 15–17).
Description
An annual plant, 15–75(100) cm high, fibrous root, adventitious roots when growing in wetlands. Stem erect, heavily branched, wiry, angular, solid, marked with small brown spots, glabrous or somewhat downy, often brownish-red. Leaves opposite, simple (but appearing trifoliate), 3- to 5-lobed (usually deeply divided into 3 narrow ovate-rhomboid to lanceolate lobes, the central one larger and wider), sharply serrate, acuminate, 3–15 cm long, dark green, petiole narrow, short and winged. Uppermost leaves sometimes undivided. Inflorescence: flower head (50–60 flowers), generally discoid, erect or inclined, solitary or not, conical, 15–25 mm long and 15–25 mm wide. Peduncle 1–6 cm long. Involucre 7–20 mm in diameter, two rows of phyllaries: inner phyllaries ovate, 6–8 mm long, brown-yellow; outer phyllaries, usually 5–8, lanceolate, leaf shaped with thorny edges, green. Bracts linear, spreading, ray flowers absent, disc flowers hermaphrodite, tubular, brownish-yellow. Fruit, glabrous achene, wedge-shaped, distinctly compressed; inner achenes 5–8 mm long, 4-angled; outer achenes 3.5–4 mm long, 2–3-angled; thorns of angles ascending below, reflexed above; pappus awns thorny, generally 2, sometimes 3–4 (2 longer), 1–3.6 mm (4–6, 9, 15, 16, 18–22).

Plant material of interest: dried aerial parts

General appearance
Entire or fragmented leafy stems, leaves and flower heads. Leaves opposite, short petiolate, 3–5-lobed or undivided, 3–7 cm in length (no longer than 15 cm), dark green. Leaf fragments crumpled, the serrated edges can be distinguished. Stems heavily branched, glabrous or somewhat downy, not more than 0.8 cm in thickness, green or greenish-violet. Stem pieces hollow or pithy, wrinkled. Flower heads, not more than 0.6–1.5 cm in diameter, somewhat drooping. Disc flowers tubular, with two awns, brownish-yellow (1, 5, 6, 16, 23).

Organoleptic properties
Odour: slight; taste: bitter and slightly astringent (1).

Microscopic characteristics
Leaf: upper and lower epidermises with undulating cell walls are distinguishable. Anomocytic stomata. Simple hairs with thin cell walls on both epidermises, 9–18 cells, sometimes filled with brown contents; very large base cell with a longitudinally striated cuticle. Simple hairs with thick cell walls on the veins and at the edges of the leaf, 2–13 cells; the hair base
multicellular with a longitudinally striated cuticle. Secretion ducts filled with dark red liquid, along veins and near the leaf edges. Flower: florets with two opposing barbed, blunt-ended pappus spines from the top of the ovary, and as long as the tubular corolla, consisting of a multicellular column of cells about 200 µm in diameter including some vascular tissue, with many thorn-like unicellular covering trichomes about 350 µm long directed towards the pappus base. Pollen grains spherical, with a spiny exine and three pores, about 30 µm in diameter (1, 23).

**Powdered plant material**
Green, brown-green or green-violet with a sprinkling of yellow. The powder has the same microscopic characteristics as the entire leaf and flower (see Microscopic characteristics) (1).

**General identity tests**
Macroscopic and microscopic examinations; thin-layer chromatography, paper chromatography and chromatography–mass-spectroscopy for the presence of flavonoids (1, 24); chemical tests for the presence of polysaccharides (precipitation with ethanol and reduction of simple sugars results after the acid hydrolysis of polysaccharides) (1).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (25).

**Chemical**
The paper chromatogram (chromatography paper FN 12, Germany; n-butanol-acetic acid-water (4:1:2); 16 hours; ultraviolet (UV) light, 360 nm) shows two dark brown zones of flavonoids with Rf values of about 0.38 and 0.58. A dark-brown zone with an Rf value of about 0.75 should not be present since it indicates the presence of flavonoids of *Bidens cernua* L.) (1).

**Foreign organic matter**
Not more than 40% stems or their fragments; not more than 8% of parts with non-characteristic colour of the plant material; not more than 3% of other foreign organic matter (fragments of non-toxic plants). For cut drug: not more than 10% of fragments having a diameter more than
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7 mm; not more than 15% of fragments having a diameter less than 0.5 mm (1).

**Total ash**
Not more than 14% (1).

**Acid-insoluble ash**
No information available.

**Sulfated ash**
No information available.

**Water-soluble extractive**
No information available.

**Alcohol-soluble extractive**
No information available.

**Loss on drying**
Not more than 13% (1).

**Swelling index**
Not applicable.

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. For other pesticides, see the *European pharmacopoeia* (24), WHO guidelines on quality control methods for medicinal plants (25) and WHO guidelines on pesticide residues (26).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (25).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (25) for the analysis of radioactive isotopes.

**Other purity tests**
Acid-insoluble, sulfated ash, water-soluble extractive and alcohol extractive tests to be established in accordance with national requirements. Content of mineral matter not more than 1% (1).
Herba Bidentis

Chemical assays
Contains not less than 3.5% polysaccharides, determined by chemical assays (1).

Major chemical constituents
The major constituents of the dried aerial parts are flavonoids (luteolin, cynaroside), related chalcones (butein, butein-7-O-β-d-glucopyranoside and marein), flavanones (isocoreopsin and flavanomarein) and aurones (sulfuretin, sulfurein, maritimetin and maritimein) (5, 16, 27, 29, 30). Dried aerial parts contain 0.05–0.11% (v/w) essential oil and 4.51–4.65% saccharides (arabinose, galactose, glucose, rhamnose and xylose) (31, 32). The presence of coumarins (umbelliferone, scopoletin and aesculetin), tridecane-derived polyacetylenes (for example trideca-1,12-dien-3,5,7,9-tetrayne), tannins, xanthophyll (a yellow pigment, widespread in nature, sometimes called lutein), organic acids, carotene and vitamin C has also been reported (5, 16, 27–30, 33, 34). The structures of the major constituents are presented below.
Medicinal uses

*Uses supported by clinical data*
Internally used for treatment of chronic dysentery, and acute and chronic enteritis (35). Oral administration and simultaneous external application have been used in patients with psoriasis (17).

*Uses described in pharmacopoeias and well-established documents*
Internally: as a mild sudorific and diuretic for treatment of bladder and kidney problems, for conditions producing blood in the urine (haematuria) (36), as an astringent, and for treatment of diarrhoea and ulcerative colitis (15, 28).

*Uses described in traditional medicine*
As a diuretic, antidiarroheal, antiallergic, anti-inflammatory (37), anthelmintic, febrifuge, diaphoretic, for gallbladder and as a kidney tonic (38). Used for the treatment of alopecia (4), scrofulosis (39), gout, arthralgia (40), furunculosis, diaphesis (a constitutional predisposition towards a particular state or condition and especially one that is abnormal or diseased), seborrhoetic dermatitis, acne vulgaris (17, 27, 41–43), eczema (44), infantile rickets (45, 46), digestive tract ailments, flatulence, fevers, bladder and kidney stones, as a styptic haemostatic and for curing insect bites (47). Used externally as a bath for various diathesis conditions, especially in children (28).

Pharmacology

*Experimental pharmacology*

**Antimalarial activity**
A 90% ethanol extract of the dried whole plant was active against *Plasmodium falciparum* at a concentration of 20 µg/ml (48).

**Choleretic activity**
Oral administration of the total flavonoids isolated from the aerial parts of the plant to rats (500 mg/kg body weight (bw)) significantly induced choleretic activity. Subsequently, an increase of cholic acids and cholesterol in bile was observed (49).

**Antiulcer activity**
Separate intragastric administration of methanol and aqueous extracts of the aerial parts to rats, at a dose of 500 mg/kg bw, showed antiulcer activ-
ity in vivo against aspirin-induced ulcers, but the extracts were inactive against indomethacin-induced ulcers (30).

**Photoprotective activity**
Haemolysis induced in vitro by psoralen and UV-A radiation (PUVA-haemolysis) was inhibited by the presence of an extract of the aerial parts of the plant in the medium during irradiation, or by the addition of the extract to the medium after PUVA-treatment. The inhibition effect was more pronounced when the extract was added during irradiation (51).

**Toxicology**
An ethanol-aqueous extract (1:1) of the aerial parts administered intraperitoneally to mice had a median lethal dose of 750 mg/kg bw (52).

**Clinical pharmacology**
Aerial parts of the plant were used in an open clinical trial, without a control group, to treat 500 patients with dysentery, 65 with acute enteritis and 248 with chronic enteritis. Several different dosage forms of the herb were used: 200 g of fresh whole herb and 100 g of dried herb in decoctions (in three divided doses per day); granules containing 5 g of dried aqueous extract, three times daily; 0.5 g tablets of dried aqueous extract, 10 tablets each time, three times daily; and injection, 2 ml per injection (dose not stated), 2–3 times daily. The herbal preparations were administered for 3–10 days to patients who had already had diarrhoea for 7–15 days. Of the 500 patients with chronic dysentery, 387 were reported to have been cured; 13 had not responded within 3 days. All 313 patients with enteritis were reported to have been cured (12 of the patients with chronic enteritis relapsed later) (35).

In an open clinical trial without a control group, a 70% ethanol extract of the aerial parts of the plant and an ointment containing 2.5% of the extract were administered to 53 patients with psoriasis. After oral administration of the extract (20 drops three times daily) and simultaneous application of the ointment to the affected areas of the skin once a day, the combination was found to have anti-inflammatory activity as well as an ability to stimulate adrenal functions. After one week of treatment, desquamation of the skin was decreased, and a decoloration of the psoriatic plaques was observed. A clinical recovery was recorded for 29 of the patients; an improvement in condition was recorded for 22 patients; and a failure of treatment for 2 patients (17).
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Adverse reactions
No information was found.

Contraindications
No irrigation therapy is recommended in people with oedema due to impaired heart or kidney function. If signs of hypersensitivity reactions appear, Herba Bidentis must not be used again.

Warnings
No information was found.

Precautions

Drug interactions
No information was found.

Other precautions
No information was found.

Pregnancy
Preparations of Herba Bidentis should not be used during pregnancy.

Nursing mothers
Preparations of Herba Bidentis should not be used by nursing mothers.

Paediatric use
Preparations of Herba Bidentis should not be used for the treatment of children under the age of 12 years.

Dosage forms
A herbal tea or a briquette of Herba Bidentis (17).

Posology
(Unless otherwise indicated)
Internal use. One tablespoon of the infusion (1:20) is administered 3–4 times a day (46, 53).
External use as a bath. One glass of an infusion of 10 g of cut herb together with 100 g of cooking salt or sea salt per bath (54).
References

Herba Bidentis

Flos Calendulae*

Definition
Flos Calendulae consists of the dried ligulate florets or composite flowers of *Calendula officinalis* L. (Asteraceae) (1–3).

Synonyms
Asteraceae are also known as Compositae.

Selected vernacular names
Atunjaq, calendula, Chinese safflower, cuc kim tiên, djamir, djomaira, feminell, flamenquilla, fleur de calandule, fleur de souci, fleur de souci officinal, fleurs de tous les mois, garden marigold, gold-bloom, Goldblume, gole hamisheh bahar, hen and chickens, Körömvirag, lellousha, maravilla, marigold, mary-bud, ok-hhawan, pot marigold, qaraqs, qawqhan, quaqahan, ringflower, Ringelblüten, saialill, sciure’e Sant’antonio, souci, souci des jardins, tabsoult, toukinsenka, tousslat, uchu k’aspa, virreina, xu xi, zergul zerzira, zobeida, zubaydah (4–7).

Geographical distribution
Indigenous to central, eastern and southern Europe. Cultivated commercially in North America, the Balkans, Eastern Europe and Germany (6, 8).

Description
An annual herb, much branched from the base, very aromatic, up to 0.3–0.6 m high; stem angular, hairy and solid. Leaves sessile, light green, with semiamplexicaul base; entire, undulate or remotely denticate; glandular hairs on both surfaces; lower leaves spatulate, obtuse, sometimes acute at the apex, 10–20 cm long and 1–4 cm wide; higher leaves oblong and mucronate, 4–7 cm long. Involucral bracts 7–15 mm long, covered with long, glandular hairs; inner involucral bracts with pellucid, scarious margin; marginal flowers in cultivated plants often multi-seriate; corolla oblong-spatulate, bright yellow or orange, 15–25 mm long and 3 mm wide,

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
1–3-toothed with 4 or 5 veins, marginally entire, covered at the base with patent, long, thick hairs; corolla of disc flowers rounded, 3-dentate top, 1.5–2.5 cm long and 4–7 mm in diameter, 5 mm long tube and moderately widened limb. Stigma short, thick, hairy; ovary oblong, 0.5 mm in length, pubescent, shrivelling after anthesis. Achenes narrowly oblong, strongly curved, faintly ribbed, thinly pubescent or glabrous, 10–12 mm long, outer achenes warty-ribbed outside, inner achenes prickly-warty, often with broad, thick margins (2, 7, 9).

**Plant material of interest: dried ligulate florets and composite flowers**

**General appearance**
Ligulate florets consist of a yellow, orange or orange-yellow ligule, 3–5 mm wide and about 7 mm in the middle part, with 3-toothed apex and hairy, partly sickle-shaped, yellowish-brown to orange-brown tube with projecting style and 2-lobed stigma; occasionally with a partly bent yellowish-brown to orange-brown ovary. Tubular florets about 5 mm long, consist of yellow, orange-red or red-violet 5-lobed corolla and yellowish-brown or orange-brown tube, hairy in its lower part, mostly with a bent yellowish-brown to orange-brown ovary (1).

**Organoleptic properties**
Odour: faint, pleasantly aromatic (10, 11); taste: bitter (2).

**Microscopic characteristics**
Inner epidermal cells of ray floret elongated, rectangular and almost straight walled, cuticle faintly striated; stomata absent; outer epidermal cells similar, but with 3 or 4 anomocytic stomata; trichomes very numerous on the tube, biseriate; stigma epidermal cells straight-walled, polygonal. In disc floret, outer epidermal cells elongated, straight or slightly sinuous-walled, stomata absent; abundant trichomes on area below point of insertion of the stamens, mainly glandular, uniseriate or biseriate. Within the upper part of the anthers, a layer of isodiametric to elongated, moderately thick-walled, lignified and pitted cells; pollen grains spherical, up to 45 µm in diameter, with 3 germinal pores, exine finely granular with numerous short spines; apex of stigma covered by short, bulbous papillae (2).

**Powdered plant material**
Yellow-green; fragments of corollas containing light yellow oil droplets; some corollas with fairly large anomocytic stomata, others containing
prismatic and very small clusters of calcium oxalate crystals. Covering trichomes biseriate, multicellular and conical; glandular trichomes with a uniseriate or biseriate, multicellular stalk and a large, ovoid, biseriate, multicellular head. Spherical pollen grains up to 45 µm in diameter, exine finely granular with numerous short spines and with 3 germinal pores; occasional fragments of stigmas with short, bulbous papillae (1).

**General identity tests**
Macroscopic and microscopic examinations, and thin-layer chromatography for flavonoid content (1, 2).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (12).

**Foreign organic matter**
Not more than 5% bracts and not more than 2% other foreign matter (1, 2).

**Total ash**
Not more than 10% (1, 2).

**Acid-insoluble ash**
Not more than 2% (2).

**Water-soluble extractive**
Not less than 20% (2).

**Loss on drying**
Not more than 10% (1).

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (13). For other pesticides, see the *European pharmacopoeia* (13), and the WHO guidelines on quality control methods for medicinal plants (12) and pesticide residues (14).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (12).
**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (12) for the analysis of radioactive isotopes.

**Other purity tests**
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 0.4% flavonoids, calculated as hyperoside, by spectrophotometry (1). A high-performance liquid chromatography method is also available (15).

**Major chemical constituents**
The major constituents are triterpene saponins (2–10%) based on oleanolic acid (i.e. calendulosides) and flavonoids (3-O-glycosides of isorhamnetin and quercetin), including astragalin, hyperoside, isoquercitrin and rutin. Other constituents include essential oil, sesquiterpenes (e.g. caryophyllene) and triterpenes (e.g. α- and β-amyris, lupeol and lupenone) (5, 6, 16). Polysaccharides have also been reported (17). The structures of the characteristic triterpene saponins and flavonoids are presented below.

\[
\begin{align*}
\text{R} & \quad \text{R}^3 \quad \text{R}^4 \quad \text{R}^5 \\
A & \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{Galp} \quad \text{CH}_2\text{OH} \\
E & \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{H} \\
F & \quad \text{Glc} \quad \text{H} \quad \text{H} \quad \text{CO}_2\text{H} \\
H & \quad \text{Glc} \quad \text{Galp} \quad \text{H} \quad \text{CO}_2\text{H}
\end{align*}
\]
**Flos Calendulae**

\[
\text{Galp} = \begin{array}{c}
\text{Glc}f = \begin{array}{c}
\text{Glc}p = \begin{array}{c}
\beta-\text{d-galactopyranosyl} \\
\beta-\text{d-glucofuranosyl} \\
\beta-\text{d-glucopyranosyl}
\end{array}
\end{array}
\end{array}
\]

- astragalin: H Glcp
- hyperoside: OH Galp
- isoquercitrin: OH Glcf
- rutin: OH Rhap-(1→6)-Glcp

\[
\text{Rhap}-(1\rightarrow6)\text{-Glc}p = \begin{array}{c}
\text{O-6-deoxy-\alpha-\text{d-mannopyranosyl(1} \rightarrow 6)\text{-\beta-\text{d-glucopyranosyl}}}
\end{array}
\]

**Medicinal uses**

*Uses supported by clinical data*

None.

*Uses described in pharmacopoeias and in traditional systems of medicine*

External treatment of superficial cuts, minor inflammations of the skin and oral mucosa, wounds and ulcus cruris (2, 18, 19).
Uses described in folk medicine, not supported by experimental or clinical data
Treatment of amenorrhoea, angina, fevers, gastritis, hypotension, jaundice, rheumatism and vomiting (2, 5, 6).

Pharmacology
Experimental pharmacology

Phagocytosis
Three polysaccharides isolated from an aqueous extract of Flos Calendulae enhanced phagocytosis in human granulocytes in vitro in the colloidal carbon clearance test (17). Intraperitoneal injection of a polysaccharide fraction isolated from an aqueous extract of the flowers to mice (10 mg/kg body weight) enhanced phagocytosis (20). Intraperitoneal administration of an unsaponifiable fraction (0.5 ml) of a hydroalcoholic extract of the flowers weakly stimulated phagocytosis in mice inoculated with Escherichia coli. However, the hydroalcoholic extract was not active (21).

Antimicrobial activity
The essential oil of the flowers inhibited the growth in vitro of Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Candida albicans (22). A flavonoid fraction isolated from the flowers inhibited the growth in vitro of S. aureus, Sarcina lutea, E. coli, Klebsiella pneumoniae and Candida monosa (23). However, chloroform, ethanol, methanol or water extracts of the flowers did not inhibit bacterial growth in vitro (24–26). Acetone, ethanol or water extracts inhibited the growth in vitro of the fungus Neurospora crassa (27). Extracts of the flowers inhibited the growth in vitro of Trichomonas vaginalis (28). Oxygenated terpenes appear to be responsible for the antimicrobial activity (29).

Antiviral activity
A tincture of the flowers suppressed the replication of herpes simplex, influenza A2 and influenza APR-8 viruses in vitro (30). However, an aqueous extract of the flowers was not active (31). A chloroform extract of the flowers inhibited the replication of HIV-1 in acutely infected lymphocytic MOLT-4 cells in vitro (IC₅₀ 0.4 mg/ml) (32). A chloroform extract also inhibited HIV-1 reverse transcriptase activity in a dose-dependent manner (ED₅₀ 51.0 µg/ml) (32). A 5% hot aqueous extract of the
flowers (2 ml) inhibited the replication of encephalitis virus after intra-peritoneal administration to mice (33).

**Anti-inflammatory activity**
Topical application of a 70% ethanol extract of the flowers to mice at a dose of 1.2 mg/ear (corresponding to 4.16 mg crude drug) reduced croton oil-induced ear oedema by 20% (34). External application of a carbon dioxide extract of the flowers (300 µg/cm²) suppressed croton oil-induced ear oedema in mice (34). The triterpene fraction of an extract of the flowers had marked anti-inflammatory activity in mice (1 µg/ear) against ear oedema induced by 12-O-tetradecanoylphorbol-13-acetate (35). Faradiol esters isolated from the flowers (240 µg/cm²) inhibited croton oil-induced ear oedema in mice (36). Intragastric administration of an aqueous extract of the flowers (100 mg/kg body weight) inhibited carrageenan-induced footpad oedema in rats (37). However, an 80% ethanol extract of the flowers was weakly active (11% inhibition) at a concentration of 100 mg/kg body weight administered orally 1 hour prior to induction of oedema (38). Isorhamnetin glycosides isolated from the flowers inhibited rat lung lipoxygenase in vitro (39).

**Wound-healing activity**
External application of a hydroalcoholic extract accelerated the rate of contraction and epithelialization of excision wounds in rats (40). A 3% freeze-dried aqueous extract of the flowers induced vascularization in the chick chorioallantoic membrane assay. Histological sections of the treated chorioallantoic membranes also indicated the presence of hyaluronan, a tissue glycosaminoglycan associated with neovascularization (41).

**Clinical pharmacology**
Although no randomized, controlled clinical trials have been performed, two case reports in the early medical literature support the traditional use of Flos Calendulae. The reports describe the use of a strong tincture of the flowers applied on compresses to reduce inflammation and suppuration, and to accelerate the healing of wounds (42, 43). These reports may be of historical value only.

**Contraindications**
Flos Calendulae is contraindicated in cases of known allergy to plants of the Asteraceae (Compositae) family (18).

**Warnings**
No information available.
Precautions

Carcinogenesis, mutagenesis, impairment of fertility
Saponins isolated from Flos Calendulae were not mutagenic at a concentration of 400 µg/ml in the Salmonella/microsome assay using S. typhimurium strain TA98, with or without S9 metabolic activation (44). Extracts of the flowers were not carcinogenic after daily intragastric administration of 0.15 g/kg body weight to rats (for 22 months) or hamsters (for 18 months) (45). Mutagenicity testing of the fluidextract in the Salmonella/microsome assay (using S. typhimurium strains TA98, TA100, TA1535 and TA1537) was negative at concentrations of up to 5 mg/plate. The mouse bone marrow micronucleus test was also negative after daily administration of up to 1 g/kg body weight for 2 days (46). A fluidextract of the flowers (100 mg/ml, 60% ethanol) was genotoxic in both mitotic crossing-over and chromosome segregation when assayed for mitotic segregation in the heterozygous diploid D-30 of Aspergillus nidulans (46).

Other precautions
No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and nonteratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Flos Calendulae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions
Weak skin-sensitization has been reported (47).

Dosage forms
Infusion for topical use; aqueous and alcohol extracts, tinctures and ointment for external use (2, 18, 19). Store in a well-closed container, protected from light (1).

Posology
(Unless otherwise indicated)
Topical application: an infusion of 1–2 g/150 ml (18). External use: a 40% alcohol extract (1:1), or tincture (1:5) in 90% alcohol (2). For the treatment of wounds, the tincture is applied undiluted; for compresses, the tincture is usually diluted at least 1:3 with sterile water (18, 48, 49). Ointment: 2–5% (48, 50).
References

5. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL, January 28, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).


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Flos Chamomillae*

Definition
Flos Chamomillae consists of the dried flowering heads of *Chamomilla recutita* (L.) Rauschert (Asteraceae) (1–4).

Synonyms
In most formularies and reference books, *Matricaria chamomilla* L. is regarded as the correct species name. However, according to the International Rules of Botanical Nomenclature, *Chamomilla recutita* (L.) Rauschert is the legitimate name for this species (5). Asteraceae are also known as Compositae.

Selected vernacular names
Baboonig, babuna, babunah camomile, babunj, bunga kamil, camamilla, camomile, chamomile, camomilla, chamomille allemande, campomilla, chamomille commune, camomille sauvage, fleurs de petite camomille, flos chamomillae, german chamomile, hungarian chamomile, Kamille, Kamillen, kamitsure, kamiture, manzanilla, manzanilla chiquita, manzanilla comun, manzanilla dulce, matricaire, matricaria flowers, pin heads, sweet false chamomille, sweet feverfew, wild chamomile (3, 6–9).

Description
Herbaceous annual; 10–30 cm in height, with erect, branching stems and alternate, tripinnately divided leaves below and bipinnately divided leaves above, both types having almost filiform lobes; the capitulum (to 1.5 cm in diameter) comprises 12–20 white ligulate florets surrounding a conical hollow receptacle on which numerous yellow tubular (disk) florets are inserted; the inflorescence is surrounded by a flattened imbricated involucre; fruit small, smooth, yellowish (3, 7, 10).

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.
Plant material of interest: flower heads

General appearance
Flos Chamomillae consists of conical flower heads, each bearing a few white ligulate florets and numerous yellowish orange to pale yellow tubular or disk florets on conical, narrow hollow receptacles with a short peduncle; disk florets perfect and without a pappus; ray florets pistillate, white, 3-toothed and 4-veined; involucre hemispherical, composed of 20–30 imbricate, oblongolate and pubescent scales; peduncles weak brown to dusky greenish yellow, longitudinally furrowed, more or less twisted and up to 2.5 cm long; achenes more or less obovoid and faintly 3- to 5-ribbed; pappus none, or slightly membranous crown (7, 11).

Organoleptic properties
Odour, pleasant, aromatic; taste, aromatic and slightly bitter (1–3).

Microscopic characteristics
Receptacle and bracteoles with schizogenous secretory ducts; vascular bundles with phloem fibres; spiral, annular and reticulate but pitted vessels; lignified cells at the bases of the ovaries absent; nearly all parts of florets bear composite-type glandular hairs with short, biseriate stalk and enlarged head, formed of several tiers, each of two cells; ovary with longitudinal bands of small mucilage cells; stigma with elongated papillae at the apex; pollen grains, spherical or triangular, with numerous short spines (3).

Powdered plant material
Powdered Flos Chamomillae is greenish yellow to yellowish brown; spiny pollen grains numerous, 18–25 µm in diameter; fragments of yellow or white corolla, with polygonal, small epidermal cells having straight or slightly wavy walls, sometimes papillosed, and sometimes bearing glandular hairs of composite type; fragments of the fibrous layer of anther; fragments from ovary, with glandular hairs and rows of small mucilage cells; green fragments of parenchyma of involucre; stigma with papillae; cells of the achenes with scalariform perforations in walls; fragments of fibrovascular bundles with spiral, annular and reticulate vessels and sclerenchyma fibres; fragments of involucral bracts with epidermis having elliptical stomata up to 30 µm in length, also vessels and fibres; occasional fibre from the stems; minute cluster crystals of calcium oxalate, up to 10 µm in diameter; fragments of lignified parenchyma of the filaments and occasional fragments of vessels (3, 7, 10).
Geographical distribution
The plant is indigenous to northern Europe and grows wild in central European countries; it is especially abundant in eastern Europe. Also found in western Asia, the Mediterranean region of northern Africa, and the United States of America. It is cultivated in many countries (3, 7–13).

General identity tests
The drug is identified by its macroscopic and microscopic characteristics, and by thin-layer chromatography (1–3).

Purity tests

Microbiology
The test for *Salmonella* spp. in Flos Chamomillae products should be negative. The maximum acceptable limits of other microorganisms are as follows (1, 14, 15). For preparation of decoction: aerobic bacteria—not more than $10^7$/g; fungi—not more than $10^5$/g; *Escherichia coli*—not more than $10^5$/g. Preparations for internal use: aerobic bacteria—not more than $10^5$/g or ml; fungi—not more than $10^4$/g or ml; enterobacteria and certain Gram-negative bacteria—not more than $10^3$/g or ml; *Escherichia coli*—0/g or ml. Preparations for external use: aerobic bacteria—not more than $10^2$/g or ml; fungi—not more than $10^2$/g or ml; enterobacteria and certain Gram-negative bacteria—not more than $10^1$/g or ml.

Foreign organic matter
Not more than 10% stems and not more than 2% foreign organic matter (3). No flowering heads of *Anthemis cotula* L. or *A. nobilis* L. (7).

Total ash
Not more than 13% (2).

Acid-insoluble ash
Not more than 4% (11).

Moisture
Not more than 12% (12).

Pesticide residues
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Flos Chamomillae is not more than 0.05 mg/kg (1). For other pesticides, see WHO guidelines.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

on quality control methods for medicinal plants (14) and guidelines for predicting dietary intake of pesticide residues (16).

Heavy metals
Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (14).

Radioactive residues
For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (14).

Other tests
Chemical, dilute ethanol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.4% v/w of essential oil (1–3). Total volatile oil content is determined by pharmacopoeial methods (1–3).

Thin-layer (1, 2) and gas–liquid (17) chromatography for volatile oil constituents, and high-performance liquid chromatography for flavonoids (18, 19).

Major chemical constituents
Flos Chamomillae contains an essential oil (0.4–1.5%), which has an intense blue colour owing to its chamazulene content (1–15%). Other major constituents include α-bisabolol and related sesquiterpenes (up to 50% of the oil). Apigenin and related flavonoid glycosides constitute up to 8% (dry weight) of the drug (10, 18).

![chemical structure of chamazulene]

CH₃

H₂C

CH₃

chamazulene

64
**Dosage forms**
Dried flower-heads, liquid extract (1:1 in 45% alcohol), tinctures and other galenicals (11). Store in well-closed containers, protected from light (1–3).

**Medicinal uses**

*Uses supported by clinical data*

**Internal use**
Symptomatic treatment of digestive ailments such as dyspepsia, epigastric bloating, impaired digestion, and flatulence (3, 7, 8, 10, 11, 20, 21). Infusions of camomile flowers have been used in the treatment of restlessness and in mild cases of insomnia due to nervous disorders (21, 22).

**External use**
Inflammation and irritations of the skin and mucosa (skin cracks, bruises, frostbite, and insect bites) (10, 23), including irritations and infections of the mouth and gums, and haemorrhoids (10, 11, 20, 21, 23).

**Inhalation**
Symptomatic relief of irritations of the respiratory tract due to the common cold (24).

*Uses described in pharmacopoeias and in traditional systems of medicine*
Adjuvant in the treatment of minor inflammatory conditions of the gastrointestinal tract (24).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Uses described in folk medicine, not supported by experimental or clinical data

As an antibacterial and antiviral agent, an emetic, and an emmenagogue. It is also used to relieve eye strain, and to treat urinary infections and diarrhoea (13).

Pharmacology

Experimental pharmacology

Both camomile extract and (−)-α-bisabolol demonstrated antipeptic activity in vitro (25, 26). A hydroalcoholic extract of camomile inhibited the growth of Staphylococcus aureus, Streptococcus mutans, group B Streptococcus, and Streptococcus salivarius, and it had a bactericidal effect in vitro on Bacillus megatherium and Leptospira icterohaemorrhagiae (27). In vitro, the volatile oil of camomile also inhibited Staphylococcus aureus and Bacillus subtilis (28). In vitro, camomile extracts inhibited both cyclooxygenase and lipooxygenase (29), and thus the production of prostaglandins and leukotrienes, known inducers of inflammation. Both bisabolol and bisabolol oxide have been shown to inhibit 5-lipoxygenase, but bisabolol was the more active of the two compounds (30). Numerous in vivo studies have demonstrated the anti-inflammatory effects of the drug. The anti-inflammatory effects of camomile extract, the essential oil, and the isolated constituents have been evaluated in yeast-induced fever in rats and against ultraviolet radiation-induced erythema in guinea-pig models (31). The principal antiinflammatory and antispasmodic constituents of camomile appear to be the terpene compounds matricin, chamazulene, (−)-α-bisabololoxides A and B, and (−)-α-bisabolol (32–39). While matricin and (−)-α-bisabolol have been isolated from the plant, chamazulene is actually an artefact formed during the heating of the flowers when an infusion or the essential oil is prepared (10). The antiinflammatory effects of these compounds in various animal models, such as inhibition of carrageenin-induced rat paw oedema, have been demonstrated (30), although their activity was somewhat less than that of salicylamide (39). In the mouse model for croton oil-induced dermatitis, topical application of either the total camomile extract, or the flavonoid fraction only, was very effective in reducing inflammation (34). Apigenin and luteolin were more active than indomethacin and phenylbutazone (34). Activity decreased in the following order: apigenin > luteolin > quercetin > myricetin > apigenin-7-glucoside > rutin (34). The spasmolytic activity of camomile has been attributed to apigenin, apigenin-7-O-glucoside (10, 36) and (−)-α-bisabolol, which have activity similar to papaverine (10, 35).
Intradermal application of liposomal apigenin-7-glucoside inhibited, in a dose-dependent manner, skin inflammations induced in rats by xanthine oxidase and cumene hydroperoxide (38).

Intraperitoneal administration to mice of a lyophilized infusion of camomile decreased basal motility, exploratory and motor activities, and potentiated hexobarbital-induced sleep (40). These results demonstrated that in mice camomile depresses the central nervous system (40).

**Clinical pharmacology**

A double-blind study of the therapeutic effects of a camomile extract on re-epithelialization and drying of wound weeping after dermabrasion demonstrated a statistically significant decrease in the wound size and drying tendency (41).

In clinical trials, topical application of a camomile extract in a cream base was found to be superior to hydrocortisone 0.25% for reducing skin inflammation (42). In an international multicentre trial camomile cream was compared with hydrocortisone 0.25%, fluocortin butyl ester 0.75% and bufexamac 5% in the treatment of eczema of the extremities (42). The camomile cream was shown to be as effective as hydrocortisone and superior to the other two treatments, but no statistical analysis was performed. Camomile preparations have also been found to be beneficial in the treatment of radiation mucositis owing to head and neck radiation and systemic chemotherapy (43).

**Contraindications**

Camomile is contraindicated in patients with a known sensitivity or allergy to plants of the Asteraceae (Compositae) such as ragweed, asters, and chrysanthemums (21).

**Warnings**

No information available.

**Precautions**

*Carcinogenesis, mutagenesis, impairment of fertility*

No mutagenic effects were found in *Salmonella typhimurium* strains TA97a, TA98, TA100 and TA104, with or without metabolic activation (44).

*Pregnancy: teratogenic effects*

No adverse effects reported in vivo (45).
Other precautions
No information available concerning general precautions, drug interactions, drug and laboratory test interactions, non-teratogenic effects on pregnancy, nursing mothers, or paediatric use.

Adverse reactions
The presence of lactones in Flos Chamomillae-based preparations may cause allergic reactions in sensitive individuals and there have been reports of contact dermatitis due to camomile preparations (46–48). It should be noted that very few cases of allergy were specifically attributed to German camomile (49). A few cases of anaphylactic reactions to the ingestion of Flos Chamomillae have also been reported (50–52).

Posology

Internal use
Adult dose of flower head: average daily dose 2–8 g, 3 times a day (7, 8, 11); of fluid extract 1:1 in 45% ethanol: dose 1–4 ml, 3 times a day (6, 11). Child dose of flower head: 2 g, 3 times daily; of fluid extract (ethanol 45–60%): single dose 0.6–2 ml (11). Should not be used by children under 3 years old.

External use
For compresses, rinses or gargles: 3–10% (30–100 g/l) infusion or 1% fluid extract or 5% tincture (11). For baths: 5 g/l of water or 0.8 g/l of alcoholic extract. For semisolid preparations: hydroalcoholic extracts corresponding to 3–10% (30–100 g/kg) of the drug. For vapour inhalation: 6 g of the drug or 0.8 g of alcoholic extract per litre of hot water (11).

References
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42. Aertgeerts P et al. Vergleichende Prüfung von Kamillosan® Creme gegenüber steroidalen (0.25% Hydrocortison, 0.75% Flucortinbutylester) und nicht-
steroidalen (5% Bufexamac) Externa in der Erhaltungstherapie von Ekzem-
Herba Chelidoni

Definition
Herba Chelidoni consists of the dried, whole or cut aerial parts of *Chelidonium majus* L. (Papaveraceae), gathered during the flowering period (1–5).

Synonyms
*Chelidonium vulgare* Renault, nom. illeg.: *C. haematodes* Moench, *C. ruderale* Salisb., *C. umbelliferum* Stokes (6).

Selected vernacular names
Aekitongpool, Asian celandine, bai qu cai, Blutkraut, büyük halile, celandine, celidonia, cenerognola maggiore, chelidoine, chelidonia maggiore, chelidonium, christessishla, cinerognola, common celandine, devil’s milk, eclair, erba da porri, erba nocca, felougue, garden celandine, gelbes millkraut, gemeines schöllkraut, glistnik jaskólze maistra, Goldwurz, grande chélidoine, grande-éclair, greater celandine, herbe aux hirondelles, herbe aux verrues, herbe de l’hirondelle, herbe d’éclair, iarbă de negi, jeotpool, kkachidari, kelta ruoho, kirlanĝic otu, kusanowo, mamiran, mimirân, otompui kina, paegkoolchae, pilewort, rangui-goli, rostopască, schellkraut, schillkraut, schöllkraut, schwelbenwurtz, ssiatong, stinkende gouwe, strurte, svalert, swallow-wort, ta-ukogi, tetterwort, tiges de chelidonine, true celandine, tshitotiel, urûq es sabbâghin, urûq surf, vereurmarohi, volosnik, warzenkraut, wulstkraut, ziele glistnika (7–23).

Geographical distribution
Indigenous to all of Europe and to the temperate and subarctic regions of Asia, and northern Africa. Found widely in Caucasia and the European part of the Newly Independent States, rare in Siberia and the Far East (7–9, 14, 16, 24–28).

Description
A herbaceous biennial or perennial, 30–100(120) cm high. Rhizome: vertical, thick, fleshy, branched into numerous roots, reddish-brown outside, yellow
inside. Stem: erect, irregularly bifurcated, with thickened nodes, glabrous above and hairy beneath (especially on the nodes). Leaves: alternate, compound, pinnate-pinnatifid or bipinnatifid, coarsely crenate or dentate margins, hairless to mostly hairless, upper surface dull green, lower surface pale green, with conspicuous veins, very thin in texture and drooping immediately upon gathering, up to 16 cm long and 8 cm wide. Each compound leaf typically has 5 leaflets, sometimes 3 (apical leaflet is usually larger), which are pinnatifid with secondary lobes, ovate or obovate in overall shape; secondary lobes have blunt tips. Lower leaves petiolated, upper leaves sessile. Rachis and petioles may have a few scattered hairs. Inflorescences, loose umbels of 3–8 flowers; flowering stalks 5–10 cm long; develop oppositely from the compound leaves. Flowers, actinomorphic, 4 yellow petals, 2 sepals that fall early, 1.2–1.8 cm in diameter, pistil with a stout style and elongated ovary, and numerous yellow stamens. Pedicels, 1.2–2.5 cm long. Fruits, slender siliqua-like capsules, ascending, monolocular, many seeded, linear-cylindrical, 2–5 cm long, tapering gradually towards the apex, outer surface is smooth, glaucous and hairless. As the fruit matures, it becomes constricted at intervals, dehiscing by two valves from the bottom. Seeds, ovoid, flattened glossy, black-brown with small white appendages. The whole plant abounds in bright, orange-coloured latex, which is emitted wherever the leaves or stems are broken. The juice stains hands strongly, has a persistent and nauseous taste, a strongly disagreeable smell, and burns the skin and eyes. The whole plant is poisonous (1, 7, 11, 24, 29–36).

Plant material of interest: dried aerial parts

General appearance

Whole or cut leafed stems with flowers, and unripe and/or ripe fruits, pieces of stems, leaves, flowers and fruits. Stems are rounded, ribbed, thin-walled, sometimes branched, whole at internodes, somewhat pubescent, yellowish to greenish-brown or olive green, up to 50 cm long and about 3–7 mm in diameter. Leaf fragments, mainly glabrous, bluish-green and glabrous on one side, and pale green and pubescent on the veins on the other side. Yellow flowers with 2 readily removed membranous sepals, 4 obovate petals, one pistil, and numerous stamens. Fruit, linear-cylindrical, siliqua-like capsules. Seeds, small, numerous, ovate, rough, brown-black (1, 2, 5).

Organoleptic properties

Odour: peculiar and irritating, the latex has a narcotic fragrance; taste: very bitter and somewhat pungent (5, 7, 24, 29).
**Microscopic characteristics**

The transverse section of the stem is circular, lightly ribbed, covered by a thin cuticle. The epidermal cells have very thick walls. One or two layers of thin-walled chlorenchymatous hypodermis partly transformed into collenchyma. Cortex consists of polygonal, very thick-walled cells (sclerenchyma). Very few covering trichomes of 5–10 cells, long, uniseriate, thin-walled. Stomata anomocytic, not numerous. The petiole has a stem-like structure. The chlorenchyma is almost entirely transformed in collenchyma. There are multicellular, very long covering trichomes. Leaf epidermis with sinuous anticlinal walls. Very few covering trichomes, long, uniserial of 5–10(20) thin-walled cells (striated cells, cellular nucleus visible). Area with papilla on the epidermis. Stomata anomocytic, exclusively on the lower epidermis. Hydathodes at the lobed margins. The mesophyll is differentiated into a layer of palisade and two layers of spongy parenchyma (transverse section), made up of thin-walled chlorenchyma. Cells of spongy parenchyma have aferfer stomata. Midrib with 1- or 2-layered collenchyma below the upper epidermis and thin-walled parenchymatous ground tissue. Palisade ratio 7.6:13.22. Calcium oxalate absent. Larger veins associated with dark brown articulated non-branched laticifers. Latex cells especially in vascular region. Pollen grains spherical, with a finely pitted exine and 3 furrows, about 35 µm in diameter (2, 5, 30, 37–39).

**Powdered plant material**

The powder shows the characteristic elements of stems, leaves and flowers: numerous fragments of leaves, the epidermal cells with sinuous walls; anomocytic stomata occur on the abaxial surface only; fragments of covering trichomes or entire ones. Groups of vascular tissue from the petiole and main veins with attached laticifers.

**General identity tests**

Macroscopic and microscopic examinations, thin-layer chromatography, paper chromatography and high-performance liquid chromatography for the presence of the characteristic alkaloids (1, 2, 12, 40). The addition of two or three drops of Mayer reagent to the acidic extract results in a purple precipitation of needles (14). Addition of two or three drops of Dragendorff’s reagent to the acidic extract results in a yellow precipitate (41). Under ultraviolet light at 365 nm without treatment, the thin-layer chromatogram of Herba Chelidoniium usually shows 2 or 3 blue and yellow-green fluorescent zones at Rf approximately 0.2; directly above this is the narrow yellow-green zone of chelerythrine, followed by the tailing
yellow zone of sanguinarine. The pale white fluorescent zone of proto-
pine is located in the same position as standard berberine: this is usually
overlapped by sanguinarine after treatment with Dragendorff-sodium ni-
trite; chelidonine (Rf approximately 0.6) and the other alkaloids from
rapidly fading brown zones. Papaverine can be used for the comparison
of Rf values (42). The addition of 1 ml of Dragendorff's reagent to the
dried residue of a chloroform extract results in a golden precipitate. Ad-
dition of one drop of chloroform extract to the filter paper shows an area
of fluorescence under an ultraviolet lamp (43).

Purity tests

Microbiological
Tests for specific microorganisms and microbial contamination limits are
as described in the WHO guidelines on quality control methods for me-
dicinal plants (44).

Chemical
No information available.

Foreign organic matter
Not more than 1% of organic matter. Not more than 3% of aerial parts
with non-natural colour (2).

Total ash
Not more than 13% (1). Not more than 15% (2, 5).

Acid-insoluble ash
Not more than 2% (2, 5).

Sulfated ash
No information available.

Water-soluble extractive
Not less than 20% (5).

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 10% (1). Not more than 14% (2).
**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. For other pesticides, see the *European pharmacopoeia* (1), and the WHO guidelines on quality control methods for medicinal plants (44) and the WHO guidelines on pesticide residues (45).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (44).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (44) for the analysis of radioactive isotopes.

**Other purity tests**
Not more than 10% of foreign matter (1). Not more than 0.5% of mineral matter (2). Chemical, sulfated ash, and alcohol-soluble extractive to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 0.6% of total alkaloids, expressed as chelidonine (1). Contains not less than 0.2% of total alkaloids, expressed as chelidonine, and assayed by potentiometric titration (2).

**Major chemical constituents**
The major constituents of dried aerial parts are alkaloids in an orangecoloured latex (5). They contain 0.1–1.30% total alkaloids (> 20 bases of the benzophenanthridine and related groups); quantitatively the most important are chelidonine, sanguinarine, coptisine and chelerythrine; also present are berberine, protopine (7), homochelidonine (24), allocryptopine (4), stylopine, oxysanguinarine, chelirubine (14, 15, 46), turkiyenine and canadine (47, 48). The plant also contains flavonoids, saponins, organic acids, vitamins, carotenoids, tyramine and several hydroxycinnamic acid derivatives including caffeoylmalic, chelidonie, malic and citric acids have also been reported. Proteolytic enzymes have been detected in the latex (4, 7, 14, 15, 25–27, 41, 49–52). The roots contain alpha-spinasterol, and the leaves 1-hexacosanol (41). The newly identified cysteine-proteinase, chelidocystatin has been isolated (53). The structures of the major constituents are presented below.
Medicinal uses

*Uses supported by clinical data*
Used for the symptomatic treatment of mild to moderate spasms of the upper gastrointestinal tract, minor gallbladder disorders, and dyspeptic complaints such as bloating and flatulence (54–56).

*Uses described in pharmacopoeias and well established documents*
Used externally as an anti-inflammatory agent (2).

*Uses described in traditional medicine*
Used for the treatment of vision disorders, gallstones, jaundice, irritable bowel syndrome, migraine, ringworm, whooping cough and warts (57–60). In Chinese medicine Herba Chelidonii is used as an anti-inflammatory agent in the treatment of oedemas, inflammation of the eyelids, and in ulcerative dermatitis (29).

Pharmacology

*Experimental pharmacology*

**Antihepatotoxic activity**
An aqueous-ethanolic extract of Herba Chelidonii, containing 41–45% of ethanol exerted significant hepatoprotective activity against carbon tetrachloride (CCl₄) toxicity in rats treated with varying doses of the extract.
Intragastric administration of 12.5, 62.5 and 125 mg/kg body weight (bw) of the extract twice weekly over 3 weeks resulted in a reduction in CCl₄-induced hepatotoxicity. Increased plasma activities of the enzymes alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and lactate dehydrogenase, as well as the increased bilirubin level, induced by CCl₄, were significantly decreased by the extract. The liver tissue appeared free from fibrosis, and cholesterol, which first decreased as a result of treatment with CCl₄, significantly increased during the treatment with the extract. Histopathological evaluation of the liver cells indicated a marked reduction in the number of necrotic cells (61). However, it is difficult to evaluate the clinical significance of these findings with regard to hepatotoxic adverse reactions (see Adverse reactions).

Anti-inflammatory activity
An extract made from a tincture of crude drug, as well as the individual alkaloids chelidonine, berberine, chelerythrine and sanguinarine, were tested in an anti-inflammatory enzyme assay in vitro to determine their ability to inhibit 5- and 12-lipoxygenases (5-LOX and 12-LOX), two enzymes in the inflammatory cascade. The two most active inhibitors of both enzymes were the quaternary alkaloids, sanguinarine (median inhibitory concentration (IC₅₀) = 0.4 µM for 5-LOX and 13 µM for 12-LOX) and chelerythrine (IC₅₀ = 0.8 µM for 5-LOX and 33 µM for 12-LOX). Chelidonine and berberine were inactive. An extract containing 0.68% total alkaloids, calculated as chelidonine inhibited 5-LOX activity with an IC₅₀ of 1.9 µM (based on the molecular weight of chelidonine) (62).

Antispasmodic activity
The effects of two dry ethanol extracts of the herb with a defined content of the main alkaloids (chelidonine, protopine and coptisine), and the alkaloids themselves were assessed in three different antispasmodic tests using ileum isolated from guinea-pigs. When ileal contractions were stimulated by barium chloride, both extracts reduced contractions, the more concentrated extract by 53.5% and the less concentrated by 49%, when added to the bath media at a concentration of 500 µg/ml. In addition, both chelidonine and protopine exhibited papaverine-like musculotropic action, whereas coptisine (in concentrations of up to 30 µg/ml) was ineffective in this model. Both carbachol and electrical-field-stimulated contractions were also reduced by all three alkaloids. The IC₅₀ of the crude drug extracts in carbachol- and electrical-field-induced ileal spasms were in the range of 250–500 µg/ml (63). An aqueous-ethanol extract of the herb containing 0.81% total alkaloids, calculated as coptisine, as well as the individual compounds,
caffeoylmalic acid and coptisine, were examined for their activity against acetylcholine-induced contractions in ileum isolated from rats. Acetylcholine-induced contractions were slightly reduced by the extract (12.7%; 2 mg/ml), and by coptisine (16.5%; 0.1 mg/ml) (64). In another study, acetylcholine-induced contractions in isolated guinea-pig ileum were antagonized by the addition of protopine and allocryptopine (IC$_{50}$ 2.3 µM) to the bath media, whereas berberine potentiated the contractions (65).

Choleretic activity
The choleretic activity of an ethanol extract of the herb was assessed in isolated perfused rat liver. The extract (70% ethanol v/v, 5:1, 1.6% total alkaloids and 1.9% hydroxycinnamic acid derivatives), as well as separated alkaloid and phenolic fractions of the extract, increased bile flow. A 70% ethanol extract of the herb significantly ($p < 0.05$) increased bile flow by 20% after pretreatment (40 minutes) at a concentration of 10 mg/ml (66).

Central nervous system effects
The effects of a 95% ethanol extract of the herb on the modulation of γ-aminobutyric acid- (GABA-) activated chloride current in acutely dissociated periaqueductal grey neurons were investigated using the nystatin-perforated patch-clamp technique. High concentrations of the extract (150 µg/ml) elicited an ion current that was blocked by bicuculline. Lower concentrations of the extract (90 µg/ml) reduced the GABA-activated current which operates through G-proteins in periaqueductal grey neurons (67).

The effect of a dry ethanol extract (95%) of the herb on the binding of radiolabelled muscimol to the GABA-A receptor was investigated in the brain cortex of male rats in vitro. At a concentration of 90 µg/assay, the extract enhanced [3H]-muscimol-specific binding by 115%, while 160 g/assay of the extract exerted a 50% inhibition of the specific binding of [3H]-muscimol. The allosteric modulation of the GABA-A receptor by the crude extract was due to the presence of protopine. Specific binding of [3H]-muscimol was inhibited only by sanguinarine and chelerythrine, with IC$_{50}$ values of 25 µM and 39 µM, respectively. However, the concentration of chelerythrine and sanguinarine in the extract was too low to account for the observed effect of the extract on [3H]-muscimol binding to the GABA-A receptor (68).

Antitumour activity
The effects of an extract of the herb on the development of gastric tumours in rats were assessed after the administration of N-methyl-N’nitro-N-nitrosoguanidine (MNNG). Sixty-four male 6-week-old
rats were divided into three groups: rats in group 1 were initially given MNNG (200 mg/kg bw) by gavage at days 0 and 14 as well as saturated sodium chloride solution (1 ml per rat) every three days during weeks 0–3 (six doses in total), and were then fed a regular diet containing 0.1% of the extract for 16 weeks starting at week 4. The rats in groups 2 and 3 were treated with MNNG together with saturated sodium chloride or saline solution (0.9% sodium chloride, 1 ml per rat), respectively, for the same time as those in group 1, but without further treatment. All surviving animals were killed at week 20 and assessed histopathologically. The number of preneoplastic pepsinogen 1 altered pyloric glands in the glandular stomach of the rats treated with MNNG + sodium chloride + extract (0.1%) (group 1) was significantly smaller \( (p < 0.02) \) than in the rats treated with MNNG + sodium chloride (groups 2 and 3). The incidences of neoplastic lesions of the fore stomach (papillomas and squamous cell carcinomas) also showed a tendency to decrease in the animals that received treatment with the extract. The results suggest that the extract exerts an inhibitory effect on glandular stomach carcinogenesis in the rat \( (69) \).

CM-Ala, a water-soluble, protein-bound polysaccharide from *Herba Chelidonii*, demonstrated cytotoxic activity in a diverse group of tumour cells \( (70) \).

A crude 40% ethanol extract of Herba Chelidonii possessed marked cytotoxicity, suppressing the growth of the human lymphoblastoid Raji cells at concentrations of 10 and 50 µg/ml \( (71) \).

Ethanolic and aqueous extracts of Herba Chelidonii were evaluated for their cytotoxic activity in the *Artemia salina* lethality bioassay using umbelliferone and colchicine as active substances. No cytotoxicity of the extracts was observed, and the results indicate the safety of Herba Chelidonii for its traditional uses \( (72) \).

**Immune stimulation**

The CM-Ala fraction, separated from an aqueous extract of Herba Chelidonii, was tested for immunostimulatory effects, including the generation of activated natural killer cells, proliferation of splenocytes and the activation of macrophages, as well as the assay of granulocyte macrophage colony forming cells. CM-Ala enhanced cytotoxicity against Yac-1 tumour cells from 0.88% to 34.18% after culturing with splenocytes for 5 days. CM-Ala also increased nitric oxide production twofold in peritoneal macrophages and exhibited cytotoxic activity. In addition, CM-Ala demonstrated mitogenic activity in both spleen cells and bone marrow cells, induced an 84-fold increase in the proliferation of splenocytes, and in-
creased the numbers of granulocyte macrophage-colony forming cells 1.48-fold as compared to the untreated splenocytes (70).

**Toxicology**

No harmful or toxic effects from therapeutic doses have been reported in rodent models. In mice, the median lethal dose (LD$_{50}$) of a decoction of the crude drug was 9.5 g/kg bw after intraperitoneal administration. The LD$_{50}$ of the isoquinoline alkaloids in mice was 300 mg/kg bw after subcutaneous administration. Intraperitoneal administration of 350 mg/kg bw of a methanol extract of the herb to mice for 7 days resulted in a 20% mortality rate (60). The median lethal intraperitoneal dose for chelidonine was 1300 mg/kg bw in mice and 2000 mg/kg bw in rats. Sublethal doses of chelidonine induced sedation, ptosis, tremor and decreased body temperature (73). The methanol and aqueous extracts of Herba Chelidonii were examined for acute oral toxicity in mice. The LD$_{50}$ for the methanol extract was 12.5 g/kg bw and that for the aqueous extract was 10.1 g/kg bw (74). Oral administration of 5 mg/kg bw of sanguinarine and chelerythrine (3:1) to pigs for 90 days did not result in any histological or biochemical changes (75).

The alkaloids sanguinarine and chelerythrine, present in low concentrations in the herb, are known to cause hepatotoxicity in rats. Intraperitoneal administration to rats of 10 mg/kg bw of sanguinarine or chelerythrine induced hepatic cell injury and increased alanine aminotransferase and aspartate aminotransferase activities by 50 and 100%, respectively. However, intraperitoneal administration of 0.2 mg/kg bw of sanguinarine or chelerythrine to rats for 55 days did not result in signs of hepatotoxicity (76, 77). Investigation of extracts of the herb, as well as of the individual alkaloids, coptisine, chelidonine, protopine, chelerythrine and sanguinarine, in primary rat hepatocytes indicated a direct correlation between the alkaloid content of the extract and hepatotoxicity. The mean hepatotoxic concentration for the extracts was 5 mg/ml, for sanguinarine 5 µg/ml, and chelerythrine 8 µg/ml.

**Clinical pharmacology**

A prospective observational study involving 608 patients treated orally with an aqueous-ethanol extract of the crude drug (5–7:1, mean daily dose 375–500 mg extract, corresponding to 9–12 mg of total alkaloids) has been reported. The outcomes were measured using the Physicians’ Global Assessment of Efficacy (4-point scale). After an average of 22 days of treatment, symptoms (dyspepsia or cramps in the upper gastrointestinal tract) were reduced in most patients and the outcome was assessed as good or very good in 87.4% of the patients (55).
A placebo-controlled, double-blind clinical trial assessed the efficacy of tablets prepared from an aqueous-ethanol extract of the crude drug corresponding to a daily dose of 24 mg of total alkaloids (calculated as chelidonine) in patients suffering from epigastric complaints or cramps in the biliary system and/or the upper gastrointestinal tract. Sixty patients were treated for 14 days with the extract or a placebo. Outcomes measured after 4 and 6 weeks included the global assessment of a clinician and the patient’s self-rating according to the von Zerssen Complaint Scale. After 6 weeks of treatment, 60% of the treated patients and 27% of the placebo group were considered to be responders ($p = 0.038$), according to the global assessment of a clinician. The von Zerssen Complaint Scale score was also 15% lower ($p = 0.003$) in patients after treatment with the extract than for those in the group treated with the placebo. The treatment reduced symptoms, such as stomach ache, bile-related complaints, flatulence, nausea and bloating (56).

**Adverse reactions**

Excessive ingestion of the decoction of the crude drug may cause nausea and other gastrointestinal symptoms (60). In rare cases, hepatic inflammation and an increase in liver enzyme activity and serum bilirubin have been reported, all of which are reversible following discontinuation of therapy (78). A case of contact dermatitis was described after external use of the aerial parts of the plant (79). Ten cases of acute hepatitis induced by preparations of the crude drug have been noted. The course of hepatitis was mild to severe. Marked cholestasis was observed in five patients, but liver failure did not occur. Other possible causes of liver disease were excluded by laboratory tests and imaging procedures, and liver biopsy specimens were consistent with drug-induced damage. After discontinuation of therapy, rapid recovery was observed in all patients and liver enzyme levels returned to normal in 2–5 months (80). One case of haemolytic anaemia after oral ingestion of an extract of crude drug was reported. Presentation included liver cytolysis, thrombocytopenia, renal failure and intravascular haemolysis. The direct antiglobulin test was positive. The patient was treated with steroids, red cell and platelet transfusion and subjected twice to haemodialysis, with complete resolution of the clinical features by about the twelfth day (81).

Cases of acute hepatitis after use of Herba Chelidonii preparations have been observed (82, 83).

A case of contact-derived allergic balanoposthitis and paraphimosis (lesions of the penis) was observed after topical application of Herba Chelidonii juice (84).
Contraindications
In patients with biliary obstructions, existing or previous liver disease or hepatitis, concomitant use of hepatotoxic substances is contraindicated (80, 85).

Warnings
Use of the crude drug and preparations of Herba Chelidonii should be restricted to short-term use (1–4 weeks) and long-term use (for more than 4 weeks) is not recommended. Due to the potential for liver toxicity, liver enzymes should be evaluated prior to and during use (81, 86, 87). Health professionals should be encouraged to report any suspected adverse reactions thought to be associated with Herba Chelidonii.

Precautions
General
Use only under professional supervision. In patients with gallstones, the product should not be used without medical advice (4). The plant is subject to legal restrictions in some countries (88, 89). The Drug and Medicinal Product Institute of Germany recommends a maximum daily dose of 2.5 mg total alkaloids, which is lower than the recommended doses prescribed by other authorities (3, 5, 89).

Drug interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
The use of Herba Chelidonii during pregnancy is not recommended (90).

Nursing mothers
The use of Herba Chelidonii while breastfeeding is not recommended (90).

Other precautions
No information was found.

Dosage forms
Crude drug, powdered drug for infusions, tablets containing 4 mg total alkaloids (56).
**Posology**
(Unless otherwise prescribed)

*Internal use.* One to two tablets each containing 4 mg total alkaloids three times a day (55, 89); 2–5 g herb, equivalent to 12–30 mg of total alkaloids calculated as chelidonine (3).

*External use as a bath.* An infusion from two tablespoonfuls of the cut herb added to 500 ml of water per bath (88).

**References**


WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)


79. Etxenagusia MA et al. Contact dermatitis from *Chelidonium majus* (Greater celandine). *Contact Dermatitis*, 2000, 43:47.
Folium cum Flore Crataegi*

Definition
Folium cum Flore Crataegi consists of the dried flower-bearing branches of Crataegus monogyna Jacq. (Lindm), C. laevigata (Poir.) DC, their hybrids or, more rarely, other Crataegus species (Rosaceae).1

Synonyms

Crataegus laevigata (Poir.) DC: C. oxyacantha L., C. oxyacantha L. ssp. Polygala Lev., C. oxyacanthoides Thuill, Mespilus oxyacantha (Gartn.) Crantz. (1, 3, 4).

Selected vernacular names
Aubeline, aubepine, biancospino, calabrice, calavrice, eenarijlige meidorn, eenstijlige meidorn, eingriffeliger Weissdorn, Einkern-Weissdorn, épine blanche, espinero, espino blanco, espino majuelo, galagonya virágzó ágvég, hagdorn, hagedorn, harthorne, haw, hawthorn, hedge thorn, majuelo, may, May thorn, Mehlebeerbaum, Mehldorn, seiyosanzashi, shanzha, sorkh valik, spina, Stumpf gelappter Weissdorn, Weissdorn, whitethorn, za bur, zu’urr el awdiyah, zweigriffeliger Weissdorn, Zweikern-Weissdorn (1, 3, 5–8).

Geographical distribution
Common to the temperate areas of the northern hemisphere, including eastern areas of North America, parts of South America, east Asia and Europe (9, 10).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
1 Fructus Crataei is included in the European pharmacopoeia (1) and in the pharmacopoeia of the People’s Republic of China (2). However, clinical and pharmacological data for this plant part are insufficient to justify monographing at this time.
Description

Crataegus monogyna: a thorny shrub; leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of C. laevigata. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, stamen with black anthers and 1 style (1, 9).

Crataegus laevigata: a thorny shrub; twigs glabrescent, brown; leaves bright green, obovate, with 3, 5 or 7 shallow, obtuse lobes. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles; fruits deep red, globose or ellipsoid (9, 11).

Plant material of interest: dried leaf with flower

General appearance

Crataegus monogyna: leaves bright green with 3 or 5 acute lobes, deeper and further apart than those of C. laevigata, with secondary venation curved outwards. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a monocarpellate, brownish-green receptacle; floral peduncles and sepals pubescent, anthers black with 1 style; sepals lanceolate, acuminate, falling over the ovary after flowering (1, 9).

Crataegus laevigata: leaves bright green with 3, 5 or 7 shallow, obtuse, converging lobes, with secondary venation curved inward. Flowers, grouped into branchy corymbs, have 5 triangular sepals, 5 white petals, and an androecium of 15–20 stamens inserted on the edge of a bi- or tricarpellate receptacle; floral peduncles and sepals glabrous, stamens with red anthers and 2–3 styles.

Organoleptic properties

Odour: characteristic, faint; taste: slightly bitter-sweet, astringent (12–15).

Microscopic characteristics

Leaf dorsoventral; cells of upper epidermis polygonal, straight-walled with striated cuticle, those of lower epidermis more sinuous; anomocytic stomata on lower epidermis only; covering trichomes on both epidermises but more numerous on the lower, which are long, tapering, unicellular or very occasionally uniseriate with 2 cells, walls moderately thickened; cluster crystals or groups of small prismatic crystals of calcium oxalate in
the cells along the veins. Epidermis of floral pedicel and receptacle contain abundant covering trichomes similar to those on the leaf, but longer and more undulating; calyx with numerous anomocytic stomata on the outer epidermis, inner epidermis with a striated cuticle; epidermal cells of corolla distinctly papillose; fibrous layer of anther with characteristic thickenings; pollen grains spherical to elliptical, up to 45 µm in diameter, with 3 germinial pores and faintly granular exine. Epidermal cells of stem have thickened anticlinal outer walls; cortex parenchymatous with prismatic and cluster crystals of calcium oxalate; dense groups of small, tightly packed pericyclic fibres with much thickened and lignified walls; xylem completely lignified, composed of scattered vessels, thick-walled fibres and parenchyma separated by distinct medullary rays containing brown-coloured matter; larger vessels with bordered pits, smaller elements with annular or spiral thickening; central pith parenchymatous and lignified, cells with moderately thickened walls and numerous pits (12, 15).

**Powdered plant material**
Yellowish-green. Unicellular covering trichomes, usually with a thick wall and wide lumen, almost straight or slightly curved, pitted at the base; fragments of leaf epidermis with cells which have sinuous to polygonal anticlinal walls and large anomocytic stomata surrounded by 4–7 subsidiary cells; parenchymatous cells of mesophyll containing cluster crystals of calcium oxalate, usually 10–20 µm in diameter; cells associated with veins contain groups of small prismatic crystals. Petal fragments showing rounded polygonal epidermal cells, strongly papillose, thick walls with clearly visible wavy striations in the cuticle; anther fragments showing endothecium with an arched and regularly thickened margin. Stem fragments containing collenchymatous cells, bordered, pitted vessels and groups of lignified sclerenchymatous fibres with narrow lumina. Numerous spherical to elliptical or triangular pollen grains up to 45 µm in diameter, with 3 germinial pores and a faintly granular exine (1).

**General identity tests**
Macroscopic and microscopic examinations, thin-layer chromatography (1, 7), and microchemical test for the presence of procyanidins (7).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (16).
Foreign organic matter
Not more than 8% lignified branches with a diameter greater than 2.5 mm (1) and not more than 2% other foreign matter (1, 15).

Total ash
Not more than 10% (1).

Loss on drying
Not more than 10% (1).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (17). For other pesticides, see the European pharmacopoeia (17), and the WHO guidelines on quality control methods for medicinal plants (16) and pesticide residues (18).

Other purity tests
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (16).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (16) for the analysis of radioactive isotopes.

Chemical assays
Contains not less than 1.5% of flavonoids, calculated as hyperoside (1), and not less than 0.6% of flavone C-glycosides, calculated as vitexin (14), determined by spectrophotometry at 410 and 336 nm, respectively (1). A high-performance liquid chromatography method is also available (19).

Major chemical constituents
The major constituents are flavonoids (rutin, hyperoside, vitexin, vitexin-2″ rhamnoside, acetylvitexin-2″ rhamnoside) and related proanthocyanidins (19, 20). In the inflorescence, flavonol glycosides, mainly in the form of hyperoside, spiraeoside and rutin, are present. The primary flavo-
noid derivatives in the leaves are *epi*-catechin (*epi*-catechol) and/or catechin (catechol), and the related procyanidins formed during condensation of 2–8 monomeric units of the above catechins (19–22), together with oligomeric procyanidins (23). The presence of simple phenolic acids (e.g. chlorogenic and caffeic acids) has also been reported. Of the non-phenolic constituents, pentacyclic triterpenes (e.g. ursolic and oleanolic acids) and the 2-α-hydroxy derivative of oleanolic acid, known as crataegolic acid, are among the characteristic components (4). The structures of the characteristic constituents are presented below.
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\[
\begin{align*}
\text{Gal} &= \ \beta-\text{o-galactopyranosyl} \\
\text{Rha} &= \ \alpha-\text{rhamnopyranosyl} = 6\text{-deoxy-}\alpha-\text{r-mannopyranosyl} \\
\text{Glc} &= \ \beta-\text{o-glucopyranosyl} \\
\text{Rha}\text{-Glc} &= \ 6\text{-deoxy-}\alpha-\text{r-mannopyranosyl}(1\rightarrow6)\beta-\text{o-glucopyranosyl}
\end{align*}
\]

\[
\begin{align*}
\text{R} &\quad \text{R}' \\
\text{catechin (catechol)} &\quad \text{OH} \quad \text{H} \\
\text{epi-catechin (epi-catechol)} &\quad \text{H} \quad \text{OH}
\end{align*}
\]
Medicinal uses

**Uses supported by clinical data**
Treatment of chronic congestive heart failure stage II, as defined by the New York Heart Association (24–34).

**Uses described in pharmacopoeias and in traditional systems of medicine**
Support of cardiac and circulatory functions (35).

**Uses described in folk medicine, not supported by experimental or clinical data**
As an antispasmodic agent in the treatment of asthma, diarrhoea, gall bladder disease and uterine contractions, and as a sedative for the treatment of insomnia (5).

**Pharmacology**

**Experimental pharmacology**

**Inotropic effects**
Positive inotropic effects of Folium cum Flore Crataegi and its constituents have been demonstrated both in vitro and in vivo. These effects are
generally attributed to the flavonoid and procyanidin constituents of the leaves with flowers (3, 36–38). A hydroalcoholic extract of the flowers with leaves, flavonoid and procyanidin fractions of the extract, and isolated constituents (e.g. biogenic amines, crataegolic acid, epi-catechin, hyperoside, luteolin 7-glucoside, rutin and vitexin) all have positive inotropic effects, and prolong the refractory period in cardiac myocytes, isolated papillary muscles and isolated guinea-pig hearts (36–48). In isolated guinea-pig hearts perfused at constant pressure, 3 µg/ml of a standardized extract increased the contractility of the heart by 9.5% (40). In isolated, electrically stimulated strips of failing human left ventricular myocardium, a standardized extract (18.75% oligomeric procyanidins) increased the force of contraction at concentrations higher than 10 µg/ml; a 100 µg/ml extract improved the force–frequency relationship (39). A standardized extract of the leaves and flowers increased the contractility of myocardial cells by 153%, at a concentration of 120 µg/ml (44). An aqueous extract of the leaves with flowers, two proanthocyanidin fractions and two flavonoid fractions of the extract dilated coronary blood vessels, and had positive inotropic effects on isolated guinea-pig hearts (extract or fraction: 0.05 mg/ml) (41).

**Chronotropic effects**

Intragastric administration of a macerate or fluid extract of the shoots, flowers or leaves to rats (12.5–25.0 mg/kg body weight) significantly inhibited arrhythmias induced by aconitine, calcium chloride or chloroform/epinephrine ($P < 0.05$) (49, 50). The extracts also reduced blood pressure in rats at the same dosage (49, 50). Aconitine-induced arrhythmias were also inhibited after intravenous administration of a 95% ethanol extract of the bark and leaves (50 mg/kg body weight) to rabbits (51). Intravenous administration of a flavonoid-enriched extract of the leaves and flowers to rabbits (20 mg/kg body weight) or rats (2 mg/kg body weight) inhibited barium chloride-induced arrhythmias (52, 53). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized dogs (7.5–30.0 mg/kg body weight) increased maximum left ventricular contraction velocity by 16.8–31.1% (54).

An aqueous extract improved cardiac performance during reperfusion, reduced lactate levels and accelerated energy metabolism in reperfused ischaemic rat heart. No increase in coronary blood flow was observed (55). Intragastric administration of single doses of a standardized extract (containing 18.75% oligomeric procyanidins) of the leaves with flowers (100 mg/kg body weight) or an oligomeric procyanidin-enriched fraction (20 mg/kg body weight) daily to rats protected against perfusion-induced
arrhythmias, hypotensive crisis and mortality (56, 57). The oligomeric procyanidin-enriched fraction did not decrease the reperfusion-induced elevation of creatine kinase plasma levels (57). Administration of powdered leaves and flowers to rats (2% of diet) reduced the release of lactate dehydrogenase after perfusion-induced heart ischaemia (58).

**Effect on coronary blood flow**
Intragastric administration of an oligomeric procyanidin fraction of a standardized leaf and flower extract to dogs at a dose of 12–70 mg/kg body weight, three times daily for 60 days, increased myocardial blood flow (59, 60). Intravenous injection of an aqueous or 95% ethanol extract of the flowers increased coronary blood flow and cardiac output, and decreased peripheral resistance in both dogs and guinea-pigs (61–63). Administration of a flavonoid-enriched extract to cats and rabbits increased coronary blood flow by 48% and 163%, respectively, and reduced pituitrin-induced coronary insufficiency in rabbits (52). Intravenous administration of a leaf with flower extract to cats (10 mg/kg body weight) or rabbits (20 mg/kg body weight) dilated coronary blood vessels, and improved coronary blood flow (53).

**Effect on action potential**
A leaf preparation (10 mg/l) prolonged the duration of the action potential and delayed the recovery of V_max in isolated guinea-pig papillary muscle (42). The electrophysiological correlation between the increase in the contraction amplitude of isolated canine papillary muscles, and vasodilatation in isolated human coronary arteries, was measured after application of an extract of the leaves with flowers. The cardiac action potential significantly increased in duration and overshoot, and maximal depolarization (P < 0.001). Hyperpolarization of the resting membrane of normal and arteriosclerotic vascular smooth muscle cells of the human coronary artery was observed after treatment with flavonoids isolated from the extract (0.1 and 100 µmol/l). The isometric wall tension decreased in both normal and arteriosclerotic vessels. The increase of peak-to-plateau repolarization in cardiac action potential and hyperpolarization of vascular smooth muscle suggest that the extract acts as a potassium channel agonist (64, 65).

**Antihypertensive effects**
In various animal models, a decrease in peripheral vascular resistance and hypertension occurred after treatment with leaf and/or flower extracts (50, 54, 66–69). Intravenous administration of a standardized fluidextract of the
leaves with flowers (equivalent to 6 mg of procyanidins/kg body weight) to anaesthetized normotensive dogs decreased norepinephrine-induced elevation of blood pressure. The extract (equivalent to 0.03 mg procyanidins/ml) also had β-blocking activity and inhibited epinephrine-induced tachycardia in isolated frog hearts (69). Hyperoside, isolated from an extract of the leaves and flowers, administered either intravenously at a dose of 1 mg/kg body weight or by infusion at 0.1 mg/kg body weight/min for 30 min, decreased blood pressure in anaesthetized dogs (68). Intravenous administration of an aqueous extract of the leaves (average dose 31 mg/kg body weight) decreased the systolic, diastolic and mean blood pressure in normotensive anaesthetized rats (66). Acute or chronic intragastric administration of a fluidextract or a glycerol/ethanol extract reduced arterial blood pressure in normotensive rats and in rats with desoxycorticosterone acetate-induced hypertension (50). Intragastric administration of a standardized extract (300 mg/kg body weight daily) decreased blood pressure by 9 mm Hg (1.20 kPa) (67). Intravenous administration of a standardized extract (containing 18.75% oligomeric procyanidins) to anaesthetized rats (30 mg/kg body weight) or dogs (15 mg/kg body weight) decreased total peripheral resistance and arterial blood pressure (54).

**Anti-inflammatory effects**

Both free radical production and lipid peroxidation are involved in various pathological processes, including cardiac ischaemia. As determined by in vitro studies, Folium cum Flore Crataegi has free radical scavenging and antioxidant activities. A standardized extract (containing 18.75% oligomeric procyanidins) and an oligomeric procyanidin-fraction of the extract inhibited lipid peroxidation (IC$_{50}$ 0.48 µg/ml (extract), 0.3 µg/ml (fraction)), and the activity of human neutrophil elastase (IC$_{50}$ 4.75 µg/ml (extract), 0.84 µg/ml (fraction)) (56). A 70% methanol extract of the flower buds inhibited lipid peroxidation in rat liver microsomes (IC$_{50}$ 23 µg/l) (70, 71). Both phenolic and flavonoid-enriched fractions of extracts of the leaves and flowers had antioxidant activity in vitro (70–72).

**Effect on signal transduction**

An aqueous or methanol extract of the leaves with flowers, as well as hyperoside, vitexin and vitexin rhamnoside, inhibited the activity of cyclic AMP-dependent phosphodiesterase isolated from guinea-pig or rat heart (73, 74). Both luteolin 7-glucoside and rutin were also active (75). Hydroalcoholic extracts of the flowers and flower heads inhibited the formation of thromboxane A$_2$ and prostaglandin I$_2$ in rabbit cardiac tissues in vitro, thus indicating an anti-inflammatory effect of the extracts (76, 77). A standardized ex-
Folium cum Flore Crataegi

tract (containing 18.75% oligomeric procyanidins) displaced $^3$H-ouabain bound to sodium- and potassium-activated adenosine triphosphatase (39).

**Anticontractile effects**
An aqueous extract of the flowers inhibited barium chloride-induced contractions in rabbit intestine in vitro (78). A flavonoid-enriched extract of the leaves with flowers inhibited both histamine- and nicotine-induced contractions in rabbit intestine in vitro and partially inhibited contractions induced by barium chloride, acetylcholine or serotonin ($\text{ED}_{50} 0.02 \text{ mg/ml}$) (52). Intravenous administration of a flavonoid-enriched extract of the leaves with flowers to cats (20 mg/kg body weight) inhibited contractions in intestinal smooth muscle, and intraperitoneal injection (400 mg/kg body weight) inhibited acetic acid-induced writhing in mice (52).

**Sedative effects**
Sedative effects have been observed in various animal models after intragastric administration of leaf with flower extracts (79, 80). A 60% ethanol extract of the flowers increased hexobarbital-induced sleeping times, and decreased spontaneous motility and exploratory behaviour in female mice (800 mg/kg body weight) (80).

**Diuretic effects**
A flavonoid-enriched fraction of a flower extract had diuretic activity in dogs (50 mg/kg body weight) (81).

**Toxicology**
Single-dose toxicity studies have demonstrated that rats and mice tolerate 3 g/kg body weight, by gastric lavage, of a standardized hydroalcoholic extract of the leaves with flowers (containing 18.75% oligomeric procyanidins) without any clinical symptoms of toxicity. The intraperitoneal median lethal dose ($\text{LD}_{50}$) was 1.17 g/kg body weight in rats and 750 mg/kg body weight in mice. No toxic effects were observed in a repeat-dose toxicity study in which rats and dogs were given a standardized extract (containing 18.75% oligomeric procyanidins) at doses of 30, 90 and 300 mg/kg body weight daily by the intragastric route for 26 weeks (82).

**Clinical pharmacology**
**Cardiac insufficiency**
Review of the pharmacological and clinical data indicates that standardized extracts of Folium cum Flore Crataegi increase myocardial performance, improve myocardial circulatory perfusion and tolerance in cases of
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oxygen deficiency, have antiarrhythmic effects and reduce afterload (29). Positive therapeutic effects of Folium cum Flore Crataegi in patients with characteristic symptoms of an activated sympathoadrenergic system, such as hypertension, tachycardia and arrhythmia (also characteristic of cardiac insufficiency stage II, as defined by the New York Heart Association (25–34)), have also been demonstrated (30). Furthermore, numerous clinical trials with and without controls have assessed the therapeutic efficacy of Folium cum Flore Crataegi extracts for the treatment of cardiac insufficiency stage II (25–34). The investigations were performed with a dried 70% methanol or 45% ethanol standardized extract (containing 2.2% flavonoids or 18.75% oligomeric procyanidins, respectively) of the leaves with flowers (30). The dosage ranged from 160 to 900 mg extract daily for 4–8 weeks. Evaluation of efficacy of the extracts was based on the following criteria: anaerobic threshold (27); Clinical Global Impression Scale (31, 32); exercise tolerance (25, 26, 28, 31, 32, 34); ventricular ejection fraction (26, 33); quality of life and improvement of subjective symptoms (defined by the New York Heart Association) (26–28, 31–34) and pressure/rate product (26, 28, 31, 32, 34). Although improvements were seen, no long-term trials have assessed the effects of Folium Cum Flore Crataegi on mortality rates in patients with chronic congestive heart failure.

Exercise tolerance
A randomized, double-blind, placebo-controlled trial assessed the efficacy of the extract containing 2.2% flavonoids on exercise-induced anaerobic threshold, as measured by spiroergometry, in 72 patients. Patients were administered an oral dose of 900 mg extract or placebo daily for 8 weeks. After treatment, oxygen uptake increased significantly in the treated group (P < 0.05), and exercise time to anaerobic threshold increased by 30 seconds in the treated group, but by only 2 seconds in the placebo group. Significant improvements in subjective symptoms were also noted in the treated group, as compared with the placebo group (P < 0.01) (27).

The efficacy of the extract containing 2.2% flavonoids on the improvement of exercise tolerance was assessed by bicycle ergometry in patients with cardiac insufficiency stage II, in three clinical trials. In a double-blind, placebo-controlled trial of 85 patients, oral administration of 300 mg extract daily for 4–8 weeks improved working capacity; however, the difference was not significant when compared with the placebo (25). A double-blind, placebo-controlled trial assessed the efficacy of oral administration of 600 mg extract daily for 8 weeks in 78 patients. Patients in the treatment group had a significant improvement in exercise tolerance as compared with the placebo group (P < 0.001). Patients who received the
extract also had lower blood pressure and heart rate during exercise, and had fewer overall symptoms, such as dyspnoea and fatigue (31). In the third trial, 132 patients were treated orally with 900 mg extract or 37.5 mg captopril daily for 8 weeks in a double-blind comparative study. Exercise tolerance, measured after 56 days of treatment, improved significantly in both groups ($P < 0.001$). In addition, the pressure/rate product was reduced, and the incidence and severity of symptoms such as dyspnoea and fatigue decreased by approximately 50% (32).

**Pressure/rate product**

Two double-blind, placebo-controlled trials assessed the efficacy of the extract containing 18.75% oligomeric procyanidins in a total of 156 patients with stage II cardiac insufficiency. Patients were treated orally with 160 mg extract or placebo daily for 8 weeks. The main parameters measured were the pressure/rate product using a bicycle ergometer, and the score of subjective symptom status. Patients treated with the extract exhibited a significant improvement in exercise tolerance, as compared with the placebo group ($P < 0.05$), and also a decrease in subjective complaints (28, 34). In addition, a slight reduction in the systolic and diastolic blood pressure was noted in both groups (28).

**Ventricular ejection fraction**

In a trial without controls involving seven patients with stages II and III cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, oral administration of 240 mg extract containing 18.75% oligomeric procyanidins daily for 4 weeks increased the ventricular ejection fraction from 29.80 to 40.45%, as measured by angiography. Symptomatic complaints (Complaint List as defined by von Zerssen) also showed improvements (33). The effects of the extract containing 18.75% oligomeric procyanidins on haemodynamics were also investigated by radionuclide angiocardiography in a study without controls. Twenty patients with stage II cardiac insufficiency, with an angiographically determined left ventricular ejection fraction of less than 55% over a period of 4 weeks, were treated with 480 mg extract. After treatment, the ejection fraction increased from 40.18 to 43.50% at rest, and from 41.51 to 46.56% under exercise conditions. Ergometric tolerance to exercise improved, blood pressure decreased and subjective complaints were reduced (26).

**Pharmacokinetics**

Absorption of a $^{14}$C-labelled oligomeric procyanidin fraction of standardized extracts of leaves with flowers was measured in mice after intragas-

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tric administration (0.6 mg). The results demonstrated that 20–30% of the total fraction, 40–81% of the trimeric procyanidins and 16–42% of the oligomeric procyanidins were absorbed within 1–7 hours after administration. After 7 hours, 0.6% of the radioactivity of the total fraction was eliminated by expiration and 6.4% was eliminated in the urine. Daily intragastric administration of 0.6 mg of a radiolabelled oligomeric procyanidin fraction to mice for 7 days led to an accumulation of radioactivity that was 2–3 times that in mice given a single dose (83).

Contraindications
None (84).

Warnings
Accurate diagnosis of stage II congestive heart failure should be obtained prior to use of Folium cum Flore Crataegi. Consult a physician if symptoms worsen, remain unchanged for longer than 6 weeks, or if water accumulates in the legs. Medical attention is absolutely necessary if pain occurs in the region of the heart, spreading out to the arms, upper abdomen or neck area, or in cases of respiratory distress (e.g. dyspnoea) (84).

Precautions

Drug interactions
None (84).

Drug and laboratory test interactions
No effects in laboratory tests (i.e. serum levels of sodium chloride, potassium chloride, calcium chloride, serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, γ-glutamyl transpeptidase, total bilirubin, cholesterol and creatinin, and blood glucose levels) were observed (34).

Carcinogenesis, mutagenesis, impairment of fertility
A standardized extract of Folium cum Flore Crataegi (containing 18.75% oligomeric procyanidins) was not mutagenic or clastogenic in the Salmonella/microsome assay, mouse lymphoma test, cytogenetic analysis in cultured human lymphocytes or in the mouse bone marrow micronucleus test (82). A fluidextract was moderately active in the Salmonella/microsome assay in S. typhimurium strain TA98 only after
metabolic activation. The mutagenic activity appeared to be due to the quercetin content of the extract; however, the amount of quercetin ingested in a normal daily diet is higher than would be obtained from the extract (85). Intragastric administration of up to 1.6 g/kg body weight had no effect on the fertility of female and male rats or the F1 generation (86).

**Pregnancy: teratogenic effects**
Intragastric administration of up to 1.6 g/kg body weight of a standardized extract of Folium cum Flore Crataegi to rats and rabbits was not teratogenic (86).

**Pregnancy: non-teratogenic effects**
No peri- or postnatal toxicity was observed in rats treated intragastrically with a standardized extract of Folium cum Flore Crataegi (1.6 g/kg body weight) (86).

**Other precautions**
No information available on general precautions or precautions concerning nursing mothers or paediatric use. Therefore, Folium cum Flore Crataegi should not be administered during lactation or to children without medical supervision.

**Adverse reactions**
None (84).

**Dosage forms**
Crude drug for infusion and hydroalcoholic extracts (35). Store in a well-closed container, protected from light and moisture (1).

**Posology**
(Unless otherwise indicated)
Daily dosage: 160–900 mg dried 45% ethanol or 70% methanol extract (drug:extract ratio 4–7:1) standardized to contain 18.75% oligomeric pro-cyanidins (calculated as epi-catechin) or 2.2% flavonoids (calculated as hyperoside), respectively (26–29, 31–34, 84); 1.0–1.5 g comminuted crude drug as an infusion 3–4 times daily (35). Therapeutic effects may require 4–6 weeks of continuous therapy (84).
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Herba Equiseti

Definition
Herba Equiseti consists of the whole or cut, dried sterile aerial parts of *Equisetum arvense* L. (Equisetaceae) (*1, 2*). The same parts collected during the summer are described in the *USSR pharmacopoeia* as Herba Equiseti arvensis (*2*).

Synonyms
*E. calderi* Boivin (*3*).

Selected vernacular names
Acker-schachtelhalm, acherschachtelhalm, ager-padderokke, åkersnelle, åkerfräken, akkerpaardestaart, at kuyrug, baimbap, at quyroughi, bottlebrush, brusca, cauda de caval, chieh hsu ts’ao, coada calului, coda caval-lina, coda equine, cola de caballo, common horsetail, corn horsetail, dhanab al khail, dhanab el khayl, dhanab et faras, dutch rushes, equiseto menor, equiseto dei boschi, equiseto dei campi, equisette, equisetto, erva carnuda, false horse-tail, field horsetail, foxtail, gongbangcho, heermoes, horse-pipe, horse pipes, horsetail, horsetail grass, horsetail rush, horse willow, hvoshtsh, jeinsol, jointed rush, kannenkraut, kattestaart, kilkah asb, klöefting, koniogon, kosa tiruma, krypfräken, librus, macho, mare’s tail, meadow pine, moeraspaardestaart, mokjeok, moonhyung, paddock-pipes, peltokorte, pest’shi, petite prèle, pewterwort, pildoochae, pildooy-eup, pine grass, pinetop, polevaja sosenka, prele, prèle des champs, poldtosi, queue de cheval, queue de rat, queue de renard, rabo de caval, rasperella, rävrumpa, scouring rush, shvita, snake grass, soettgi, soksaë, sugina, toadpipe, tolkatshnik, tomahwang, tsukushi, vara de oro, wen ch-ing, western horsetail, zinngras, zinnkraut (*3–16*).

Geographical distribution
Distributed throughout the temperate zone of the northern hemisphere. Indigenous to all of America, Europe and North Africa, as well as parts of Asia. Found widely throughout the Newly Independent States region,
with the exception of deserts, *paramos* and the northern regions (4, 5, 7, 8, 17–21).

**Description**

A perennial plant with sterile and fertile stems. Rhizomes: horizontal, up to 3 mm in diameter, layered, extending to a depth of about 1 m, brownish-black, branched, creeping, with blackish tubers up to 7 mm in diameter. Roots: at the bases of lateral branch buds, on both rhizomes and erect shoots. Fertile stems: ephemeral, appear early in the spring, 15–20 cm high, up to 5 mm in diameter, unbranched, succulent, reddish or yellowish, jointed, with 6–12 blackish-brown lanceolate teeth at the joints. Cones: apical, ovate-cylindrical, blunt-tipped, 1–3.5 cm long. The strobile is situated under peltate polygons, which are pileus-like bodies, arranged in whorls; 4–7 spiral filaments surround the green globular spores, which roll up closely around them when moist, and uncoil when dry. The fertile stem never turns green. The green, sterile shoots develop later from the rhizome, by which time the fertile shoots have usually wilted. Sterile stems: 5–15(80) cm high, erect, 6–18(20) grooved, hollow, jointed, up to 20 whorls of slender branches. Leaves scale-like, deciduous, inconspicuous, in whorls at the nodes, are connected at their bases (4, 5, 18, 19, 22–27).

**Plant material of interest: dried sterile aerial parts**

**General appearance**

Whole sterile stems, 20–80 cm long (up to 30 cm long according to the *USSR pharmacopoeia* 1990 (2)), or fragments of 0.5–2 cm in length, and 3–5 mm in diameter, with 6–18(20) deep longitudinal grooves, light green to greenish-grey, rough to the touch, brittle and crunchy when crushed, hollow and jointed at the nodes, which occur at intervals of about 1.5–4.5 cm. Vaginas covering the stem nodes are cylindrical, 4–8 mm long, with teeth; the teeth are triangular-lanceolate, dark brown, with white-scaled margins, half as long as vagina, concrescent in groups of 2 or 3. Fracture short, exposing a large central cavity and the vascular canals of the cortex in the stems. Numerous solid branches arranged in whorls, pointing upwards, unbranched, 5–20 cm long, 1–2 mm in diameter, with 4–5 deep grooves. Leaf vaginas on the branches are cylindrical, green and have 4–5 teeth, which represent the extremely reduced leaves; the number of teeth corresponds to the number of grooves on the branches; the teeth are pale green or brownish, oblong-lanceolate, with acuminate apices; half or one third as long as vagina; connected between each other (alter-
Herba Equiseti

nate) scales, forming a specific vaginate structure in the nodes of the branches, which is usually called a “sheath” (1, 2, 28, 29).

**Organoleptic properties**
Odour: slight or no odour; taste: slightly acidic or no taste (2, 28, 29).

**Microscopic characteristics**
Epidermis with elongated, wavy-walled cells, silicified, often thickened and beaded. The paracytic stomata with the 2 subsidiary cells cover the guard cells and have conspicuous radial ridges. In transverse sectional view the epidermis is crenate, with the protuberances formed from the contiguous mass of 2 U-shaped cells. (No single-celled protuberances should be present – absence of E. palustre L.) The cortex of stems of thin-walled cells with many large lacunae; non-lignified, collenchymatous fibrous cells up to 1 mm long with oblique or bifurcate apices in the ridges; xylem of lignified, annularly or spirally thickened vessels occurring singly or in small groups; slightly lignified annularly thickened tracheids and bundles of long non-lignified fibres with narrow lumens. Large parenchymatous cells packed with minute starch grains; large central cavity. Branches have four vascular bundles and lack a central cavity; the silicified collenchyma is reduced, cortex lacunae are absent (1, 28–31).

**Powdered plant material**
Greenish-grey or dull green. The powder shows characteristic elements of stems (see Microscopic characteristics) (1, 28, 29).

**General identity tests**
Macroscopic and microscopic examinations, and thin-layer chromatography for the characteristic constituents: caffeic acid, hyperoside and rutin (1, 28), quercetin 3-glucoside (5) and flavone-5-glucosides (2).

**Purity tests**
**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (32).

**Chemical**
No information available.
Foreign organic matter
Maximum of 5% of stems from other *Equisetum* species and hybrids, and not more than 2% (1) or 1% of other foreign matter. For other parts of *Equisetum arvense* L., not more than 1% of other foreign matter and 4% of other *Equisetum* species (2). Blackish rhizome fragments and other foreign matter, not more than 5% (33).

Total ash
Minimum 12% and maximum 27% (1). Not more than 20% (28, 29).

Acid-insoluble ash
Minimum 3%, maximum 15% (1). Not more than 10% (28, 29).

Sulfated ash
No information available.

Water-soluble extractive
Not less than 15% (28, 29).

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 10% (1).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg. For other pesticides, see the European pharmacopoeia (1), the WHO guidelines on quality control methods for medicinal plants (32) and the WHO guidelines on pesticide residues (34).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on control methods for medicinal plants (32).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (32) for the analysis of radioactive isotopes.

Other purity tests
No single-celled protuberances should be present (absence of *E. palustre* L.) (28, 29). Not more than 2% foreign matter (29). Not more than
Herba Equiseti

0.5% mineral matter (2). Thin-layer chromatography for determining the absence of other Equisetum species and hybrids (1, 30). Chemical, sulfated ash and alcohol-soluble extractive limits to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.3% of total flavonoids expressed as isoquercitrone (isoquercitrin) (1).

Major chemical constituents
Asian and North American varieties contain a large amount of quercetin 3-O-β-D-glucopyranoside (isoquercitrin) and its malonyl esters. Apigenin- and luteolin 5-O-glucosides, as well as their malonyl esters are also present. In the European chemotype, the flavonoids are mainly quercetin 3-O-sophoroside together with genkwanin and kaempferol derivatives, among them protogenkwanin 4′-O-β-D-glucopyranoside (23, 35), genkwanin-5-O-glucoside, kaempferol 3,7-di-O-glucoside, kaempferol-3-O-(6′-O-malonyl-glucoside)-7-O-glucoside, kaempferol-3-O-sophoroside and glycosides of luteolin (among them the 5-glucopyranoside, galuteolin), onitin and onitin-9-O-glucoside (4, 36, 37). The plant also contains more than 10% inorganic constituents of which two thirds are silicates (which can constitute as much as 15% (17)) and potassium salts (5). Small amounts of gold (0.03–0.075 ppm) and silver (0.23 ppm) and lanthanides have been reported (38) as well as traces of alkaloids, including nicotine and spermidine-type bases, and palustrine. The sterols β-sitosterol, campesterol, iso-fucosterol and cholesterol are present (37). Other constituents reported include methoxypyridine, equisetolin, equisetoside, sapogenin and equisetogenin (7, 8). In addition, there are saponins, carotenoids, polyenic acids, rare dicarboxylic acids (5) and organic acids (aconitic, arabinonic, caffeic, citric, equisetolic, fumaric, gallic, gluconic, glyceric, malic, malonic, protocatechuic and quinic), and rhodoxanthin, threonic, p-coumaric, 4-hydroxybenzoic and vanillic acid among others (7, 8, 37, 39). The structures of some characteristic constituents are presented below.

\[
\text{equisetolic acid}
\]

\[
\text{palustrine}
\]
Medicinal uses

Uses supported by clinical data
An open clinical trial has indicated a possible diuretic effect (40).

Uses described in pharmacopoeias and well-established documents
Used internally for kidney and bladder diseases, oedema and as an adjuvant in slimming diets (41). It is applied as irrigation therapy for infectious and inflammatory diseases of the genitourinary tract, and kidney stones (12, 23, 42). Used externally as supportive treatment for slowhealing wounds (43).

Uses described in traditional medicine
Symptomatic treatment of chronic swelling of the legs, slow-healing sprains and fractures, irritable skin conditions, gout, rheumatism, arthritis, hepatitis, fractures, sore throat, dermatological problems and haemorrhoids (44–47). In folk medicine Herba Equiseti is used as an analgesic, antihypertensive, clotting agent, haemostatic, depurative, astringent, diuretic and anti-inflammatory (48–50). In Indian Ayurvedic medicine it is used for the treatment of inflammation or benign enlargement of the prostate gland, for urinary incontinence and for enuresis in children (51).

Pharmacology

Experimental pharmacology
Antinociceptive and anti-inflammatory activity
An aqueous-ethanol extract of the stems of Equisetum arvense at concentrations of 10, 25, 50 and 100 µg/g, administered intraperitoneally, reduced the writhing induced in mice by acetic acid (49, 57, 93 and 98%, respectively). The results of treatment with the extract were positive but less marked in the formalin and carrageenan paw oedema tests, but were negative in the hotplate test. The antinociceptive and anti-inflammatory effects of the extract are thus confirmed in chemical models of nociception in vivo (52).

Sedative and anticonvulsant effects
In an open-field test in rats, an aqueous-ethanol extract of the aerial parts of Equisetum arvense, at doses of 200 and 400 mg/kg body weight (bw), had anticonvulsant activity. The treatment enhanced the number of falls in the rota-rod test, reducing the time of permanence on the bar. An increase in barbiturate-induced sleeping time was also observed (46% and
74%, at the 200 and 400 mg/kg bw doses, respectively). The extract increased the pentylenetetrazole-induced convulsion latency, diminished the severity of convulsions, reduced the percentage of rats which developed convulsions (25% and 50% at the 200 and 400 mg/kg bw doses, respectively) and protected animals from death, thus confirming the anticonvulsant effect of the extract (53).

**Antiuroliathiasis activity**

Intravenous infusion of a hot aqueous extract of the dried aerial parts (dose not stated) to female Wistar rats showed antiuroliathiasis activity both in prevention and in treatment of kidney stone formation (54).

**Antimicrobial activity**

The antibacterial activities of 90–95% ethanol extracts of the dried aerial parts were assessed in vitro. At a concentration of 500 µg/disc, the extracts exhibited weak activity against *Bacillus subtilis* and *Streptococcus faecalis*, but were inactive against *Escherichia coli*, *Aerobacter aerogenes*, *Bacillus globifer*, *Bacillus mycoides*, *Proteus morganii*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Serratia marcescens* and *Streptococcus aureus* (55, 56). A methanol extract of the dried leaves at a maximum inhibitory concentration >500 µg/ml was inactive against *Mycobacterium avium* and *Mycobacterium smegmatis* in a study using a broth culture method (57).

The disc diffusion method was also used for the evaluation of the antimicrobial activity of the essential oil from the stems of *Equisetum arvense* against *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella enteritidis*, *Aspergillus niger* and *Candida albicans*. A 1:10 dilution of the essential oil was shown to possess a broad spectrum of antimicrobial activity against all strains tested (58).

A dried extract of the fresh aerial parts was active against *Aspergillus flavus* in vitro (concentration not stated) (59). The antifungal activity of an aqueous–ethanol extract of dried stems (1:1), at a concentration of 500 g/ml/agar plate was assessed. The results showed that the extract was inactive against *Aspergillus fumigatus*, *Aspergillus niger*, *Botrytis cinerea*, *Penicillium digitatum*, *Rhizopus nigricans*, *Trichophyton mentagrophytes*, *Candida albicans* and *Saccharomyces pastorianus* (56, 60). A 95% ethanol extract at various concentrations was inactive against *Fusarium culmorum*, *Fusarium solani*, *Penicillium notatum* and *Scopulariopsis species* (55). An aqueous-methanol extract (1:1) of the dried aerial parts inhibited HIV-1 reverse transcriptase activity in cell culture at a concentration of 10% (61).
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**Antiplatelet activity**
An aqueous extract of the dried aerial parts at a concentration of 1 mg/ml significantly inhibited collagen-, thrombin- and ADP-induced platelet aggregation in vitro (91.9%, $p < 0.001$). This antiaggregatory effect was dose-dependent (62, 63).

**Antioxidant, hepatoprotective and radical scavenging effects**
An aqueous extract of the dried aerial parts (30 µl) exhibited radical scavenging effects in cultured lines of microsomes (64). The antioxidative activity of water and ethanol extracts of the aerial parts was investigated using different methods. The content of total phenolic components was higher in the ethanol extract, but the protein content was higher in the aqueous extract. The extracts had remarkable antioxidative activities, similar to those of 5 mM ascorbic acid. Water extracts showed high superoxide anion radical-scavenging activities. Hydroxyl radicals were effectively scavenged by ethanol extracts. The effects may be due to the presence of vitamins C and E, copper and zinc (65). Compounds isolated from the methanol extract of the plant (the phenolic petrosin onitin and flavonoid luteolin) exhibited hepatoprotective activities in vitro against tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying median effective concentrations ($EC_{50}$) values of 85.8 ± 9.3 µM and 20.2 ± 1.4 µM, respectively. Silybin, used as a positive control, showed an $EC_{50}$ value of 69.0 ± 3.3 µM. The isolated compounds also showed superoxide scavenging effects ($IC_{50}$, 35.3 ± 0.2 µM and 5.9 ± 0.3 µM, respectively) and 1,1-diphenyl-2-picrylhydrazyl-2,2-di(4-tert-octylphenyl)-1–picrylhydrazyl free radical scavenging effect ($IC_{50}$, 35.8 ± 0.4 µM and 22.7 ± 2.8 µM, respectively) (36).

**Uterine stimulant activity**
A weak in vitro uterine stimulant effect of a methanol extract of the aerial parts was observed using isolated uterus (unspecified condition) preparations from female rats at a dose of 5 mg/ml (66).

**Toxicology**
A methanol extract of the plant at a median effective dose of 20 µg/ml had a cytotoxic effect in a human leukaemia cell line (L1210) (67). A 10% aqueous extract and a methanol extract at a concentration of 50 µg/ml showed no cytotoxic activity in either HeLa or 9KB cell cultures (68, 69). Oral administration of the dried entire plant (in rations) at variable concentrations (20% or more) caused an acute vitamin B$_1$ deficiency (antithiamine activity) in horses within 2–5 weeks, an effect known as equisetosis (38, 70).
Clinical pharmacology
In an open uncontrolled clinical trial, sap from the aerial parts of Herba Equiseti, at a dose of one tablespoon (15 g) three times a day, was tested in patients with cardiac failure and oedema. All patients showed an augmentation of diuresis. In the same study, an infusion of 15 g of the plant in 180 ml of water was given in divided doses (one tablespoon every 2 hours) to a group of patients with oedema. Again, an increase in diuresis was observed in more than 50% of patients (40).

Adverse reactions
A cholesterol-rich diet (0.5% cholesterol and 0.15% sodium cholate for 14 days), to which 4% of Herba Equiseti powder had been added, caused dermatitis of the neck, head and back in 65% of rats. The effect was not observed when the rats were fed on a normal diet (71).

Contraindications
No irrigation therapy (hydrocolon therapy) is recommended in patients with oedema due to impaired heart and kidney function (40). If signs of hypersensitivity reactions appear, Herba Equiseti must not be used again.

Warnings
Ingestion of large amounts of Herba Equiseti is not recommended in combination with a cholesterol-rich diet (72).

Precautions
General
Care is necessary in the presence of diseases associated with serious renal lesions and inflammation (nephritis, nephrosis) due to the irritant action of Herba Equiseti (73, 74). Do not use Herba Equiseti for more than 6 weeks except under professional supervision, as it may cause irritation of the digestive tract (43). A physician should be consulted when the drug is used as a bath additive in cases of major skin lesions, acute skin lesions of unknown origin, major feverish and infectious diseases, cardiac insufficiency or hypertension (12). If symptoms worsen or persist for longer than 5 days or in case of increased body temperature or presence of blood in urine, a physician should be consulted.

Drug interactions
No information was found.
Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
Because of the uterine stimulant activity (See Pharmacology) the herbal substance and its herbal preparations should not be used during pregnancy.

Nursing mothers
The herbal substance and its herbal preparations should not be used by nursing mothers.

Paediatric use
The herb in its powdered form is not recommended for children due to the inorganic silica content. Toxicity of the herb was found to be similar to nicotine poisoning in children who chewed the stems (38).

Dosage forms
Cut herb for infusions, decoctions and other equivalent Galenical preparations.

Posology
(Unless otherwise indicated)
For internal use. Average daily dose 6 g of herb as a decoction or infusion (1:5) given in divided doses three times daily (75). Fluid ethanol extract: 1:1 (g/ml), half a teaspoon (2 ml) 2 times daily (76). Tincture: 1:5 (g/ml), 10 ml three times daily.
For external use. To prepare a decoction for use in making a cataplasm or compress: add 10 g of herb to 1 l of boiling water for direct application to the skin (23). As a bath additive: add 2 g of herb to 1 l of hot water and steep for 1 hour, then add it to water in the bath (51).

References
44. Knuth V. Equisetum arvense, the Bottle Brush. Pharmazie, 1947, 2:222–223.


Fructus Foeniculi*

Definition
Fructus Foeniculi consists of the dried ripe fruits of *Foeniculum vulgare* Mill. (Apiaceae) (1–8).  

Synonyms

Selected vernacular names
Aneth doux, arap saçi, besbes, bitter fennel, Bitterfenchel, brotanis, common fennel, dill, édeskömény, erva doce, fânksal, fannel, Fencel, Fenchel, fenchul, Fennekel, fennel, Fennichl, fennikel, Fennkol, fenouil, fenuchielo, fenuchio, fenylie, finkel, Finkel, finichio, finoccio, finucco, fiohlo, florence fennel, Foenoli doux, Funcho, gemeiner Fenchel, Gemüsefenchel, giant fennel, gymphuri, hierba de anis, hinojo, hui-hsiang, imboziso, insilal, koper wloski, lady’s chewing tobacco, large fennel, madesi souf, madhurika, marathoron, maratrum, marui, misi, nafa, panmauri, razianeh, razianaj, sanu, shamar, shomar, sladkij ukrop, sohoehyang, sopu, spingel, sup, thian klaep phlueak, thian klaep, venkel, sweet fennel, uikyo, uikeyou, vegetable fennel, vinkel, wild fennel, xiao hui, xiaohuixiang, yi-ra (2, 3, 6, 8, 9, 11–14).

* Adopted from the volume 3 of WHO monographs on selected medicinal plants.

† The European pharmacopoeia (7) recognizes *Foeniculum vulgare* Mill. ssp. vulgare var. vulgare (*Foeniculi amari fructus, Bitter Fennel*) and *F. vulgare* Mill. ssp. vulgare var. dulcis (*Foeniculums dulcis fructus, Sweet Fennel*) as distinct entities for which separate monographs are provided. However, in the biological literature, a clear delineation at the variety level is generally not made. Therefore, this monograph has not made the distinction between the “bitter” and “sweet” varieties.
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Geographical distribution
Indigenous to the Mediterranean region. Cultivated in Europe, Asia and temperate regions of Africa and South America (2, 12, 15).

Description
Perennial aromatic herb, 1–3 m high with green, glaucous, furrowed, branched stems bearing alternate leaves, 2–5 times pinnate with extremely narrow leaflets. Superior leaves with sheaths longer than the blade. Umbels compound, large, nearly regular, on long peduncles. Flowers yellow, no involucre; calyx with five very slight teeth; petals five, entire, tips involute; stamens five; ovary two-celled; stylopodium large, conical. Fruit an oblong cremocarp, 6–10 mm long, 1–4 mm in diameter, greenish; glabrous mericarp compressed dorsally, semicylindrical, with five prominent, nearly regular ribs. Seeds somewhat concave, with longitudinal furrows (3, 15, 16).

Plant material of interest: dried ripe fruits
General appearance
Cremocarp, oblong 3.5–10.0 mm long, 1–3 mm wide, externally greyish yellow-green to greyish yellow often with pedicel 2–10 mm long. Mericarps usually free, glabrous, each bearing five prominent slightly crenated ridges (1–4, 7, 8).

Organoleptic properties
Odour: characteristic, aromatic; taste: sweet to bitter (1–4, 8).

Microscopic characteristics
Outer epidermis of the pericarp consists of thick-walled, rectangular, polygonal, colourless cells, with smooth cuticle, few stomata and no hairs. Mesocarp consists of brownish parenchyma; traversed longitudinally by six large schizogenous vittae, appearing elliptical in section and possessing brown epithelial cells; traversed in the ridges by vascular bundles, each having one inner xylem strand and two lateral phloem strands, and accompanied by strongly lignified fibres; some of the mesocarp cells, especially those about the vascular bundles, possess lignified, reticulate cells. Endocarp composed of one layer of flattened thin-walled cells varying in length, but mostly 4–6 µm thick, arranged parallel to one another in groups of five to seven. Endosperm, formed of somewhat thick-walled polygonal cellulosic parenchyma containing fixed oil, several aleurone grains (up to 6 µm in diameter) enclosing a globoid, and one or more mi-
Fructus Foeniculi

crorolette crystals of calcium oxalate, about 3 µm in diameter. Carpophore often not split, with thick-walled sclerenchyma in two strands (2, 8).

**Powdered plant material**
Greyish-brown to greyish-yellow. Yellowish-brown-walled polygonal secretory cells, frequently associated with a layer of thin-walled transversely elongated cells 2–9 µm wide, in a parquet arrangement; reticulate parenchyma of the mesocarp; numerous fibre bundles from the ridges, often accompanied by narrow spiral vessels; very numerous endosperm fragments containing aleurone grains, very small microrosette crystals of calcium oxalate, and fibre bundles from the carpophore (7).

**General identity tests**
Macroscopic and microscopic examinations (1–4, 7, 8), thin-layer chromatography for the presence of anethole and fenchone (7), and gas chromatography for the presence of anethole, fenchone and estragole (7).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (17).

**Foreign organic matter**
Not more than 1.5% peduncles and not more than 1.5% other foreign matter (4, 7).

**Total ash**
Not more than 10% (1, 4, 7, 8, 18).

**Acid-insoluble ash**
Not more than 1.5% (1, 2, 4).

**Water-soluble extractive**
Not less than 20% (3).

**Alcohol-soluble extractive**
Not less than 11% (3).

**Moisture**
Not more than 8% (7).
**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (19). For other pesticides, see the *European pharmacopoeia* (19) and the WHO guidelines on quality control methods for medicinal plants (17) and pesticide residues (20).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (17).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (17) for the analysis of radioactive isotopes.

**Other purity tests**
Chemical and sulfated ash tests to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 1.4% v/w essential oil (1, 2, 4, 6).

**Major chemical constituents**
The major constituent is the essential oil (2–6%), which contains trans-anethole (50–82%), (+)-fenchone (6–27%), estragole (methylchavicol) (3–20%), limonene (2–13%), p-anisaldehyde (6–27%), α-pinene (1–5%) and α-phellandrene (0.1–19.8%) (9, 12, 14, 21, 22). Representative structures are presented below.

**Medicinal uses**

**Uses supported by clinical data**
None.

**Uses described in pharmacopoeias and well established documents**
Symptomatic treatment of dyspepsia, bloating and flatulence (9, 23–25). As an expectorant for mild inflammation of the upper respiratory tract (24, 26). Treatment of pain in scrotal hernia, and dysmenorrhoea (8).

**Uses described in traditional medicine**
Treatment of blepharitis, bronchitis, constipation, conjunctivitis, diabetes, diarrhoea, dyspnoea, fever, gastritis, headache, pain, poor appetite and...
Fructus Foeniculi

respiratory and urinary tract infections (14). As an aphrodisiac, anthelmintic, emmenagogue, galactagogue and vermicide (14, 27, 28).

Pharmacology

Experimental pharmacology

Analgesic and antipyretic activities

Intragastric administration of 500 mg/kg body weight (bw) of a 95% ethanol extract of Fructus Foeniculi to mice reduced the perception of pain as measured in the hot-plate test, and decreased yeast-induced pyrexia (29). Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats had significant ($P < 0.05$) analgesic activity in the hot-plate reaction test (30). In mice with yeast-induced pyrexia, treatment with 500.0 mg/kg bw of the same extract reduced rectal temperature from 36.5 ºC to 34.7 ºC 90 minutes after administration (30).

Antimicrobial activity

An essential oil from the fruits inhibited the growth of Alternaria species, Aspergillus flavus, A. nidulans, A. niger, Cladosporium herbarum, Cunninghamella echinulata, Helminthosporium saccharii, Microsporum gypseum, Mucor mucedo, Penicillium digitatum, Rhizopus nigricans, Trichophyton roseum and T. rubrum in vitro (31, 32). In another study, an essential oil was not active against Aspergillus species in vitro but a methanol extract of the fruits inhibited the growth of Helicobacter pylori (the bacterium associated with gastritis and peptic ulcer disease) in vitro, minimum inhibitory concentration 50.0 µg/ml (33). An essential oil from the fruits inhibited the growth of Candida albicans, Escherichia coli, Lentinus lepideus, Lenzites trabea, Polyporus versicolor, Pseudomonas aeruginosa and Staphylococcus aureus (34), and Kloeckera apiculata, Rhodotorula rubra and Torulopsis glabrata (35) in vitro. An ethyl acetate extract of the seeds inhibited the growth of Shigella flexneri (36), and an 80% ethanol extract of the seeds inhibited the growth of Bacillus subtilis and Salmonella typhi at concentrations of 250.0 µg/ml in vitro (37).

Antispasmodic activity

An ethanol extract of the fruits, 2.5–10.0 ml/l, 1 part fruits:3.5 parts 31% ethanol, inhibited acetylcholine- and histamine-induced guinea-pig ileal contractions in vitro (23). An essential oil from the fruits reduced intestinal spasms in mouse intestine, and was 26% as active as papaverine (38). Intragastric administration of 2.0–3.0 g/kg bw of an infusion of the fruits to cats inhibited acetylcholine- and histamine-induced ileum spasms by 50% (39).
An essential oil from the fruits, 25.0 µg/ml and 10.0 µg/ml, respectively, inhibited oxytocin- and prostaglandin E₂-induced contractions of isolated rat uterus and reduced the frequency of the latter but not the former (40).

**Cardiovascular effects**

Intravenous administration of a 50% ethanol extract of the fruits (dose not specified) reduced blood pressure in dogs (41). An aqueous extract of the fruits, 10% in the diet, reduced blood pressure in rats. The effect was abolished by pretreatment of the animals with atropine (42). An unspecified extract of the seeds had diuretic effects in rabbits after intragastric administration. The effect was blocked by pretreatment of the animals with morphine (43).

Intragastric administration of 500.0 mg/kg bw of a 95% ethanol extract of the fruits to rats induced diuresis. The effect was comparable to that observed in animals treated with 960.0 mg/kg bw of urea, and was almost double that in controls (30).

**Estrogenic and antiandrogenic activities**

Intragastric administration of 2.5 mg/kg bw of an acetone extract of the seeds daily for 15 days to male rats decreased the protein concentration in the testes and vas deferens, and increased it in the seminal vesicles and prostate gland (44). The same dose of the same extract administered to female rats daily for 10 days increased the weight of the mammary glands, while higher doses induced vaginal cornification, increased the weight of the oviduct, endometrium, myometrium, cervix and vagina, and induced estrus (44). A follow-up study demonstrated that the acetone extract induced cellular growth and proliferation of the endometrium, and stimulated metabolic changes in the myometrium of rats. These changes appeared to favour the survival of spermatocytes and the implantation of the zygote in the uterus (45). Conversely, intragastric administration of 2.0 g/kg bw of an aqueous extract of the seeds per day for 25 days significantly \( P < 0.025 \) reduced female fertility in mice compared with controls. No effect was observed in male mice (46).

Intragastric administration of 0.5 mg/kg bw or 2.5 mg/kg bw of an acetone extract of the fruits per day for 10 days to ovariectomized female rats had estrogenic effects (45). Intragastric administration (dose not specified) of an essential oil from the fruits to goats increased the amount of milk produced and the fat content of the milk (47). Lactating mice fed the fruits in the diet (concentration not specified) produced pups that ate a larger quantity of fennel-containing foods, suggesting that the constituents of the fruits may be passed in breast milk (48). Intragastric administration of
250.0 mg/kg bw of unspecified extracts of the fruits induced estrus and increased the size of the mammary glands and oviducts in adult ovariectomized rats, and exerted an antiandrogenic effect in adult male mice. It also increased the weight of the cervix and vagina of ovariectomized mice, and increased the concentration of nucleic acids and protein in cervical and vaginal tissues. The hyperplasia and hypertrophy of the cervix and vagina were similar to changes seen during estrus in normal female rats (45).

Subcutaneous administration of anethole (dose not specified) to sexually immature female rats increased uterine weight and induced estrus. However, in ovariectomized mice the same treatment was not estrogenic (49). Intramuscular injection of 100.0 mg/kg bw or 500.0 mg/kg bw of anethole per day for 7 days to rats induced a significant decrease in dorso-lateral prostate weight ($P < 0.05$) (50). Intragastric administration of 50.0 mg/kg bw, 70.0 mg/kg bw or 80.0 mg/kg bw of trans-anethole to rats had anti-implantation effects, with the maximum effect (100%) at the highest dose (51). The compound showed estrogenic effects, and did not demonstrate anti-estrogenic, progestational or androgenic effects (51).

**Expectorant and secretolytic effects**

Application of an infusion of Fructus Foeniculi, 9.14 mg/ml, to isolated ciliated frog oesophagus epithelium increased the transport velocity of fluid by 12%, suggesting an expectorant effect (52). Administration of 1.0–9.0 mg/kg bw anethole and 1.0–27.0 mg/kg bw fenchone by inhalation to urethanized rabbits produced a decrease in the specific gravity of the respiratory fluid and enhanced the volume output of respiratory tract fluid (53).

**Gastrointestinal effects**

Intragastric administration of 24.0 mg/kg bw of the fruits increased spontaneous gastric motility in unanaesthetized rabbits; at a dose of 25.0 mg/kg bw the fruits reversed the reduction of gastric motility induced by pentobarbital (54).

**Sedative effects**

Intragastric administration of an essential oil from the fruits (dose not specified) to mice reduced locomotor activity and induced sedation (55). A single intraperitoneal administration of 200.0 mg/kg bw of an ether extract of the seeds enhanced barbiturate induced sleeping time in mice. However, intragastric administration of 200.0 mg/kg bw of the extract per day for 7 days decreased barbiturate-induced sleeping time (56).
Toxicology
Intragastric administration of 3.0 g/kg bw of a 95% ethanol extract of the fruits induced piloerection and reduced locomotor activity in mice (30). Acute (24-hour) and chronic (90-day) oral toxicity studies with an ethanol extract of the fruits were performed in rodents. Acute doses were 0.5 g/kg, 1.0 g/kg and 3.0 g/kg per day; the chronic dose was 100.0 mg/kg per day. No acute or chronic toxic effects were observed (57). The acute median lethal dose (LD$_{50}$) of anethole in rats was 3.8 mg/kg bw after intragastric administration (58, 59). Intragastric or subcutaneous administration of 10.0–16.0 g/kg bw of a 50% ethanol extract of the fruits to mice had no toxic effects (60). The oral LD$_{50}$ of an essential oil from the fruits in mice was 1326.0 mg/kg bw (61).

Chronic use of high doses of trans-anethole in rodent dietary studies has been shown to induce cytotoxicity, cell necrosis and cell proliferation. In rats, hepatotoxicity was observed when dietary intake exceeded 30.0 mg/kg bw per day (62). In female rats, chronic hepatotoxicity and a low incidence of liver tumours were reported with a dietary intake of trans-anethole of 550.0 mg/kg bw per day, a dose about 100 times higher than the normal human intake (62). In chronic feeding studies, administration of trans-anethole, 0.25%, 0.5% or 1% in the diet, for 117–121 weeks had no effect on mortality or haematology, but produced a slight increase in hepatic lesions in the treated groups compared with controls (63).

Unscheduled DNA synthesis was not induced in vitro by anethole, but was induced by estragole, an effect that was positively correlated with rodent hepatocarcinogenicity (64). However, the dose of estragole used (dose not specified) in the rodent studies was much higher than the dose normally administered to humans. Low doses of estragole are primarily metabolized by O-demethylation, whereas higher doses are metabolized primarily by 1’-hydroxylation, and the synthesis of 1’-hydroxyestragole, a carcinogenic metabolite of estragole (65, 66).

Clinical pharmacology
No information available.

Adverse reactions
In rare cases, allergic reactions such as asthma, contact dermatitis and rhinoconjunctivitis have been reported in sensitive patients (67, 68).

Contraindications
The fruits are contraindicated in cases of known sensitivity to plants in the Apiaceae (69, 70). Owing to the potential estrogenic effects of the es-
essential oil from the seeds and anethole (44, 45, 50), its traditional use as an emmenagogue, and the lack of human studies demonstrating efficacy, Fructus Foeniculi should not be used in pregnancy. Pure essential oils should not be given to infants and young children owing to the danger of laryngeal spasm, dyspnoea and central nervous system excitation (12).

**Warnings**
The pure essential oil from the fruits may cause inflammation, and has an irritant action on the gastrointestinal tract.

**Precautions**

*Carcinogenesis, mutagenesis, impairment of fertility*
An aqueous extract of the fruits, up to 100.0 mg/ml, was not mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA100 with or without metabolic activation with homogenized rat liver microsomes (71, 72). Aqueous and methanol extracts of the fruits, up to 100.0 mg/ml, were not mutagenic in the *Bacillus subtilis* recombination assay (71). However, a 95% ethanol extract, 10.0 mg/plate, was mutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA98 and TA102 (73). An essential oil from the fruits, 2.5 mg/plate, had mutagenic effects in the *Salmonella*/microsome assay in *Salmonella typhimurium* strain TA100 with metabolic activation (74), and in the *Bacillus subtilis* recombination assay (75). A similar essential oil had no effects in the chromosomal aberration test using Chinese hamster fibroblast cell lines (76).

*Pregnancy: teratogenic effects*
An essential oil from the fruits, up to 500.0 µg/ml, had no teratogenic effects in cultured rat limb bud cells (61).

*Pregnancy: non-teratogenic effects*
See Contraindications.

*Nursing mothers*
No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds.

*Paediatric use*
No restrictions on the use of infusions prepared from Fructus Foeniculi or the seeds. See also Contraindications.
Other precautions
No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test reactions.

Dosage forms
Dried fruits, syrup and tinctures. Store the dried fruits in a well-closed container, protected from light and moisture (7).

Posology
(Unless otherwise indicated)
Daily dose: fruits 5–7 g as an infusion or similar preparations, higher daily doses (> 7 g fruits) should not be taken for more than several weeks without medical advice (25); fennel syrup or honey 10–20 g; compound fennel tincture 5–7.5 g (5–7.5 ml).

References
Fructus Foeniculi

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Radix Ginseng*

Definition
Radix Ginseng is the dried root of *Panax ginseng* C.A. Meyer (Araliaceae) (1–5).1

Synonyms
*Panax schinseng* Nees (2).
Other *Panax* species, including *P. quinquefolius* L. (American ginseng), *P. notoginseng* Burk. (San-chi ginseng), *P. pseudoginseng* Wall. ssp. *japonicus* Hara = *P. japonicus* C.A. Meyer (Japanese chikutsu ginseng) and *P. notoginseng* ssp. *himalaicus* (Himalayan ginseng) have also been referred to as “ginseng” and used medically (6, 7). However, scientific documentation of these species is insufficient to justify the preparation of a monograph at this time.

Selected vernacular names
Chosen ninjin, ginseng, Ginsengwurzel, hakusan, hakushan, higeninjin, hongshen, hungseng, hungshen, hunseng, jenseng, jenshen, jinpi, kao-li-seng, Korean ginseng, minjin, nhan sam, ninjin, ninzin, niuhuan, Oriental ginseng, otane ninjin, renshen, san-pi, shanshen, sheng-sai-seng, shenshaishen, shengshaishen, t’ang-seng, tyosenninzin, yakuyo ninjin, yakuyo ninzin, yeh-shan-seng, yuan-seng, yuanshen (1, 2, 4–10).

Description
A perennial herb with characteristic branched roots extending from the middle of the main root in the form of a human figure. Stem erect, simple, and not branching. Leaves verticillate, compound, digitate, leaflets 5, with the 3 terminal leaflets larger than the lateral ones, elliptical or slightly

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* Adopted from the volume 1 of WHO monographs on selected medicinal plants.
1 Steamed *Panax ginseng* root is listed in the Japanese pharmacopoeia as "Red Ginseng (Ginseng Radix Rubra)" (2).
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ovoic, 4–15 cm long by 2–6.5 cm wide; apex acuminate; base cuneate; margin serrulate or finely bidentate. In general, 1 leaf in the first year with 1 leaflet added annually until the sixth year. Inflorescence a small terminal umbel, hemispherical in early summer. Flowers polygamous, pink. Calyx vaguely 5-toothed. Petals 5, stamens 5. Fruit a small berry, nearly drupaceous, and red when ripe in autumn (8).

Plant material of interest: dried root

General appearance
The main root is fusiform or cylindrical, 2.5–20 cm long by 0.5–3.0 cm in diameter; externally greyish yellow; upper part or entire root exhibiting sparse, shallow, interrupted, and coarse transverse striations and distinct longitudinal wrinkles; lower part bearing 2–5 branching lateral roots and numerous slender rootlets with inconspicuous minute tubercles. Rhizomes 1–4 cm long by 0.3–1.5 cm in diameter, mostly constricted and curved, bearing adventitious roots and sparse depressed circular stem scars. Texture relatively hard, fracture yellowish white, cambium ring brownish yellow, starchy (1–5).

Organoleptic properties
Colour, greyish white to amber-yellow; odour, characteristic; taste, slightly sweet at first, followed by a slight bitterness (1, 2).

Microscopic characteristics
The transverse section shows cork consisting of several rows of cells; cortex narrow; phloem showing clefts in the outer part, and parenchymatous cells densely arranged and scattered with resin canals containing yellow secretions in the inner part; cambium in a ring; xylem rays broad, vessels singly scattered or grouped in an interrupted radial arrangement, and occasionally accompanied by non-lignified fibres; parenchyma cells containing abundant starch grains and a few clusters of calcium oxalate (1, 3–5).

Powdered plant material
Yellowish white; fragments of resin canals containing yellow secretions; clusters of calcium oxalate (20–68 µm in diameter), few, with acute angles; cork cells subsquare or polygonal, with thin and sinuous walls; reticulate and scalariform vessels 10–56 µm in diameter; starch granules fairly abundant, simple, subspheroidal, semicircular, or irregular polygonal (4–30 µm in diameter), singly or in groups of two to four (1–5).
Geographical distribution
Mountain regions of China (Manchuria), the Democratic People’s Republic of Korea, Japan, the Republic of Korea, and the Russian Federation (eastern Siberia) (7, 8). It is commercially produced mainly by cultivation (6).

General identity tests
Macroscopic and microscopic examinations, microchemical tests, and thin-layer chromatographic analysis (1–5).

Purity tests

Microbiology
The test for Salmonella spp. in Radix Ginseng products should be negative. The maximum acceptable limits of other microorganisms are as follows (11–13). For preparation of decoction: aerobic bacteria—not more than $10^7$/g; fungi—not more than $10^5$/g; Escherichia coli—not more than $10^2$/g. Preparations for internal use: aerobic bacteria—not more than $10^9$/g or ml; fungi—not more than $10^4$/g or ml; enterobacteria and certain Gram negative bacteria—not more than $10^5$/g or ml; Escherichia coli—0/g or ml.

Foreign organic matter
Not more than 2% (2, 3).

Total ash
Not more than 4.2% (2).

Acid-insoluble ash
Not more than 1% (4).

Sulfated ash
Not more than 12% (5).

Alcohol-soluble extractive
Not less than 14.0% (2).

Pesticide residues
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Ginseng is not more than 0.05 mg/kg (13). For other pesticides, see WHO guidelines on
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

quality control methods for medicinal plants (11) and guidelines for predicting dietary intake of pesticide residues (14).

**Heavy metals**

Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (11).

**Radioactive residues**

For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (11).

**Other purity tests**

Chemical and water-soluble extractive tests to be established in accordance with national requirements.

**Chemical assays**

Microchemical, thin-layer chromatographic, and spectrophotometric methods are used for the qualitative and quantitative analysis of ginsenosides (1–5). High-performance liquid chromatography (15–17) and liquid chromatography–mass spectrometry (18) methods are also available.

Characteristic saponins known as ginsenosides, not less than 1.5% calculated as ginsenoside Rg1 (d-glucopyranosyl-6β-glucopyranosyl-20S-protopanaxatriol, relative molecular mass 800) (3, 5).

**Major chemical constituents**

The major chemical constituents are triterpene saponins. More than 30 are based on the dammarane structure, and one (ginsenoside Ro) is derived from oleanolic acid (6, 7, 17, 19). The dammarane saponins are derivatives of either protopanaxadiol or protopanaxatriol. Members of the former group include ginsenosides Ra₁, Ra₂, Rb₁, Rb₂, Rc, Rd, Rf, Rd₂, and Rh₂; (20S)-ginsenoside Rg₁; and malonyl ginsenosides Rb₁, Rb₂, Rc, and Rd. Examples of protopanaxatriol saponins are ginsenosides Re₂, Re₃, Rf, Rg₁, Rg₂, and Rh₁; 20-gluc-o-ginsenoside Rf; and (20R)-ginsenosides Rg₁ and Rh₁. Those considered most important are ginsenosides Rb₁, Rb₂, Rc, Rd, Rf, Rg₁, and Rg₂; Rb₁, Rb₂, and Rg₁ are the most abundant. Representative structures are presented below.
Radix Ginseng

Panaxadiols

\[
\text{ginsenoside R}_1 \quad \text{glc-}(1\rightarrow2)-\text{glc-} \quad \text{glc-}
\]

\[
\text{ginsenoside R}_2 \quad \text{glc-}(1\rightarrow2)-\text{glc-} \quad \text{ara(p)-(1\rightarrow6)-glc-}
\]

\[
\text{ginsenoside R}_c \quad \text{glc-}(1\rightarrow2)-\text{glc-} \quad \text{ara(f)-(1\rightarrow6)-glc-}
\]

\[
\text{ginsenoside R}_d \quad \text{glc-}(1\rightarrow2)-\text{glc-} \quad \text{glc-}
\]

Panaxatriols

\[
\text{ginsenoside R}_e \quad \text{glc-} \quad \text{rha-(1\rightarrow2)-glc-}
\]

\[
\text{ginsenoside R}_f \quad \text{H-} \quad \text{glc-}
\]

\[
\text{ginsenoside R}_g^1 \quad \text{glic-} \quad \text{glc-}
\]

\[
\text{ginsenoside R}_g^2 \quad \text{H-} \quad \text{rha-(1\rightarrow2)-glc-}
\]
Dosage forms
Crude plant material, capsules and tablets of powdered drugs, extracts, tonic drinks, wines, and lozenges. Store in a cool, dry place in well-sealed containers (20).

Medicinal uses

Uses supported by clinical data
Radix Ginseng is used as a prophylactic and restorative agent for enhancement of mental and physical capacities, in cases of weakness, exhaustion, tiredness, and loss of concentration, and during convalescence (21–29).

Uses described in pharmacopoeias and in traditional systems of medicine
Radix Ginseng has been used clinically in the treatment of diabetes (1), but further clinical studies are needed. The drug is also used in the treatment of impotence, prevention of hepatotoxicity, and gastrointestinal disorders such as gastritis and ulcers (1, 7).

Uses described in folk medicine, not supported by experimental or clinical data
Treatment of liver disease, coughs, fever, tuberculosis, rheumatism, vomiting of pregnancy, hypothermia, dyspnoea, and nervous disorders (7).

Pharmacology

Experimental pharmacology
The suggested mode of action of Radix Ginseng is twofold. First, the drug has an “adaptogenic” effect (30), which produces a non-specific increase
in the body’s own defences against exogenous stress factors and noxious chemicals (31). Secondly, the drug promotes an overall improvement in physical and mental performance (30–33).

Treatment of cultured mammalian cells, isolated organs, and animal models (primarily mice and rats) with Radix Ginseng before or during exposure to physical, chemical, or psychological stress increased the ability of the respective model systems to resist the damaging effects of various stressors (31). These results were demonstrated in cases of radiation poisoning (34–36), viral infection and tumour load (37, 38), alcohol or carbon tetrachloride poisoning (39–41), oxygen deprivation and hypobaric pressure (42, 43), light or temperature stress, emotional stress, and electrical shock or restricted movement (44, 45, 46). The mechanism by which the drug exerts its activity is most likely through the hypothalamus–pituitary–adrenal axis (47–49) and through its immunostimulant effect (50).

Intraperitoneal administration to rats of ginseng saponin fractions or the ginsenosides Rb1, Rb2, Rc, Rd, and Re elevated serum levels of adrenocorticotropic hormone (ACTH) and corticosterone (51, 52). Pretreatment with dexamethasone, which blocks hypothalamus and pituitary functions, prevented ginseng saponin-mediated release of ACTH and corticosterone, and thereby demonstrated that the increase in serum corticosterone by ginseng occurs indirectly through release of ACTH from the pituitary (51, 52).

The immunomodulatory activity of ginseng appears to be at least partly responsible for its adaptogenic effect (50, 53, 54). Alcohol extracts of Radix Ginseng stimulated phagocytosis in vitro, were mitogenic in cultured human lymphocytes, stimulated the production of interferon, and enhanced the activity of natural killer cells (55, 56). Intraperitoneal administration of an extract of the drug to mice stimulated cell-mediated immunity against Semliki Forest virus, elevated antibody levels against sheep red blood cells and natural killer cells (57), and stimulated the production of interferon (58).

Improvement in physical and mental performance has been observed in mice and rats after oral or intraperitoneal administration of the drug (59–63). Oral administration of ginseng saponin fractions to mice increased endurance and prolonged swimming time in swimming tests (63). However, two studies concluded that ginseng had no positive effects on the physical performance in mice and rats (64, 65). The adaptogenic effects of Radix Ginseng are generally attributed to the ginsenosides (66, 67). The ginsenosides have been shown to alter mechanisms of fuel homeostasis during prolonged exercise, by increasing the capacity of skeletal muscle to oxidize free fatty acids in preference to glucose for cellular en...
ergy production (59). Other constituents of Radix Ginseng, such as vanillic and salicylic acid, have also been reported to have “antifatigue” activity in rats (68). Furthermore, the antioxidant activity of ginseng was associated with both the ginsenosides and the flavonoid constituents (31, 69). The ginsenosides protected pulmonary vascular endothelium against free-radical-induced injury (69).

Mice given ginseng extract or ginsenosides Rb1 and Rg2 orally during passive avoidance response tests showed an improvement in learning ability which was negatively influenced by stress (30), and rats showed improved retention of learned behaviour (70). Ginsenosides Rg1 and Rb1 are the active nootropic constituents of the drug (66), and improve memory and learning in normal as well as cognition-impaired animals. The mode of action involves an increase in the synthesis and release of acetylcholine, and a decrease of brain serotonin levels (66). In cerebral and coronary blood vessels, extracts of Radix Ginseng produced vasodilatation, which improved brain and coronary blood flow (71). The vasodilatory activity of the ginsenosides appears to be primarily due to relaxation of vascular smooth muscles. The ginsenosides block the constricting effects of norepinephrine in isolated aorta strips, and inhibit the uptake of 45Ca2+ in the membrane and sarclemma of rabbit heart tissue. Inhibition of Ca2+ uptake in the muscle membrane contributes to the mechanism of vasodilatation (71).

A number of polypeptides and glycans isolated from Radix Ginseng, named GP and panaxans A–E, respectively, have demonstrated hypoglycaemic activity when given intraperitoneally to mice (72, 73). Two of the glycans, panaxans A and B, have been shown to stimulate hepatic glucose utilization by increasing the activity of glucose-6-phosphate 1-dehydrogenase, phosphorylase α, and phosphofructokinase (72). Panaxan A did not affect plasma insulin levels or insulin sensitivity, but panaxan B elevated the plasma insulin level by stimulating insulin secretion from pancreatic islets, and further enhanced insulin sensitivity by increasing insulin binding to receptors (72). The panaxans are not active after oral administration. Administration of GP (intravenously or subcutaneously) to mice or rats decreased blood glucose and liver glycogen levels (73). Radix Ginseng also contains a number of other constituents with hypoglycaemic activity (72, 74). Adenosine, isolated from a water extract of Radix Ginseng, enhanced lipogenesis and cyclic AMP accumulation of adipocytes, and some of the ginsenosides inhibited ACTH-induced lipolysis, suppressed insulin-stimulated lipogenesis, and stimulated the release of insulin from cultured islets (72).

Subcutaneous administration of a ginseng extract enhanced the mating behaviour of male rats (75). The drug further stimulated spermatogenesis
in rat (76), and rabbit testes, and increased the motility and survival of rabbit sperm outside the body (75).

Intragastric or intradermal administration of an ethanol extract of the drug to rats decreased histamine-, pentagastrin-, carbachol- and vagal stimulation-induced gastric secretion, and inhibited gastric ulcers induced by stress or by pyloric ligation (77–79).

Liver-protectant activity of ginseng has been demonstrated in vitro and in vivo (80, 81). Intraperitoneal administration of Radix Ginseng extracts to normal and dexamethasone-treated rats did not influence the blood chemistry of normal rats, but it decreased aspartate aminotransferase and alanine aminotransferase levels in dexamethasone-treated animals, thereby demonstrating a liver-protectant effect (81). However, another study demonstrated that an intraperitoneal injection of a methanol extract of Radix Ginseng had no protective activity against carbon tetrachloride-induced hepatotoxicity in rats (82).

Clinical pharmacology

Antifatigue activity

The results of clinical studies measuring increased performance and antifatigue effects of ginseng extracts are conflicting and, in general, most studies suffer from poor methodology, lack of proper controls, and no standardization of the ginseng extracts used. The influence of chronic Radix Ginseng administration (2 g/day orally for 4 weeks) on substrate utilization, hormone production, endurance, metabolism, and perception of effort during consecutive days of exhaustive exercise in 11 naval cadets was reported. No significant differences were observed between the control group and the group receiving the ginseng supplementation (83). Another clinical trial with eight participants reported no significant difference between placebo and ginseng administration during exhaustive exercise after 7 days of treatment (84). A randomized, double-blind, cross-over study sought the effects of ginseng on circulatory, respiratory, and metabolic functions during maximal exercise in 50 men (21–47 years old) (24). Total tolerated workload and maximal oxygen uptake were significantly higher following ginseng administration than with placebo. At the same workload, oxygen consumption, plasma lactate levels, ventilation, carbon dioxide production, and heart rate during exercise were all lower in the ginseng treatment group. The results indicated that the ginseng preparations effectively increased the work capacity of the participants by improving oxygen utilization (24). A placebo-controlled, cross-over study determined the effects of ginseng on the physical fitness of 43 male triathletes (25). The participants received 200 mg of a ginseng
preparation twice daily for two consecutive training periods of 10 weeks. No significant changes were observed during the first 10-week period, but ginseng appeared to prevent the loss of physical fitness (as measured by oxygen uptake and oxygen pulse) during the second 10-week period (25). Two further studies with athletes given 100 mg of a standardized ginseng extract twice daily for 9 weeks reported significant improvement in aerobic capacity and reduction in blood lactate and heart rates (26, 27), but placebos or controls were not used in either of the two studies. Further extension of these studies using placebo-controlled, double-blind trials demonstrated significant improvement in the ginseng group as compared with the placebo group (28). Similar results were reported in another study on athletes, and the differences between the ginseng and placebo groups lasted for approximately 3 weeks after the last ginseng dose (29). The effects of 1200 mg of Radix Ginseng in a placebo-controlled, double-blind cross-over study in fatigued night nurses were assessed and the results were compared with placebo and with effects on nurses engaged in daytime work (22). Ginseng restored ratings on tests of mood, competence, and general performance, and the study concluded that ginseng had anti-fatigue activity (22).

Aqueous and standardized ginseng extracts were tested in a placebo-controlled, double-blind study for immunomodulatory actions (85). Sixty healthy volunteers were divided into three groups of 20 each and were given either a placebo or 100 mg of aqueous ginseng extract or 100 mg of standardized ginseng extract, every 12 hours for 8 weeks. Blood samples drawn from the volunteers revealed an increase in chemotaxis of polymorphonuclear leukocytes, the phagocytic index, and the total number of T3 and T4 lymphocytes after 4 and 8 weeks of ginseng therapy, as compared with the placebo group. The group receiving the standardized extract also increased their T4:T8 ratio and the activity of natural killer cells. The conclusion of this study was that ginseng extract stimulated the immune system in humans, and that the standardized extract was more effective than the aqueous extract (85).

Psychomotor activity
A double-blind, placebo-controlled clinical study assessed the effect of standardized ginseng extract (100 mg twice daily for 12 weeks) on psychomotor performance in 16 healthy individuals (23). Various tests of psychomotor performance found a favourable effect on attention, processing, integrated sensory–motor function, and auditory reaction time. The study concluded that the drug was superior to the placebo in improving certain psychomotor functions in healthy subjects (23).
Antidiabetic activity
Radix Ginseng has been shown in clinical studies to have beneficial effects in both insulin-dependent and non-insulin-dependent diabetic patients (86, 87). Oral administration of ginseng tablets (200 mg daily for 8 weeks) to 36 non-insulin-dependent patients elevated mood, improved physical performance, reduced fasting blood glucose and serum aminoterminal propeptide of type III procollagen concentrations, and lowered glycated haemoglobin (87).

Impotence
Ginseng extracts improved sperm production in men and may have some usefulness in treating impotence (32). The ginsenosides, which appear to be the active components, are thought to depress blood prolactin levels, thereby increasing libido (32). In one clinical study, 90 patients with erectile dysfunction were treated with ginseng saponins (600 mg orally per day). Treatment improved rigidity, tumescence, and libido, but not the frequency of coitus (88).

Contraindications
None (21, 50, 89, 90).

Warnings
No information available.

Precautions
General
Diabetic patients should consult a physician prior to taking Radix Ginseng, as ginseng intake may slightly reduce blood glucose levels (86, 87).

Drug interactions
There are two reports of an interaction between Radix Ginseng and phenelzine, a monoamine oxidase inhibitor (91, 92). The clinical significance of this interaction has not been evaluated.

Drug and laboratory test interactions
None reported.

Carcinogenesis, mutagenesis, impairment of fertility
Radix Ginseng is not carcinogenic or mutagenic in vitro, and does not have any effect on fertility (90).
**Pregnancy: teratogenic effects**
Radix Ginseng is not teratogenic in vivo (90).

**Pregnancy: non-teratogenic effects**
The safety of Radix Ginseng for use in pregnancy has not been established.

**Nursing mothers**
Excretion of Radix Ginseng compounds into breast milk and its effects on the newborn have not been established.

**Paediatric use**
The safety and efficacy of Radix Ginseng use in children have not been established.

**Adverse reactions**
Various researchers who studied Radix Ginseng extracts using conventional toxicological methods in five different animal models reported no acute or chronic toxicity of the extract (89, 90, 93).

On the basis of Radix Ginseng’s long use, and the relative infrequency of significant demonstrable side-effects, it has been concluded that the use of Radix Ginseng is not associated with serious adverse effects if taken at the recommended dose (90, 93). However, in Siegel’s open study of 133 patients ingesting large quantities, ginseng was reported to result in hypertension, nervousness, irritability, diarrhoea, skin eruptions, and insomnia, which were collectively called ginseng abuse syndrome (GAS) (94). Critical analysis of this report has shown that there were no controls or analyses to determine the type of ginseng being ingested or the constituents of the preparation taken, and that some of the amounts ingested were clearly excessive (as much as 15 g per day, where the recommended daily dose is 0.5–2 g) (50, 90, 95). When the dose was decreased to 1.7 g/day the symptoms of the “syndrome” were rare. Thus the only conclusion that can be validly extracted from the Siegel study is that the excessive and uncontrolled intake of ginseng products should be avoided (90). One case of ginseng-associated cerebral arteritis has been reported in a patient consuming a high dose of an ethanol extract of ginseng root (approximately 6 g in one dose) (96). However, again the type and quantity of ginseng extract were not reported. Two cases of mydriasis and disturbance in accommodation, as well as dizziness have been reported after ingestion of large doses (3–9 g) of an unspecified type of ginseng preparation (97).
Estrogenic-like side-effects have been reported in both premenopausal and postmenopausal women following the use of ginseng. Seven cases of mastalgia (98–100) and one case of vaginal bleeding in a postmenopausal woman (101) were reported after ingestion of unspecified ginseng products. An increased libido in premenopausal women has also been reported (100). Specific studies on the possible hormonal side-effects of ginseng have been carried out with a standardized ginseng extract (102–104). Under physiological conditions, there is no interaction of the ginseng extract with either cytosolic estrogen receptors isolated from mature rat uterus or progesterone receptors from human myometrium (102). Furthermore, clinical studies have demonstrated that a standardized ginseng extract does not cause a change in male and female hormonal status (103, 104).

Posology
Unless otherwise prescribed, daily dose (taken in the morning): dried root 0.5–2 g by decoction; doses of other preparations should be calculated accordingly (21, 23, 89).

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Radix Glycyrrhizae*

Definition
Radix Glycyrrhizae consists of the dried roots and rhizomes of *Glycyrrhiza glabra* L. and its varieties (1–7) or of *Glycyrrhiza uralensis* Fisch. (6, 7) (Fabaceae).1

Synonyms
*Liquiritae officinalis* Moench is a synonym of *Glycyrrhiza glabra* L. (1).

Selected vernacular names

*Glycyrrhiza glabra* L. and its varieties

*Glycyrrhiza uralensis* Fisch.

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.

1 Glycyrrhiza infl ata Bat. is listed in the Chinese pharmacopoeia (6). However, literature references to botanical, chemical, and biological studies on this species are rare. Therefore, it has not been included in this monograph.
Description

_Glycyrrhiza glabra L. and its varieties_

A perennial plant, up to more than 1m in height, erect, with highly developed stoloniferous roots. Leaves compound, 9–17 alternate imparipinnate leaflets, oblong to elliptical-lanceolate, acute or obtuse; racemes loose, shorter than the leaves or a little longer. Flowers 1 cm long. Flat pods oblong to linear, 1–3 cm long by 6 mm wide, more or less densely echinate glandular, many-seeded or abbreviated, 2- or 3-seeded (1, 11).

_Glycyrrhiza uralensis Fisch._

A perennial glandular herb, 30–100 cm high. Stem erect, with short white hairs and echinate glandular hairs; the lower part of the stem is woody. Leaves alternate, imparipinnate; leaflets 7–17, ovate-elliptical, 2–5.5 cm long by 1–3 cm wide; apex obtuse-rounded; base rounded; both surfaces covered with glandular hairs and short hairs. Stipules lanceolate. Inflorescence an axillary cluster. Flowers purplish, papilionaceous; calyx villous. Fruit a flat pod, oblong, sometimes falcate, 6–9 mm wide, densely covered with brownish echinate glandular hairs. Seeds 2–8. The root is cylindrical, fibrous, flexible, 20–22 cm long and 15 mm in diameter, with or without cork, cork reddish, furrowed, light yellow inside (16).

Plant material of interest: dried root and rhizome

_General appearance_ 

_Glycyrrhiza glabra L. and its varieties_

The commercial variety, _G. glabra var. typica_ Regel & Herd, known as Spanish liquorice, consists generally of roots and rhizomes in nearly cylindrical pieces, up to 1 m long and 5–20 mm in diameter; externally, the bark is brownish grey to dark brown, longitudinally wrinkled, occasionally bearing small dark buds in rhizomes or small circular or transverse rootlet-scarcs in roots. The peeled root is yellow, smooth, fibrous, finely striated; fracture, fibrous in the bark and splintery in the wood; internally, bright yellow. A distinct cambium ring separates the yellowish grey bark from the finely radiate yellow wood; central pith, only in rhizomes (1, 2, 7).

The commercial variety, _G. glabra var. glandulifera_ (Wald et Kit) Regel & Herd, known as Russian liquorice, consists mainly of roots, in cylindrical pieces somewhat tapering and sometimes longitudinally split; 15–40 cm long, 1–5 cm in diameter. The enlarged crown of the root may attain up to 10 cm in diameter; externally, the unpeeled root purplish brown, somewhat scaly, with stem scars at the top; the peeled root yellowish, coarsely striated; fracture as for Spanish type; internally, yellow, radiating (1).
Glycyrrhiza uralensis Fisch.
The roots and rhizomes are cylindrical, fibrous, flexible, 20–100 cm long, 0.6–3.5 cm in diameter, with or without cork. Externally reddish brown or greyish brown, longitudinally wrinkled, furrowed, lenticellate, and with sparse rootlet scars. Texture compact, fracture slightly fibrous, yellowish white, starchy; cambium ring distinct, rays radiate, some with clefts. Rhizomes cylindrical, externally with bud scars, pith present in the centre of fracture (6, 7, 16, 17).

**Organoleptic properties**
Odour slight and characteristic (1, 6, 7); taste, very sweet (1, 6, 7, 13, 15, 17).

**Microscopic characteristics**
In transverse section the cork is thick, brown or purplish brown, formed of several layers of flattened polygonal thin-walled cells; cortex of phelloderm in root somewhat narrow, yellow fibres of parenchyma cells contain isolated prisms of calcium oxalate; phloem, wide, yellow, traversed by numerous wavy parenchymatous medullary rays, 1–8 cells wide and consisting of numerous radial groups of fibres, each surrounded by a crystal sheath of parenchyma cells. Each cell usually contains a prism of calcium oxalate and layers of parenchyma alternating with sieve tissue, the latter occasionally obliterated, appearing as refractive irregular structures; phloem fibres, very long, with very narrow lumen and strongly thickened stratified walls which are cellulosic in the inner part of the phloem and slightly lignified in the outer; xylem, yellow, distinctly radiate; xylem rays, consisting of small pale yellow parenchyma, groups of fibres similar to those of the phloem but more lignified, and surrounded by crystal-sheath, tracheids, and large wide lumen vessels, 80–200 µm in diameter, with thick yellow reticulate walls or with numerous oval bordered pits with slit-shaped openings. Other parenchyma cells contain small round or oval starch granules. Pith, only in rhizome, dark yellow, parenchymatous. Root, with 4-arch primary xylem, no pith and shows 4 broad primary medullary rays, radiating from the centre at right angles to one another. In peeled liquorice, the cork, cortex, and sometimes part of the phloem are absent (1).

**Powdered plant material**
Light yellow in the peeled or brownish yellow or purplish brown in the unpeeled root. Characterized by the numerous fragments of the fibres accompanied by crystal-sheath, the fibres 8–25 µm, mostly 10–15 µm, in diameter; dark yellow fragments of vessels, 80–200 µm in diameter, containing solitary prismatic crystals of calcium oxalate, free or in cells 10–
35 µm (mostly 15–25 µm) long; numerous simple oval, round or fusiform starch granules, free or in parenchyma cells, with no striation but occasionally showing hilum, 2–20 µm (mostly about 10 µm) in diameter; cork may be present (1, 2, 7).

**Geographical distribution**

**Glycyrrhiza glabra**
Native to central and south-western Asia and the Mediterranean region (11, 12, 13). It is cultivated in the Mediterranean basin of Africa, in southern Europe, and in India (1, 11–13).

**Glycyrrhiza uralensis**
Northern China, Mongolia, and Siberia (16, 17).

**General identity tests**
Macroscopic, microscopic, and microchemical examinations (1–7); and thin-layer chromatographic analysis for the presence of glycyrrhizin (2–7).

**Purity tests**

**Microbiology**
The test for *Salmonella* spp. in Radix Glycyrrhizae products should be negative. The maximum acceptable limits of other microorganisms are as follows (18–20). For preparation of decoction: aerobic bacteria—not more than $10^7$/g; fungi—not more than $10^5$/g; *Escherichia coli*—not more than $10^6$/g. Preparations for internal use: aerobic bacteria—not more than $10^5$/g or ml; fungi—not more than $10^4$/g or ml; enterobacteria and certain Gram-negative bacteria—not more than $10^3$/g or ml; *Escherichia coli*—0/g or ml.

**Total ash**
Not more than 7% (6, 7).

**Acid-insoluble ash**
Not more than 2% (1–3, 6, 7).

**Sulfated ash**
Not more than 10% (2).

**Water-soluble extractive**
Not less than 20% (8).

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Dilute alcohol-soluble extractive
Not less than 25% (7).

Pesticide residues
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Glycyrrhizae is not more than 0.05 mg/kg (20). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (18) and guidelines for predicting dietary intake of pesticide residues (21).

Heavy metals
Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (18).

Radioactive residues
For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (18).

Other purity tests
Alcohol-soluble extractive, chemical, and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays
Assay for glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) content (at least 4%) by means of spectrophotometric (1, 2), thin-layer chromatographic–densitometric (22, 23) or high-performance liquid chromatographic methods (24–26).

Major chemical constituents
The major constituents are triterpene saponins. Glycyrrhizin (glycyrrhizic acid, glycyrrhizinic acid) is the major component (2–9%); minor components occur in proportions that vary depending on the species and geographical location (24–27). Glycyrrhizin occurs as a mixture of potassium and calcium salts (9). It is a monodesmoside, which on hydrolysis releases two molecules of D-glucuronic acid and the aglycone glycyrrhetinic (glycyrrhetinic) acid (enoxolone) (28). Glycyrrhizin is generally regarded as the active principle of Radix Glycyrrhizae and is responsible for its sweetness, which is 50 times that of sucrose (27). Flavonoid constituents include liquiritigenin and isoliquiritigenin.
**Dosage forms**
Crude plant material, dried extract and liquid extract. Store in a well-closed container, protected from light and moisture (1, 3).

**Medicinal uses**

*Uses supported by clinical data*
None.

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Uses described in pharmacopoeias and in traditional systems of medicine

As a demulcent in the treatment of sore throats, and as an expectorant in the treatment of coughs and bronchial catarrh. Also in the prophylaxis and treatment of gastric and duodenal ulcers, and dyspepsia (1, 6, 8, 27–29). As an anti-inflammatory agent in the treatment of allergic reactions (27), rheumatism and arthritis (9), to prevent liver toxicity, and to treat tuberculosis and adrenocorticoid insufficiency (9, 30).

Uses described in folk medicine, not supported by experimental or clinical data

As a laxative, emmenagogue, contraceptive, galactagogue, antiasthmatic drug, and antiviral agent (15). In the treatment of dental caries, kidney stones, heart disease (15), “consumption”, epilepsy, loss of appetite, appendicitis, dizziness, tetanus, diphtheria, snake bite, and haemorrhoids (11, 13).

Pharmacology

Experimental pharmacology

The demulcent action of the drug is due primarily to glycyrrhizin (27). The antitussive and expectorant properties of the drug have also been attributed to glycyrrhizin, which accelerates tracheal mucus secretion (27).

The antiulcer activity of Radix Glycyrrhizae has been demonstrated both experimentally and clinically. Intraperitoneal, intraduodenal, or oral administration of aqueous or alcoholic extracts of Radix Glycyrrhizae reduced gastric secretions in rats, and it inhibited the formation of gastric ulcers induced by pyloric ligation, aspirin, and ibuprofen (27, 31–32). Glycyrrhizin and its aglycone (glycyrrhetic acid, enoxolone), two of the active constituents of Radix Glycyrrhizae, both have anti-phlogistic activity and increase the rate of mucus secretion by the gastric mucosa (9). Deglycyrrhizinated liquorice (97% of glycyrrhizin is removed) effectively treated stress-induced ulcers in animal models (31–34). The mechanism of antiulcer activity involves acceleration of mucin excretion through increasing the synthesis of glycoprotein at the gastric mucosa, prolonging the life of the epithelial cells, and antipepsin activity (32).

The spasmolytic activity of Radix Glycyrrhizae has been demonstrated in vivo (guinea-pig, rabbit, and dog) (35–37), and appears to be due to the flavonoids liquiritigenin and isoliquiritigenin (38).
Glycyrrhizin reduces the toxic action of carbon tetrachloride- and galactosamine-induced cytotoxicity in cultured rat hepatocytes, through its antioxidant activity (9, 27). Glycyrrhizin inhibited histamine release from rat mast cells and prevented carbon tetrachloride-induced liver lesions and macrophage-mediated cytotoxicity (27). Intragastic administration of a flavonoid fraction isolated from Radix Glycyrrhizae to mice protected against carbon tetrachloride hepatotoxicity (39). Glycyrrhizin protected the liver apparently through its membrane stabilization effects (27).

The anti-inflammatory and antiallergic actions of the drug have been attributed to the corticosteroid-like activity of glycyrrhizin and glycyrhetic acid (enoxolone). These compounds act indirectly by potentiating the activity of corticosteroids. In vitro, glycyrhetic acid inhibits Δ4β-reductase, an enzyme that competitively inactivates steroid hormones, and 11β-hydroxysteroid dehydrogenase, the enzyme that deactivates cortisol (27). Glycyrrhizin given intraperitoneally suppressed contact dermatitis in mice, and was more effective than prednisolone, but no effects were observed after oral administration (9).

In vitro, the drug inhibits the growth of Bacillus subtilis (40), Mycobacterium tuberculosis (41), Aspergillus spp. (42), Staphylococcus aureus, Mycobacterium smegmatis, and Candida albicans (43).

Clinical pharmacology
Oral administration of Radix Glycyrrhizae to 15 patients with peptic ulcer reduced symptoms and improved healing in 75% of the cases (44). Glycyrrhetic acid (enoxolone), the active constituent, produced its antiulcer activity by inhibiting 15-hydroxyprostaglandin dehydrogenase and Δ13-prostaglandin reductase (45). Inhibition of these two enzymes stimulated an increase in the concentration of prostaglandins E and F2α in the stomach, which promoted the healing of peptic ulcers owing to a cytoprotective effect on the gastric mucosa (45). Carbenoxolone, a derivative of glycyrhetic acid, has been used clinically for years in the treatment of gastric and duodenal ulcers (46).

Oral administration of deglycyrrhizinated liquorice (380 mg, 3 times daily) to 169 patients with chronic duodenal ulcers was as effective as antacid or cimetidine treatments (47). These results indicate that, in addition to glycyrhetic acid, other unidentified constituents of Radix Glycyrrhizae contribute to its antiulcer activity.

Reports on the usefulness of liquorice extracts on body fluid homeostasis in patients with Addison disease are contradictory. One study found no positive effects (48), while three other studies noted an increase in weight gain and sodium retention (49–51).
Radix Glycyrrhizae

Contraindications
Radix Glycyrrhizae is contraindicated in patients with hypertension, cholestatic disorders or cirrhosis of the liver, hypokalaemia, or chronic renal insufficiency, and during pregnancy (9, 29).

Warnings
Prolonged use of large doses (>50g/day) of the drug for extended periods (>6 weeks) may increase water accumulation, causing swelling of the hands and feet. Sodium excretion is reduced and potassium excretion is increased. Blood pressure may rise.

Precautions
General
Radix Glycyrrhizae should not be taken concurrently with corticosteroid treatment. If sore throat or cough persists for more than 3 days, the patient should consult a physician.

Drug interactions
Because it increases potassium loss, Radix Glycyrrhizae should not be administered for prolonged use with thiazide and loop diuretics or cardiac glycosides (29). Because it reduces sodium and water excretion, the effectiveness of drugs used in the treatment of hypertension may be reduced. Radix Glycyrrhizae should not be administered in conjunction with spironolactone or amiloride (52).

Carcinogenesis, mutagenesis, impairment of fertility
Radix Glycyrrhizae is not mutagenic in vitro (53–55).

Pregnancy: teratogenic effects
The drug is not teratogenic in animal models (56).

Pregnancy: non-teratogenic effects
The safety of Radix Glycyrrhizae preparations during pregnancy has not been established. As a precautionary measure the drug should not be used during pregnancy.

Nursing mothers
The safety of Radix Glycyrrhizae preparations during lactation has not been established. As a precautionary measure the drug should not be used during lactation except on medical advice.
Paediatric use
The safety and effectiveness of the drug in children have not been established.

Other precautions
No information available about drug and laboratory test interactions.

Adverse reactions
No adverse reactions have been associated with the drug when used within the recommended dosage and treatment period.

Prolonged use (>6 weeks) of excessive doses (>50 g/day) can lead to pseudoaldosteronism, which includes potassium depletion, sodium retention, oedema, hypertension, and weight gain (9, 57, 58). In rare cases, myoglobinuria and myopathy can occur (59).

Posology
Unless otherwise prescribed, average daily dose of crude plant material, 5–15 g, corresponding to 200–800 mg of glycyrrhizin. Doses of other preparations should be calculated accordingly (29). Radix Glycyrrhizae should not be used for longer than 4–6 weeks without medical advice.

References
Radix Glycyrrhizae

15. Farnsworth NR, ed. *NAPRALERT database*. University of Illinois at Chicago, IL, August 21, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)


Flos Helichrysi arenarii

Definition
Flos Helichrysi arenarii consists of the dried inflorescences of *Helichrysum arenarium* (L.) Moench (Asteraceae) collected during the budding phase (1, 2).

Synonyms
*Antennaria arenarium* L., *Gnaphalium arenarium* L. (3, 4).

Selected vernacular names
Bessmertnik pestshan’i, bonässla, common shrubby everlasting, elicriso, eternal flower, everlasting, evighetsblomster, dwarf everlasting, fleur de pied de chat, flores gnaphalii arenerii, gyllene kattförter, Fuhrmannsrösch- en, goldilocks, harilik käökuld, harnblumen, hietaolkikukka, immortelle, ką kē dā dzeltē, Katzenpfötchenblüten, kumloku buzništši, motten- krautblume, olmezciek, rainblume, ruhr herb, ruhrkraut, sandgold- blume, sandimmortelle, sand-strohblume, sandy everlasting, sandy imm- ortelles, siminoc, stoechados fl os, strawflower, strobloem, Strohblume, suhotsvet, tsmin, yellow chaste weed, yellow chasteweed, yellow immor- telle, zolotistka, zoloto solnetshnoje (4–13).

Geographical distribution
Indigenous to central, eastern, and southern Europe, the plant is both col- lected in the wild and cultivated commercially. The plant also grows in North America. In the Newly Independent States, it is found mainly in the European regions, but it is also grown in central Asia and west Siberia. The main suppliers are the former USSR, Poland and Turkey (5, 7, 14, 15).

Description
A perennial herb, 10–30(60) cm high. Rhizome: short, strong, obliquely descendent, from 1–4 to 5–7(15) mm in diameter. Stems: fertile and ster- ile, erect, unbranched, eglandulous, grey, adpressed-tomentose. Leaves: alternate, grey-tomentose like the stems; basal leaves petiolate, linear-ob lanceolate to spatulate, 7–60 mm long, 2–8 mm wide; stem leaves ses-
sile, lanceolate, narrowing to linear above, sometimes with crisply undul-ate margins. The leaves of sterile stems are oblong-spatulate, oblong-elliptic, restricted to the petiole. Inflorescence: capitula, numerous, globose, 3–6(9) mm in diameter; 10–30(100) capitula grouped in false umbels. Phyllaries, about 50, in 4–6(7) rows, membranous, flat or cucullate, yellow or yellowish-orange; inner ones oblong-spatulate to linear, outer ones obovate or elliptical, hairy. Flowers: hermaphrodite, tubular or tubular-infundibulate; corolla orange; pappus of about 30 yellowish-white hairs, as long as the corolla; pollinated by insects. Fruit: achene, pentagonal, oblong, brown, 0.7–1.2 mm long, with a pappus (3, 5, 14, 16–18).

**Plant material of interest: dried flower heads**

**General appearance**
Flower heads in budding phase or at the beginning of flowering phase, spherical, about 7–9 mm in diameter, yellow, solitary or in groups, tangled together into false umbels. The receptacles are glabrous; the peduncles are woolly-pubescent, up to 1 cm long. The involucral bracts are somewhat spreading, characteristic, straw-like, shiny, imbricate, lemon-yellow in colour; outer bracts are ovate, middle ones are oblong-spatulate, inner ones are narrow, linear. The bracts enclose the tubular and ligulate flowers. The tubular flowers are small, orange-yellow, with a light yellow pappus. The ligulate florets are usually absent or inconspicuous (1, 5).

**Organoleptic properties**
Odour: slightly aromatic; taste: slightly bitter, spicy and aromatic (1, 5).

**Microscopic characteristics**
The bracts epidermis with oblong spongiose cells. The narrow parts of the bracts and the peduncle are covered by numerous, long, slender covering trichomes having few short basal cells and a long terminal cell; glandular trichomes characteristic of the Asteraceae family, with 8–12 cells, each pair of cells superposed on two others. Ovary, oval with unicellular club-shaped glandular trichomes and pappus hairs. Corolla with numerous glandular trichomes having a 12–14-cellular stalk and unicellular head (1, 5).

**Powdered plant material**
No information available.
**General identity tests**
Macroscopic and microscopic examinations, chemical analysis and thin-layer chromatography tests for flavonoids, which are the characteristic constituents (1, 2, 5).

**Purity tests**

*Microbiological*
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (19).

*Chemical*
The thin-layer chromatogram must not show an orange zone above the brownish main zone (purity test for other *Helichrysum* species) (2).

*Foreign organic matter*
Foreign organic matter not more than 0.5%. Maximum 5% of flower heads with long flower stalks greater than 1 cm. Not more than 5% of broken flower heads, with a diameter less than 2 mm (1). Absence of *Helichrysum angustifolium* DC and *H. stoechas* flower heads as adulterants (5). Foreign matter, not more than 2% (2, 20); absence of *H. italicum* (Roth) Guss. and *H. stoechas* flower heads (20).

*Total ash*
Not more than 8% (1). Not more than 7% (2).

*Acid-insoluble ash*
No information available.

*Sulfated ash*
Not more than 8.5% (20).

*Water-soluble extractive*
No information available.

*Alcohol-soluble extractive*
No information available.

*Loss on drying*
Not more than 12% (1). Not more than 10% (21).
**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (22). For other pesticides, see the *European pharmacopoeia* (22) and the WHO guidelines on quality control methods for medicinal plant materials (19) and pesticide residues (23).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (19).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (19) for the analysis of radioactive isotopes.

**Other purity tests**
Content of mineral matter not more than 0.5% (1). Tests for acid-insoluble ash, alcohol-soluble extractive and water-soluble extractive to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 6% of total flavonoids, expressed as isosalipurposide (1). Flavonoids, not less than 0.5% calculated as quercetin (5, 21). Flavonoids, not less than 0.6% calculated as hyperoside (2).

**Major chemical constituents**
The major constituents of the inflorescences are flavonoids: isosalipurposide (approximately 0.4% and pyranone derivatives responsible for the yellow colour of the involucral bracts), naringenin and its 5-O-diglucoside, helichrysin A (salipurposide) and helichrysin B, kaempferol glucosides, apigenin and its 7-O-glucoside, luteolin-7-O-glucoside, quercetin-3-O-glucoside and 3,5-dihydroxy-6,7,8-trimethoxyflavone. Also present are essential oil (approximately 0.05%; β-caryophyllene, heneicosane, linalool, α-terpineol, anethol, thymol, carvacrol and others), phthalides (5-methoxy-7-hydroxy-phthalide and its monoglucoside), coumarins (scopoletin, umbelliferone, aesculetin), pyranone derivatives (the yellow-coloured arenol and homoarenol), sterols (campesterol, β-sitosterol), caffic acid derivatives, polysaccharides, carotenoids, tannins (3, 5, 15, 24–29). The structures of the major constituents are presented below.
Medicinal uses

*Uses supported by clinical data*
No information was found.

*Uses described in pharmacopoeias and well established documents*
Flowers of *Helichrysum arenarium* are used for the treatment of dyspeptic disorders (30).

*Uses described in traditional medicine*
*Helichrysum arenarium* has been known in Europe as a medicinal plant for its choleretic, hepatoprotective and detoxifying activities (27, 31). In traditional medicine, the drug is also employed as a diuretic. The flowers contain antibacterial constituents and bitter substances, which may also promote gastric and pancreatic secretion (32). Used as a mild spasmylytic and as an adjuvant in the treatment of chronic cholecystitis and cramp-like gall-bladder and biliary duct disorders, and peptic discomfort (5, 33). It is also indicated for indigestion as well as for loss of appetite (34–36).

Pharmacology

*Experimental pharmacology*
Radical scavenging and antihyperlipidaemic effects
Methanol extracts of *Helichrysum* species were screened in vitro for antioxidant activity by two complementary test systems (2,2-diphenyl-1-pic-
rylhydrazyl radical (DPPH) free radical-scavenging and β-carotene/linoleic acid). In the first test system, the extracts showed no antioxidant activity. In the second test system, inhibition rates of the oxidation of linoleic acid were comparable to those of the synthetic antioxidant butylated hydroxytoluene (96%). It could be useful to consider use of the extract as an alternative antioxidant for the food processing industries (37).

The antioxidant properties of lyophilized water extracts from the dried inflorescences of *Helichrysum arenarium* with different polyphenol and flavonoid contents were examined in microsomal fractions of rat liver. Enzymatically-induced lipid peroxidation and nicotinamide adenine dinucleotide phosphate (NADPH) cytochrome C-reductase activity in liver microsomes were measured by a spectrophotometric method. The extracts have weak DPPH free radical scavenging activity in microsomal fractions of rat liver at a concentration of 1 µg/ml measured by a chemiluminometric method. The activity was comparable to that of the flavonoid silibinin, the main constituent of *Silybum marianum* (31). Lyophilized water extracts of Flos Helichrysi diminished the enzymatically induced lipid peroxidation and reduced cytochrome C in a concentration-dependent manner. The same extracts inhibited NADPH-induced lipid peroxide formation at a concentration of 20 µg/ml and stimulated NADPH cytochrome C reductase in rat liver microsomes at a concentration of 100 µg/ml. The extracts were observed to be more effective than silibinin at the concentrations tested (38).

A methanolic extract obtained from inflorescences of *Helichrysum arenarium* was evaporated and the dry residue was dissolved in hot water. The solution was stored at 4 ºC and the precipitate discarded. The remaining solution was divided into three aliquots a, b and c. Part a was extracted with ethyl acetate to obtain extract A, part b was extracted with diethyl ether to obtain extract B and part c was subjected to alkaline hydrolysis and then extracted with diethyl ether to obtain extract C. After evaporation, the dry residues A, B and C were further investigated for phenolic compound content by thin-layer chromatography and high-performance liquid chromatography (HPLC), as well as for 2,2-diphenyl-1-picrylhydrazyl-antiradical activity. Residue C exhibited stronger antiradical properties than non-hydrolysed residues A and B. HPLC analysis showed a greater increase in the strong antioxidant, caffeic acid, in residue C, resulting in an increase in the antiradical activity observed with residue C (39).

**Antimicrobial activity**

A 95% ethanol extract of the dried flowers and leaves of the plant was found to have weak antibacterial activity against *Pseudomonas aerugi-
nosa at a concentration of 1mg/ml/agar plate. No activity was exhibited against *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella paratyphi* A, *Salmonella typhi*, *Shigella flexneri* and *Staphylococcus albus* and *Staphylococcus aureus*, at the same concentration (40). Fractionation of the dichloromethane extract of Flos Helichrysi yielded seven isolates, which exhibited varying antimicrobial activity against Gram-positive bacteria (41).

A 10% aqueous extract of the dried flowers of the plant demonstrated antiviral activity against herpes virus (type 2), influenza virus A2 (Manheim 57) and Vaccini virus, and was inactive against poliovirus type II in cell culture (42, 43).

**Spasmolytic activity**

Aqueous solutions of the active constituents of the plant, naringenin-5-glucoside (I), kaempferol-3-glucoside (II) and apigenin, dissolved in phosphate-buffered sodium hydroxide (III) were intravenously injected at a dose of 4 mg/100 g body weight (bw) in rats. All preparations showed spasmolytic activity and had similar choleric effects in rats (approximately 33% of that of dehydrocholic acid). This activity was highest following treatment with extract III, lower for II and least for I. Similar pharmacological tests were carried out with 5-methoxy-7-hydroxyphthalide isolated from the plant, but the results were negative. An alcohol extract containing all flavonoids and an aqueous extract containing no flavonoids (50 mg/100 g bw) were also tested. The extract with all flavonoids demonstrated spasmolytic activity similar to that of preparations I, II and III. The extract containing no flavonoids elicited a spastic response in smooth muscles isolated from rat intestine and gall-bladder. The researchers concluded that the activity of Galenical preparations of *Helichrysum arenarium* depended only on the flavonoid content. Infusions and decoctions (10%) of *Helichrysum arenarium* showed a rather weak spasmolytic effect (44).

**Diuretic activity**

No diuretic activity was observed when a decoction, infusion and various extracts (ether, ethanol, aqueous) of the dried whole plant were administered by the intraduodenal route to dogs and the intragastric route to rats at a dose of 10 mg/kg bw and 50 mg/kg bw, respectively. A parallel pharmacokinetic study in dogs showed poor absorption of the decoction from the gastrointestinal tract. An intravenous injection of the same doses of the drug to dogs had a significant diuretic effect (44).
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Hypotensive activity
Intravenous injection of ethanol, aqueous and ether extracts of dried whole plant to dogs and rats at doses of 50 mg/kg and 500 mg/kg bw, respectively, produced a hypotensive effect (44).

Cytotoxic activity
A 10% aqueous extract of the dried flowers of the plant was inactive against HeLa cells in cell culture (43).

Clinical pharmacology
No information was found.

Adverse reactions
No information was found.

Contraindications
Due to the bile-stimulating effect of the drug, it should not be administered when there is obstruction of the bile ducts due to gallstones. It should only be used in patients with gallstones after consultation with a physician (30, 45).

Precautions
General
Increased health risks or adverse effects following the correct administration of Helichrysum arenarium at therapeutic dosages have not been recorded, however chronic use may cause development of bile congestion (46).

Drug interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
No information was found.

Nursing mothers
No information was found.

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**Pediatric use**
No information was found.

**Dosage forms**
Comminuted herb for teas and other Galenical preparations for internal use (30).

**Posology**
(Unless otherwise indicated)
The average daily dosage is 3 g of the drug or equivalent preparations (30).

*Internal use.* Infusion: one tablespoonful of the infusion (prepared by adding flowers to 200 ml of boiling water and infusing for 15 minutes), three times daily 20–40 minutes before meals (47). Decoction: one tablespoonful of a decoction (prepared by adding 10 g of cut flowers to 200 ml of boiling water and infusing for 30 minutes), three times daily before meals (47). Dry extract: granulated powder from the flowers, 1 g three times daily for 23 weeks (48).

**References**
13. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005 (http://www.napralert.org).
Fructus Hippophaës recens

Definition
Fructus Hippophaës recens consists of the ripe, fresh fruits of *Hippophaë rhamnoides* L. (Elaeagnaceae) (1, 2).

Synonyms

Selected vernacular names
Abm, argasse, argousier, argoussier, astelpaju, bautphut, buckthorn, câtină, câtină albă, charma, ch-liu, chuk, chuma, dhuchuk, duindoorn, echter sanddorn, espino armarillo, espino falso, ghâ, gorra, griset, haft-dorn, kaham, kalabisa, kâm, kando, milech, miles, neichak, oblebiha krušhitovidnaja, olivella spinosa, pangi, sallow thorn, sanddorn, sarla, scheitbeziëen, sea berry, sea buckthorn, seedorn, sendjed-e-talkh, shallow thorn, shawk el qassâr, sirma, sirna, smiltsërkišis, starbu, stechdorn, stranddorn, súl rûmi, suts, olivella, olivello spinoso, rakytnik řešetlákovy, rakytnik řešetliakovitý, ramnoida hiopogevo, tarru, tarwa, tasru, tîrku, tsakanda, tsarap, tsarmaniechak, tsarker, tswak, tynni, vetrice spinosa, weidendorn, willow thorn, yabani igde ağ, zhongguoshaji (4, 6–18).

Geographical distribution
Indigenous to Europe and some northern regions of Asia, it is widely distributed throughout the temperate regions of Asian countries. In the Newly Independent States, it is grown in the Caucasus and the Ural Federal District, in southern Siberia, and also in Altai and the Sayan Mountains. It is domesticated in various parts of the world (4, 9, 19–26).
Description
Shrub or small tree, deciduous, thorny, 1.5–5(10) m tall, with a lifespan of 5–20 years. Extensive root system with nitrogen-fixing nodules. Stems, many stout branches, round greyish-green crown, brown or black rough bark, thorny grey twigs. Leaves, alternate, almost sessile, linear to lanceolate, enrolled margins, dark green on the upper surface, silver-grey on the lower surface, main central vein prominent, 2–8 cm long, up to 8 mm wide. Dioecious, anemophilous. Flowers, unisexual; male flowers in catkin-like spikes, 2-sepalled calyx, brown-spotted ovate sepals, 4 stamens and no corolla; female flowers in short racemes of 2–5 flowers at the axils of the small branches, one pistil; calyx is a tight tube clasping the ovary with erect, inward-inclined tips, brown and reed-like on the outside. The flowers are covered with brownish scaly hairs. The pollinate greenish flowers appear before the leaves. Fruits, oval drupes, 3–11 mm long, 3–5(9) mm in diameter, turn yellow to orange when mature and persist through winter. Seeds, ovate-oblong, 3–7 mm long, 3–5 mm in diameter, dark brown to black, shiny (4, 8, 9, 20, 22, 27–32).

Plant material of interest: ripe fresh berries

General appearance
The fruit is an oval, ovoid or subglobose drupe, with or without peduncle. The fruit contains an embryo encased in a seed coat that is surrounded by a thin seed sac or pericarp, all of which is enclosed in the hypanthium (fleshy portion of the fruit). The shape and colour of the fruits vary. Length between 3.5 and 11 mm and diameter up to 8.8 mm. The colour varies from yellow or bright orange to reddish orange or brownish orange. The content of carotenoids is higher in reddish-orange fruits. The fruits are easily crushed. The seed is oblong, smooth, shiny, with a longitudinal furrow, colour ranges from light or dark brown to nearly black. The average weight of 100 seeds is 1.6–2.1 g, and that of 100 berries is 57–96 g. Harvesting by removing the pedicel from the fruit, rips the epidermis, exposes fruit flesh and results in loss of juice from the fruit (4, 9, 33–35).

Organoleptic properties
Odour: light and pleasant; taste: acid, pineapple-like (9, 33, 34, 36).

Microscopic characteristics
The hypanthium, a false fruit, consists of epicarp and mesocarp. The epicarp has polygonal or polygonal-oval cells with straight irregularly thickened walls and it is confluent with the exterior of the peduncle. The epider-
Fructus Hippophaës recens

mis has corymb-like trichomes characteristic for the Elaeagnaceae. The corymb-like trichomes have a continuous multicellular disc with ray-serrate edge and a multicellular stalk. The trichome stalk consists of 6–8 radial cells, which surround one or a few (2–4) smaller cells; there are numerous solitary stalks after detaching of the broken corymb-like disc. Multicellular stalks are visible through the transparent corymb. The mesocarp of ripened fruit is liquefied. It represents a mixture of entire cells, cytoplasm, oil droplets, chromoplasts and chaotic vascular bundles. The calyx of the fruit is slightly open. There are hairs in the calyx opening, in the seed cavity and on the tail of the seed sac. The peduncle has an epidermis with corymb-like trichomes and external thick-walled cells, cortical parenchyma with sclerenchymatic cells and some primary vascular bundles arranged in circles.

The achene, the true fruit, usually known as the “seed”, consists of tegument, perisperm and endosperm. The tegument is formed by thick-walled palisade cells, perpendicularly arranged on 2–3 layers of compressed parenchyma. The perisperm consists of 3–4 layers of compressed small thin-walled cells. Endosperm is a range of cells containing aleurone. The palisade cells of the cotyledons contain oil and aleurone (2, 37, 38).

**Powdered plant material**
Not applicable to fresh berries.

**General identity tests**
Macroscopic and microscopic examinations, chemical analysis and thin-layer chromatography tests for the characteristic constituents, isorhamnetin and quercetin (39). Flavonoids may be rapidly determined by capillary zone electrophoresis (40).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (41).

**Chemical**
A chromatographic analytical method has been described (42).

**Foreign organic matter**
Not more than 1% fragments of stems and other parts of plant. Not more than 1% of unripe berries. Not more than 2% of fruits damaged by ver-
min. Not more than 35% of bruised fruits if the juice is not lost \((1, 2)\). Not more than 4% in dried fruits \(39\).

**Total ash**
Not more than 1% \((1)\). Not more than 6% in dried fruits \(39\).

**Acid-insoluble ash**
No information available on fresh fruits. Not more than 3% in dried fruits \(39\).

**Sulfated ash**
No information available on fresh fruits. Not less than 25% in dried fruits \(39\).

**Water-soluble extractive**
No information available.

**Alcohol-soluble extractive**
No information available.

**Loss on drying**
Not more than 87% \((1)\).

**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg \((43)\). For other pesticides, see the *European pharmacopoeia* \((43)\) and the WHO guidelines on quality control methods for medicinal plant materials \((41)\) and pesticide residues \((44)\).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials \((41)\).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials \((41)\) for the analysis of radioactive isotopes.

**Other purity tests**
Content of mineral matter not more than 0.5%. Content of acids in the fruits not more than 3% \((1, 2)\). Chemical, sulfated ash, and water-soluble
extractive tests are to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 10 mg% of total carotenoids expressed as β-carotene (1, 2). Not less than 1.5% of total flavonoids, calculated as rutin, based on the dried drug; not less than 0.10% of isorhamnetin, calculated for the dried drug (39).

**Major chemical constituents**
Vitamins and related compounds are the major biologically active constituents. Among these are carotenoids (0.04–0.1%, β- and γ-carotene together with lycopene, zeaxanthine and others), vitamin C (0.2–1.4%), vitamins of the B group (0.1–0.16%), tocopherols and tocotrienols. Other significant constituents are flavonoids (especially kaempferol, isorhamnetin, rutin and catechin, as well as quercetin tri- and tetra-glycosides). The fatty oil (in seeds commonly about 10% and up to 15–16%), consists of triglycerides rich in the two fatty acids, linoleic and α-linolenic acid; other glycerides include 1,3-decapryloyl-2-linoleylglycerol; other major fatty acids are oleic, palmitic, stearic and vaccenic acids). The fruits also contain sterols (up to 0.2% in seeds and 0.04% in soft parts, mainly β-sitosterol), tannins (hippophhaenin A and B), fruit acids (chiefly malic acid), the sugar alcohols: mannitol, inositol and quebrachitol. Minerals present include selenium, zinc, calcium, iron, manganese, potassium, sodium, phosphorus, boron and copper, among others (4, 8, 22, 23, 25, 34, 46–53). The structures of the characteristic constituents are presented below.
Medicinal uses

Uses supported by clinical data
The fruits of *Hippophaë rhamnoides* are used in the treatment of cirrhosis of the liver (54).

Uses described in pharmacopoeias and well established documents
The fruits of *Hippophaë rhamnoides* are used to relieve cough with profuse expectoration, to promote digestion in people with prolonged gastrointestinal transit with abdominal pain, and for treatment of amenorrhea (39). Fruit decoctions are used externally as a wash to treat traumatic swelling and cutaneous eruptions (21).

Uses described in traditional medicine
In the Islamic Republic of Iran, ethanol extracts of *Hippophaë* fruits are used internally as an astringent and anthelminthic. There are data on the use of dried fruits in patients with scurvy. *Hippophaë* fruits have been used extensively in India and Tibet for the treatment of circulatory disorders, ischaemic heart disease and hepatic injury (55, 56).

Pharmacology

Experimental pharmacology
Antioxidant, radioprotective and immunomodulatory activities
The effects of an extract from fresh *H. rhamnoides* fruits and of vitamin E (positive control) against nicotine-induced oxidative stress were assessed in vitro in rat blood. Alterations in erythrocyte malondialdehyde levels, activity of some erythrocyte antioxidant enzymes, and plasma levels of vitamins E and A were determined. Groups of eight rats each were treated with: nicotine (0.5 mg/kg/day, administered intraperitoneally); nicotine + vitamin E (75 mg/kg/day, administered intragastrically); nicotine + extract (1 ml/kg/day, administered intragastrically); and a control group received no treatment. It was observed that nicotine-induced increase of malondialdehyde levels was prevented by the extract and by vitamin E. Nicotine-induced decrease in superoxide dismutase activity was prevented by the extract, but not by vitamin E. Glutathione activity was higher in the group of rats given the extract. These results suggest that extracts of *H. rhamnoides* may prevent nicotine-induced oxidative stress (57). The effect of an ethanol extract of *Hippophaë* fruits on radiation and chemical oxidant-mediated DNA damage was evaluated. Antioxidant activity was assessed using 2-deoxyribose degradation and 2,2-bipiridyl assays in mice. Both the in vitro and ex vivo samples were exposed to gamma ra-
radiation of 1.786 Gy/sec. A dose-dependent inhibition of degradation of 2-deoxyribose was observed with a half maximal inhibitory concentration (IC₅₀) of 500 µg/ml. At concentrations of 100 and 120 µg/ml the extract inhibited radiation and DNA strand-breaks in a dose-dependent manner. At a concentration of 120 µg/ml, the extract induced chromatin compaction. A dose-dependent inhibition of degradation of 2-deoxyribose was observed with an IC₅₀ of 500 µg/ml. At a concentration of 1000 µg/ml, 67% scavenging of hydroxyl radicals was observed. In ex vivo experiments, the extract prevented strand-breaks in a dose-dependent manner with a maximum effective concentration of 100 µg/ml. Post-irradiation treatment with high concentrations of the extract (150 µg/ml or more) resulted in dense compaction of chromatin (58, 59). In another study, an extract of the fresh fruits was investigated for radioprotective effects in mitochondria isolated from mouse liver. Superoxide anions, reduced and oxidized succinate-cytochrome C oxidoreductase, lipid peroxidation and protein oxidation were used to measure extract-mediated radioprotection. Pretreatment of mice with the extract (30 mg/kg body weight (bw) administered intraperitoneally) before irradiation significantly inhibited radiation-induced increases in superoxide anions, glutathione levels, thiobarbituric acid reactive substances, NADH-ubiquinone oxidoreductase, NADH-cytochrome C oxidoreductase activity and mitochondrial membrane potential (p < 0.05). This study suggests that pre-irradiation treatment of mice with the extract protects the functional integrity of the mitochondria from radiation-induced oxidative stress (60). The protective effect of an ethanol extract (30 mg/kg bw) of the fruits against cobalt 60 gamma-irradiation (10 Gy) was evaluated in mice either alone or 30 minutes before irradiation. After 24 hours of irradiation, a significant reduction in splenocyte proliferation was observed (159 ± 45 counts/min/10⁶ cells; in comparison with controls 607 ± 142 counts/min). Treatment with the extract before irradiation reduced the steep decrease and maintained the count at 444 ± 153 counts/min (as measured by the 3H-thymidine uptake method). At 24 hours after irradiation, the CD4/CDB lymphocyte ratio was reduced to 1.5 in comparison with the non-irradiated control (1.9), but treatment with the extract before irradiation resulted in a ratio of 2.1. These findings indicated that the immunostimulatory activity of the extract might play an important role in the manifestation of its radioprotective efficacy (61).

**Neuroprotective action**

An in vivo study examined the effect of juice from *Hippophaë* fruits on lead-induced memory impairment and neuronal damage in the brains of...
mice. Mice were administered an aqueous solution of lead acetate (10 mg/kg bw per day) by intraperitoneal injection for 20 days. The juice (20% and 40%) prevented lead-induced decreases in the step-through latency test. In the water maze test, the swimming time was lengthened in mice treated with lead acetate, but was decreased in mice which received juice. The increase in malondialdehyde levels in lead-treated mice was reduced in a dose-dependent manner by the juice at concentrations of 20% and 40%. The significantly increased activities of acetylcholinesterase and monoamine oxidase in the lead-treated group were decreased by juice at a concentration of 40%. The significantly decreased levels of norepinephrine, serotonin and 5-hydroxyindole acetic acid in the lead-treated mice were normalized by the juice at a concentration of 40% (62).

**Antibacterial activity**
Ethanol and aqueous extracts of *H. rhamnoides* fruits were screened for anti-*Helicobacter pylori* activity in vitro. The final concentrations of extracts in the medium were 200, 100, 60, 40, 20, 10 and 5 µg/ml. By using the agar dilution method, significant anti-*H. pylori* activity was detected at a minimum inhibitory concentration of approximately 60 µg/ml (63).

**Antitumour activity**
An experimental in vivo model of liver, lung and kidney carcinomas was developed by feeding Wistar rats with aminopyrine plus sodium nitrite. The control group received aminopyrine plus sodium nitrite (2 g/kg each), and the other two groups were given aminopyrine plus sodium nitrite with the addition of either ascorbic acid or the juice of *H. rhamnoides*. After 38 weeks, microscopic examination of the livers of the rats in the group that had received the juice showed fewer foci of carcinogenesis than the other groups. In addition, the average life-span was significantly longer (270 days) than that of the animals that received ascorbic acid (195 days, $p < 0.01$). The results suggest that the juice could block the in vivo synthesis of nitroso compounds in rats more effectively than ascorbic acid (64).

**Antimutagenic effects**
A study was performed to investigate the effect of juice from *Hippophaë* fruits against the genotoxic action of cisplatin in male Swiss albino mice. Both positive and negative control groups were included in the study. Freshly prepared juice (0.3 ml) was given to mice by gavage for 5 or 10 days. Three hours after the last gavage, mice received cisplatin at doses of either 1.2 or 2.4 mg/kg bw, administered intraperitoneally. The frequency of micronuclei was studied in bone marrow polychromatic eryth-
Fructus Hippophaës recens

eryocytes 24 hours after the injection of cisplatin. The abnormality of sperm heads was studied by microscopy. Administration of the juice decreased the number of micronuclei in bone marrow cells induced by a dose of 1.2 mg/kg of cisplatin by 36.5% and 47.9% after being given juice for 5 and 10 days, respectively (the difference between the two periods was not significant, \( p > 0.05 \)), and by 19% (a statistically insignificant reduction, \( p > 0.05 \)) when the dose of cisplatin was 2.4 mg/kg. The juice of Fructus Hippophaës recens thus significantly decreased the genotoxic effect of cisplatin (1.2 mg/kg) on somatic (bone marrow) and germ (sperm) cells but the decrease was not significant when the dose of cisplatin was 2.4 mg/kg. The juice similarly protected sperm heads from damage at the lower dose of cisplatin, but there was no significant protection at the higher dose (65).

Toxicology
The median lethal dose (LD\(_{50}\)) of a 50% ethanol-aqueous extract of the fruits has been reported as greater than 1000 mg/kg (administered by intraperitoneal injection) in mice (66).

Clinical pharmacology
Liver cirrhosis
The effect of an ethanol extract of Hippophaë fruits on the liver was assessed in a randomized clinical trial with positive controls in 50 patients with cirrhosis of the liver, which had resulted from hepatitis B or alcoholism (grades A and B according to the Child-Pugh Classification of Severity of Liver Disease). The patients were divided into two groups. Patients in the first group \((n = 30)\) received 15 g of the extract by the oral route, three times a day for 6 months. Subjects in the second group \((n = 20)\) took one tablet of vitamin B complex, three times a day for 6 months. The serum levels of tumour necrosis factor (TNF\(\alpha\)), interleukin-6, serum albumin, type IV collagen, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured before and after the treatment in both groups. These substances have many biological functions, such as promoting cell proliferation and differentiation, and participation in the process of immunological reaction and inflammation. Before treatment, the peripheral blood level of the above-listed factors was significantly higher in the subjects with liver cirrhosis. After a course of treatment with the extract of Hippophaë fruits, the rates of normalization were 80% for ALT and AST, compared to 56% following treatment with vitamin B. The serum levels of collagen type IV, TNF\(\alpha\), and interleukin-6, were significantly lower in the group treated with the extract of Hippophaë fruit than in the group that received vitamin B \((p < 0.05)\).
results showed that the extract of *Hippophaë* fruits could reduce the serum level of factors producing liver fibrosis (54).

**Adverse reactions**
No information was found.

**Contraindications**
If signs of hypersensitivity reactions appear (rash, pruritus, urticaria, swelling of mouth and skin), *Hippophaë* fruits must not be used again.

**Precautions**
If symptoms worsen or persist for longer than 1 week or in any case of unclear symptoms, such as night sweats, increased body temperature or loss of weight, a physician should be consulted.

**Drug interactions**
No information was found.

**Drug and laboratory test interactions**
No information was found.

**Carcinogenesis, mutagenesis, impairment of fertility**
No information was found.

**Pregnancy**
No information was found.

**Nursing mothers**
No information was found.

**Paediatric use**
No information was found.

**Dosage forms**
Fresh fruits and derived infusion, tincture, oil, fresh juice and syrup (13, 28, 67).

**Posology**
(Unless otherwise indicated)
For internal use. Infusion: 40–50 g of the fresh fruit per litre of water, 2–3 cups per day (68). Tincture (1:5): 30–50 drops 1–3 times per day (68). Dosage of oil of *Hippophaë* fruit for internal use: one teaspoon 2–3 times daily, 30–40 minutes before meals (69, 70).

For external use. 5–10 ml of oil per tampon, used for wetting of tampons (71).

References
1. Technical standard of USSR, 1989 (TU 64-4-87-89).
14. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005.


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Herba Hyperici*

Definition
Herba Hyperici consists of the dried flowering tops or aerial parts of Hypericum perforatum L. (Clusiaceae) (1–3).

Synonyms
Hypericum officinarum Crantz, Hypericum officinale Gater ex. Steud., Hypericum vulgare Lam. (4). Clusiaceae is also referred to as Guttiferae or Hypericaceae.

Selected vernacular names
Balsana, bassan, bossant, common St John’s Wort, corazóncillo, dendlu, devil’s scourge, echtes Johanniskraut, Eisenblut, erba di San Giovanni, flor de sao joao, fuga daemonum, hardhay, Hartheu, herbe à mille trous, herbe de millepertuis, Herrgottsblut, Hexenkraut, hierba de San Juan, hiperico, hipericon, houfarighoun, iperico, Jageteufel, Johannisblut, Johanniskraut, John’s wort, Jottannesort, klamath weed, Konradskraut, Liebeskraut, Lord God’s wonder plant, Mannskraft, millepertuis, pelicao, perforata, perforate St John’s wort, pinillo de oro, quian-ceng lou, St Jan’s kraut, St John’s Wort, seiyouotogiri, sint janskuid, tenturotou, Teufelsflucht, Tüpfelhartheu, witches’s herb, zwieroboij (2, 4–7).

Geographical distribution
Indigenous to northern Africa, South Africa, South America, Asia, Australia, Europe and New Zealand, and is naturalized in the United States of America (2, 7, 8). The plant material is harvested at flowering time (1).

Description
A herbaceous, aromatic perennial plant, up to 1 m high; glabrous throughout, green or sometimes glaucous. Stems rounded, 2-winged, erect and branched at top. Leaves oval, linear-oblong, broadly elliptic, subcordate,

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

flat or more or less revolute-marginated with pellucid glands and sometimes a number of brown-black glandular dots. Flowers numerous, forming a broadly paniculate, compound cymose inflorescence. Petals oblong to oblong-elliptic, inequilateral with numerous glandular dots. Seed 1 mm long, cylindrical, brown, minutely pitted longitudinally (2, 8, 9).

**Plant material of interest: dried flowering tops or aerial parts**

**General appearance**
Stem glabrous greenish-yellow to brownish-yellow branching, 2-winged, cylindrical with 2 equidistant longitudinal bands. Leaves glabrous, generally sessile, opposite, greenish-grey, oval, 8–35 mm long, with entire margins; laminal margin often more or less revolute-marginated. Brown-black glandular dots sometimes present along the edges; numerous pellucid glands on the entire surface. Flowers, 2 cm in diameter, regular, forming a broadly paniculate, compound cymose inflorescence at top of stem, composed of: 5 green, lanceolate sepals, containing punctiform, black glandular dots on the edges; 5 golden-yellow petals, with numerous glandular dots along margins; and 3 staminal blades, each divided into multiple golden-yellow stamens. Anthers with single, terminal, dark pigment dot. Ovary elongated and conical, parietal placentation, carries 3 styles. Fruits trilocular capsules containing numerous brown, triangular seeds (1–3, 9).

**Organoleptic properties**
Odour: weak, aromatic, balsamic; taste: bitter, acrid (9–11).

**Microscopic characteristics**
Transverse section of the stem circular and presents 2 lateral edges corresponding to the 2 longitudinal bands. From the exterior inwards are seen: epidermal layer formed of large polygonal cells; continuous collenchymal layer, slightly more developed at the 2 lateral edges; a cortical parenchyma containing crystals of calcium oxalate in the shape of a sea urchin; a ring of continuous phloem, distinct from the xylem, which consists of large vessels and a lignified parenchyma with a visible cambium; and a lacunose medullary parenchyma. Secretory pockets, almost invisible, rarely present in the endoderm. Upper surface of leaf section shows polygonal cells with sinuous, slightly beaded, anticlinal walls; cells of lower surface smaller, anticlinal walls more wavy with frequent paracytic, sometimes anomocytic, stomata; smooth cuticle, thicker on upper surface; straight-walled, elongated epidermal cells of veins occasionally
beaded. Dorsodorsal surface of leaf consists of a single palisade layer and large oil glands. Midrib shows single, collateral bundle with small area of lignified xylem. Microscopic characteristics of the sepal resemble those of the leaf. Petal narrow, elongated, thin-walled, epidermal cells with straight anticlinal walls on outer surface and wavy on inner surface. Stamens lignified fibrous layer of anther wall; elongated, thin-walled cells of filament with striated cuticle. Pollen grains spherical or elliptical, 20–28 µm in diameter, with 3 germinal pores and smooth exine. Ovary small polygonal cells with underlying oil glands. Seed testa brown, thick-walled hexagonal cells (2, 3, 9).

**Powdered plant material**

Yellowish-green or brownish-green. Leaf fragments abundant, most containing large characteristic hypericin oil glands with brown to red contents. Fragments of leaf epidermis, the adaxial side with thick-walled punctate, slightly sinuate cells, and abaxial side with sinuate cells and paracytic stomata; mesophyll fragments with large secretory pockets which are spherical, bright, containing strongly refractive oil droplets; fragments of palisade parenchyma; stem fragments with reticulate spiral vessels, areolate punctation, long fibres with thick walls, ligneous parenchyma, and small number of thick-walled, characteristically punctate medullary cells; fragments of petals made of elongated rectangular cells with irregular nodulous thickenings, containing numerous yellow droplets and large, round to oval secretory pockets; fragments of anthers; pollen grains 20–28 µm in diameter, smooth spherical or elliptical with 3 germinal pores; clusters of calcium oxalate crystals (1, 2).

**General identity tests**

Macroscopic and microscopic examinations and thin-layer chromatography for the presence of characteristic compounds (hypericin, pseudohypericin, chlorogenic acid, hyperoside) (1, 9–11). Additionally, a liquid chromatography–mass spectrometry method is available (12). The presence of hyperforin and rutin in Herba Hyperici is used to differentiate Hypericum perforatum from other Hypericum species (2).

**Purity tests**

**Microbiological**

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (13).
Foreign organic matter
Not more than 3% stems with a diameter greater than 5 mm (1) and not more than 2% other foreign matter (1, 3).

Total ash
Not more than 7% (1).

Acid-insoluble ash
Not more than 2.5% (9).

Sulfated ash
Not more than 2.5% (9).

Water-soluble extractive
Not less than 12% (9).

Loss on drying
Not more than 10% (1, 3).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (14). For other pesticides, see the European pharmacopoeia (14), and the WHO guidelines on quality control methods for medicinal plants (13) and pesticide residues (15).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (13).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (13) for the analysis of radioactive isotopes.

Other purity tests
Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Contains not less than 0.08% hypericins calculated as hypericin, as determined by spectrophotometry (1). Quantitation can also be obtained by high-performance liquid chromatography (2, 16).
Major chemical constituents
The major characteristic constituents include 0.05–0.30% naphthodianthrones (hypericin, pseudohypericin, hyperforin, adhyperforin); 2–4% flavonoids (hyperoside, quericitrin, isoquercitrin, rutin); and 7–15% catechin tannins (2, 4, 7, 17). The structures of the representative constituents are presented below.

![Diagram of chemical structures](image)

<table>
<thead>
<tr>
<th>Substance</th>
<th>R Value</th>
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<tbody>
<tr>
<td>hypericin</td>
<td>H</td>
</tr>
<tr>
<td>pseudohypericin</td>
<td>OH</td>
</tr>
<tr>
<td>hyperforin</td>
<td>H</td>
</tr>
<tr>
<td>adhyperforin</td>
<td>CH₃</td>
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<tr>
<td>and epimer at C*</td>
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</tbody>
</table>

hypericin \( R = H \)

pseudohypericin \( R = OH \)

hyperforin \( R = H \)

adhyperforin \( R = CH₃ \)
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Medicinal uses

Uses supported by clinical data
Symptomatic treatment of mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in the International statistical classification of diseases and related health problems, Tenth revision (ICD-10) (18)) (19–31).
**Uses reported in pharmacopoeias and in traditional systems of medicine**

Externally for the treatment of minor cuts, burns and skin ulcers (8, 32). Topically for viral infections (33).

**Uses described in folk medicine, not supported by experimental or clinical data**

As an antiphlogistic agent in the treatment of inflammation of the bronchi and urogenital tract; treatment of biliary disorders, bladder irritation, the common cold, diabetes mellitus, dyspepsia, haemorrhoids, neuralgia, migraine headaches, sciatica and ulcers (5, 8). Also used as a diuretic, an emmenagogue and an antimalarial agent (5, 8).

**Pharmacology**

**Experimental pharmacology**

**Antidepressant activity**

Behavioural studies, performed primarily in rodents, have demonstrated the antidepressant activity of Herba Hyperici by measuring the exploratory and locomotor activities of animals in an unknown environment (34, 35). Intragastric administration of a 95% ethanol extract of the herb to male gerbils (2 mg/kg body weight) suppressed clonidine-induced depression. Intragastric administration of the extract to male mice (5 mg/kg body weight) enhanced exploratory activity in a foreign environment and significantly prolonged narcotic-induced sleeping time in a dose-dependent manner; the treated mice also exhibited reserpine antagonism. Similar to standard antidepressant drugs, the extract (6 mg/kg body weight) increased the activity of mice in the waterwheel test following a single dose; prolonged administration (6 mg/kg body weight, daily for 3 weeks) decreased aggressiveness in socially isolated male mice (35). Intraperitoneal administration of a 50% ethanol extract of the herb to mice (250 mg/kg body weight) reduced the tail flick response to radiant heat, and significantly decreased swimming time in the forced swimming test ($P < 0.05$) and walking time on a rotating rod ($P < 0.005$), as well as exploratory activity ($P < 0.05$) (36). Significant, dose-dependent, antidepressant activities were observed in the behavioural despair test and the learned helplessness paradigm in rats treated intragastrically with a carbon dioxide extract of the crude drug containing 38.8% hyperforin (30 mg/kg body weight) or an ethanol extract containing 4.5% hyperforin (300 mg/kg body weight) ($P < 0.001$). The results were comparable to those obtained following intraperitoneal administration of imipramine (10 mg/kg body weight) (37). Intragastric adminis-
tration of an ethanol extract containing 4.5% hyperforin (50, 150 and 300 mg/kg body weight, daily for 3 days) or a carbon dioxide extract devoid of hypericin but containing 38.8% hyperforin (5, 15 and 30 mg/kg body weight, daily for 3 days) had similar antidepressant activity in rodents (rats and mice) (38, 39). In the same dosage range, the ethanol extract potentiated dopaminergic behavioural responses, whereas these effects were either absent or less pronounced in rodents treated with the carbon dioxide extract. In contrast, serotonergic effects of the carbon dioxide extract were more pronounced than those of the ethanol extract (38). Intragastric administration of a methanol extract containing both hypericin and pseudohypericin (500 mg/kg body weight) to mice produced a dose-dependent increase in ketamine-induced sleeping time and also increased body temperature. The extract also decreased immobility time in the tail suspension test and forced swimming tests, which are both regarded as indicative of antidepressant activity (40). Intragastric administration of a 50% ethanol extract of the herb prolonged pentobarbital-induced sleeping time (13.25 mg/kg body weight) and depressed the central nervous system in male mice (25.50 mg/kg body weight). The observed effects were similar to those seen in mice treated with diazepam (2 mg/kg body weight) (41). Measurement of some metabolites of biological amines in the urine of various animal models has established a correlation between the excretion in the urine of 3-methoxy-4-hydroxyphenylglycol, the main metabolite of noradrenaline, with the start of the therapeutic antidepressant activity (42).

A hydroalcoholic extract of the herb inhibited serotonin (5-hydroxytryptamine, 5-HT) receptor expression in mouse brain synaptosome preparations in vitro (50 µmol/l), and similar effects were observed during ex vivo experiments (43). In other studies, hydroalcoholic extracts of the herb inhibited serotonin reuptake (IC_{50} 6.2–25.0 µg/ml) (44, 45), and inhibited both γ-aminobutyric acid (GABA) reuptake (IC_{50} 1 µg/ml) and GABA type A receptor binding (IC_{30} 3 µg/ml) in vitro (46).

A hydroalcoholic extract of the fresh flowers and buds of _H. perforatum_ (containing 0.1% hypericin) was subjected to a series of assays involving 39 receptor types and two enzymes. Receptor assays exhibiting at least 50% radioligand displacement or 50% inhibition of monamine oxidase (MAO) were considered to be active. The extract demonstrated specific affinity for the GABA (types A and B), serotonin, benzodiazepine and inositol triphosphate receptors, nonspecific affinity for adenosine receptors and inhibited MAO types A and B. Purified hypericin lacked any significant MAO (type A or B)-inhibitory activity at concentrations up to 10 µmol/l, and had affinity only for N-methyl-D-aspartate (NMDA) receptors in rat forebrain membranes (47).
An ethanol extract of the herb inhibited radioligand binding to the NMDA, GABA type A and GABA type B receptors (IC$_{50}$ 7.025, 3.240 and 3.310 µg/ml, respectively). The extract also inhibited synaptosomal GABA and L-glutamate uptake in vitro (IC$_{50}$ 1.11 and 21.25 µg/ml, respectively) (48).

A methanol or carbon dioxide extract of the herb, and pure hyperforin significantly inhibited synaptosomal uptake of serotonin, noradrenaline, dopamine, L-glutamate and GABA in vitro (49). The carbon dioxide extract (containing 38.8% hyperforin) was more active than the methanol extract (containing 4.5% hyperforin), due to the higher hyperforin concentration. Inhibition was most pronounced with purified hyperforin, showing the following order of affinity: noradrenaline ≥ dopamine > GABA ≥ serotonin >> glutamate (IC$_{50}$ 0.043–0.445 µg/ml) (49, 50). Neither hyperforin nor the carbon dioxide extract inhibited the activity of MAO type A or B at concentrations up to 50 µg/ml (49).

A methanol extract of dried _H. perforatum_ flowers inhibited radio-labelled-flumazenil binding to the benzodiazepine sites of the GABA receptor in rat brain preparations in vitro (IC$_{50}$ 6.83 µg/ml) (51). The number of serotonergic 5-HT$_1$A and 5-HT$_2$A receptors significantly increased in the brains of rats treated with an ethanol extract of the herb (2.7 g/kg body weight) daily for 26 weeks, whereas the affinity of both serotonergic receptors remained unaltered. These data suggest that prolonged administration of the extract induced upregulation of the 5-HT$_1$A and 5-HT$_2$A receptors (52). The affinity of hypericin for 30 types of receptor and reuptake sites was determined in vitro. At 1 µmol/l, hypericin inhibited less than 40% specific radioligand binding at all sites tested, except binding at the acetylcholine and sigma receptors (53).

The mechanism of the antidepressant effect of Herba Hyperici is not well understood. Early studies focused on the inhibition of MAO and catechol-O-methyltransferase (COMT), the two enzymes responsible for the catabolism of biological amines, such as serotonin. Initial investigations analysed the in vitro inhibition of MAO using a series of xanthones isolated from extracts of the herb (54, 55). In later studies, hypericin was reported to inhibit MAO type A (IC$_{50}$ 6.8 × 10$^{-5}$ mol/l) and type B (IC$_{50}$ 4.2 × 10$^{-5}$ mol/l) in rat brain mitochondria in vitro (56). However, analysis of the hypericin fraction used in these experiments revealed that at least 20% of the extract was composed of other constituents, including some flavonoid derivatives (8). Xanthone-containing fractions, free of hypericin and tannins, of a hydroalcoholic extract of _H. perforatum_ showed significant inhibition in vitro of MAO type A (which is specific for serotonin) (57). In other investigations, only the flavone aglycone,
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quercitrin, and the xanthone derivative, norethyriol, showed significant inhibition of MAO type A (57–59). Hypericin was excluded as the active constituent, and the flavonols and 1,3,6,7-tetrahydroxynanthone were reported to be the active constituents of a crude extract of the herb (57–59). Molecular modelling studies of the constituents of the herb also indicated that the flavonoids may be the most likely candidates for inhibitors of MAO, as their structures are similar to those of known MAO type A inhibitors, toloxotone and brofaromine (60).

The MAO-inhibiting activity of six fractions of a hydroalcoholic extract of the herb was determined in vitro and ex vivo. In vitro inhibition of MAO type A in rat brain homogenates could only be shown at a concentration of 1–10 mmol/l of a crude extract or a flavonoid-rich fraction. In ex vivo studies using albino rats, neither the crude extract nor the xanthone-containing fractions inhibited MAO type A or MAO type B after intraperitoneal administration of 300 mg/kg body weight of the extract or 1–10 nmol/l of the fractions. In addition, purified hypericin did not inhibit MAO type A either in vitro or ex vivo (61).

The in vitro effects of hypericin, an ethanol extract, and fractions of the extract were tested for inhibition of MAO and COMT obtained from pig liver. Inhibition of MAO was seen with hypericin (1 mmol/l),1 ethanol extract (0.1 mmol/l),1 and a fraction containing hypericins and flavonols (0.01 mmol/l).1 Weak inhibition of COMT was observed with hypericin and the ethanol extract (both at a concentration of 1 mmol/l),1 whereas two fractions, containing flavonols and xanthones, inhibited COMT to a greater extent at 0.1 mmol/l 1 (62). However, the inhibitory concentrations observed during this study appear to be too high to be of any clinical significance.

Other possible mechanisms of the antidepressant effect of Herba Hyperici include its ability to modulate the production of mediators of inflammation such as cytokines, particularly interleukins. Strong suppression of interleukin-6 (IL-6) release was observed in blood samples from depressed patients treated with H. perforatum extract (63). IL-6 is involved in the modulation of the hypothalamic-pituitary-adrenal (HPA) axis within the nervous/immune system. Elevated IL-6 levels activate the HPA axis, thus increasing levels of adrenal hormones that play a role in depression.

1 Molar concentrations were based on a mean molar mass of 500 (62).

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Effect on smooth muscle contraction
A 95% ethanol extract or tincture of the herb (200 µg/ml) inhibited barium- and histamine-induced smooth muscle contractions of guinea-pig ileum in vitro (64), and contractions of cat and mouse intestine (65). An ethyl acetate extract of the herb (0.1 mg/ml) inhibited potassium chloride- and histamine-induced contractions in pig coronary artery in vitro (66).

Antibacterial and antiviral activity
A methanol extract of Herba Hyperici inhibited the growth in vitro of *Escherichia coli*, *Proteus vulgaris*, *Streptococcus mutans*, *Streptococcus sanguis*, *Staphylococcus oxford* and *Staphylococcus aureus* (MIC 0.31–1.25 mg/ml) (67). An acetone, hot aqueous or ethyl acetate extract of the herb was active against influenza virus A2 (Mannheim 57), herpes simplex virus 2, poliovirus II and vaccinia virus in vitro (68, 69). However, a decoction or hydroalcoholic extract of *H. perforatum* dried stem was not active against herpes simplex virus 1 or 2, or HIV in vitro (100 µg/ml) (70). In vitro activity of hypericin has been demonstrated against Friend murine leukaemia virus, hepatitis B virus, murine cytomegalovirus, human cytomegalovirus (Davis strain), parainfluenza 3 virus, Sindbis virus, vaccinia virus, vesicular stomatitis virus and equine infectious anaemia virus (71–77). Hypericin and pseudohypericin also inhibited herpes simplex virus types 1 and 2, and HIV-1 in vitro (75, 77–83). Hypericin inhibited the activity of HIV reverse transcriptase in vitro (IC₅₀ 0.77 mmol/l) (74, 80, 84), and inhibited herpes simplex virus, Rauscher murine leukaemia and Friend murine leukaemia viruses in mice after intravenous, intraperitoneal or intragastric administration (80–82). Intraperitoneal administration of a 5% aqueous extract of the herb to mice resulted in viricidal activity against tick-borne encephalitis virus (85). Hypericin displayed marginal activity in vitro against Molony murine leukaemia virus and did not show selective activity against herpes simplex virus, influenza virus A, adenovirus or poliovirus (82). However, incubation of the virus with hypericin prior to infection resulted in viricidal activity against all enveloped viruses tested (IC₅₀ 1.56–25 µg/ml), but not against non-enveloped viruses (82). The antiviral activity of hypericin appears to involve a photoactivation process that forms a singlet oxygen and inactivates both viral fusion and syncytia formation (72, 75, 86).

Protein kinase C inhibition
Numerous in vitro studies have demonstrated that hypericin is a potent inhibitor of protein kinase C (87–92). Hypericin treatment of glioma cell lines inhibited growth and also induced cell death due to protein kinase C...
(93). Receptor tyrosine kinase activity of epidermal growth factor is also inhibited by hypericin and may be linked to its antiviral and antineoplastic effects (89, 94). The inhibition of protein kinase C may contribute to the anti-inflammatory effects of Herba Hyperici, as hypericin also inhibited the release of arachidonic acid and leukotriene B4 (94).

**Wound healing**
External application of a 20% aqueous extract of the crude drug to the skin of guinea-pigs and rabbits accelerated healing of experimentally induced wounds (95, 96). Intragastric administration of a 60% ethanol extract of the dried leaves to rats (0.1 ml/animal) accelerated healing of experimentally induced wounds by enhancing the strength and rate of wound contraction and epithelialization (97).

**Clinical pharmacology**
**Antidepressant activity**

**Clinical trials without controls**
The safety and efficacy of oral administration of Herba Hyperici has been assessed in more than 5000 patients in numerous case-reports and studies (22, 23, 31, 98). In a drug-monitoring study involving 3250 patients, 49% were assessed as being mildly depressed, 46% as moderately depressed and 3% as severely depressed at the beginning of the trial. The patients were treated with 300 mg of a dried 80% methanol extract of the herb three times daily, and evaluated after 2 and 4 weeks of therapy. After treatment, 80% of patients had improved or were symptom-free, while 13–16% remained unchanged or were worse. Minor adverse reactions were reported in 2.4% of patients (31). A postmarketing trial was performed with 2404 patients with symptoms of mild to moderate depression who were treated with 2–4 capsules of an ethanol extract of the herb (equivalent to 0.6–1.8 mg total hypericin) daily for 4–6 weeks. Symptomatic improvement was evaluated as good to very good in 77% of patients and satisfactory in 15% (99).

The effects of an ethanol extract of the herb on the electroencephalogram (EEG) of 40 patients with depression were determined following administration of the extract (equivalent to 0.5 mg total hypericin or 1.4 g crude drug) daily for 4 weeks. An increase in theta-activity, a decrease in alpha-activity and no change in beta-activity were observed, indicating the induction of relaxation (100). A significant increase in nocturnal melatonin plasma concentration was observed in 13 healthy subjects treated with a hydroethanolic extract of the herb (equivalent to 0.53 mg total...
hypericin) daily for 3 weeks (101). A significant increase in the concentration of neurotransmitters in the urine was observed 2 hours after administration of a standardized ethanol extract of the crude drug to six women with symptoms of depression (42).

Reviews of clinical trials
The results from over 28 controlled clinical trials involving oral administration of Herba Hyperici have been published. Twelve of the trials, involving 950 patients, were conducted using an ethanol extract of the herb, while the other 16 trials of 1170 patients used a dried 80% methanol extract (26). A systematic review and meta-analysis of 23 of the randomized clinical trials involving 1757 patients assessed the efficacy of the herb in the symptomatic treatment of mild to moderate depression. Twenty trials were double-blind, one was single-blind and two were open studies. Fifteen of the trials involving 1008 patients were placebo-controlled and eight studies of 749 patients were comparison trials with other antidepressant drugs. With the exception of two trials, all studies had treatment periods of 4–8 weeks. The daily dosage ranged from 0.4 to 2.7 mg hypericin in 300–1000 mg of a standardized extract of the herb. Seventeen trials used the Hamilton Rating Scale for Depression (Hamilton Depression Rating Scale), which focuses primarily on somatic symptoms, to measure effectiveness, while 12 trials used the Clinical Global Impression Scale. The latter involves observer-rated analysis of severity of illness, global improvement and efficacy. The meta-analysis concluded that the herb was significantly superior to the placebo and was as effective as standard antidepressants such as maprotiline or imipramine (75 mg three times daily). Fewer side-effects were seen in the herb-treated patients (19.8%) than in those receiving standard antidepressants (52.8%) (21).

A systematic, criteria-based review of 18 controlled clinical trials using either ethanol or methanol extracts of the herb as a treatment for depression was carried out. Twelve of the trials (nine placebo-controlled and three comparison trials) met the methodological inclusion criteria and were included in the review. The results of the cumulative data show that extracts of the herb were superior to the placebo for the symptomatic treatment of depression as measured by the Hamilton Depression Rating Scale. Results of the comparison studies with maprotiline (75 mg daily) and imipramine (50–75 mg daily) and other standard antidepressants suggest that extracts of the herb have a similar therapeutic profile. Some flaws in the reported studies included no intention to treat analysis, lack of control over compliance, and insufficient description of the extract or placebo used (19).
A review of 12 double-blind, placebo-controlled and three comparison clinical trials assessed the efficacy of the herb for the treatment of mild to moderate depression, and the methodology used to perform the studies. The review concluded that the antidepressant activity of a standardized extract of the herb (300 mg standardized to contain 0.9 mg hypericin three times daily for 4–8 weeks) was sufficiently documented. However, it also concluded that no dose-finding studies had been conducted, and that studies on inpatients with severe depression and endogenously depressed patients were lacking. In the three comparison studies, the daily dose of 75 mg maprotiline or 30 mg amitriptyline was viewed as too low. The review concluded that further trials of longer duration in comparison with higher doses of standard antidepressants are warranted (27).

A double-blind, randomized, multicentre study was performed to evaluate the efficacy, safety and tolerability of a daily dose of 900 mg hydroalcoholic extract of the herb or 75 mg amitriptyline. After a 1-week placebo run-in phase, 156 patients were treated with 300 mg extract or 25 mg amitriptyline, three times daily for 6 weeks. The patients were assessed before and after treatment. The Hamilton Depression Rating Scale changed from 20 to 10 in the extract-treated patients and from 21 to 6 in the amitriptyline-treated patients ($P < 0.05$). The Montgomery-Asberg Rating Scale for Depression changed from 27 to 13 in the extract-treated patients, and from 26 to 6.5 in the amitriptyline-treated patients ($P < 0.05$). Similar scores in the Clinical Global Impression Scale were observed in both groups (29). In a randomized, double-blind, multicentre trial the effectiveness of a standardized dried 80% methanol extract of the herb (containing 0.3% hypericin) was compared with that of imipramine in 209 patients with recurrent depressive disorder, current episode severe without psychotic symptoms (18). Patients were treated daily with 1800 mg extract or 150 mg imipramine for 6 weeks. Assessment of patients before and after treatment revealed the following changes. In the Hamilton Depression Rating Scale: from 25.3 to 14.4 in the extract-treated patients, and from 26.1 to 13.4 in the imipramine-treated patients ($P < 0.021$). In the von Zerssen Depression Scale: from 28.9 to 13.6 in the extract-treated patients, and from 26 to 6.5 in the imipramine-treated patients ($P < 0.05$). Results in the Clinical Global Impression Scale showed a trend in favour of imipramine. Although the efficacy of the extract was not significantly different from that of imipramine, analysis of the patient subgroups showed that it was most effective in patients with moderately severe depression (28).

A prospective, randomized, double-blind, placebo-controlled, multicentre study assessed the safety and efficacy of a standardized ethanol ex-
tract of the herb for the treatment of 151 patients with mild and moderate depressive episodes (classified as F32.0 and F32.1, respectively, in ICD-10 (18)). Patients received either one 250 mg tablet of the extract (equivalent to 1 mg hypericin) or a placebo twice daily for 6 weeks. The primary efficacy variable was the Hamilton Depression Rating Scale, and secondary variables were the risk–benefit Clinical Global Impression Scales I–III and Visual Analogue Scale (a validated, patient self-assessment test). Decreases were seen in the Hamilton Depression Rating Scale in 56% of patients treated with the extract, whereas decreases were seen in only 15% of patients who received the placebo (24). A randomized, double-blind, placebo-controlled, multicentre study assessed the clinical efficacy and safety of two extracts of the herb differing in their hyperforin content (0.5% or 5.0% hyperforin) in 147 patients suffering from mild to moderate depression as classified in the Diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV) of the American Psychiatric Association (102). The patients received either 900 mg of one of the extracts or a placebo daily for 42 days. The patients who received the extract containing 5% hyperforin showed the largest decrease in the Hamilton Depression Rating Scale (a reduction of 10.3; \( P = 0.004 \), compared to the placebo). A reduction of 8.5 following treatment with the extract containing 0.5% hyperforin and of 7.9 in the placebo-treated group was seen (20).

In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers treated with a dried hydromethanolic extract of the herb (300 mg three times daily for 4 weeks) showed improved sleep quality with an increase in deep-sleep phases (25). A randomized, double-blind, placebo-controlled study of 54 healthy volunteers evaluated the central pharmacodynamic effects of two extracts of the herb with different hyperforin contents (0.5% or 5.0%) but identical hypericin content. Healthy volunteers received either 900 mg (300 mg three times daily) of one of the extracts or a placebo daily for 8 days. A quantitative topographic electroencephalogram (qEEG) was performed on days 1 and 8 as an indicator of drug-induced pharmacological activity. In both treatment groups, reproducible central pharmacodynamic effects were observed between 4 and 8 hours after administration, and were confirmed on day 8. The extract containing 5% hyperforin showed a marked tendency to produce greater increases in qEEG baseline power performances than the extract containing 0.5% hyperforin. Higher baseline outputs were observed on day 8 in the delta-, theta- and alpha-1 frequencies. Patients treated with the extract containing 5% hyperforin had an increase in qEEG power performance in the delta-frequency after a single dose and in the theta- and alpha-1 frequencies after 8 days of treatment, when compared with placebo treatment (103).
In a double-blind, placebo-controlled, crossover study, 12 healthy volunteers were treated with 900 mg (300 mg three times daily) of a dried hydromethanolic extract of the herb for 6 weeks, and the effects on the EEG were assessed. A reduction in alpha-activity and audiovisual latencies in evoked potentials and an increase in beta- and theta-activities were demonstrated (104). Another randomized, double-blind, clinical trial of 24 healthy volunteers compared the effects of a dried hydromethanolic extract of the herb with those of maprotiline on the resting EEG and audiovisual latencies in evoked potentials. After 4 weeks of treatment, an increase in theta- and beta-2 activity was observed in patients treated with 900 mg of a standardized hydroalcoholic extract (300 mg three times daily), while a decrease in theta-activity was seen in patients treated with 30 mg maprotiline (10 mg three times daily) (105). The extract also induced an increase of deep sleep as demonstrated by visual analysis of the sleeping phases and automatic analysis of slow-wave EEG activities. Rapid eye movement sleep was not influenced (25).

A randomized, single-blind study evaluated the efficacy of the herb for the treatment of seasonal affective disorders (SAD) in conjunction with light therapy. Twenty patients with SAD were treated with 900 mg (300 mg three times daily) of a hydroalcoholic extract of the herb daily for 4 weeks, combined with either bright (3000 lux) or dim light (<300 lux) conditions. Light therapy was carried out for 2 hours daily. A significant reduction of the Hamilton Depression Rating Scale in both groups, but no statistically significant difference between the two groups, was observed (106, 107).

**Photodynamic effects**
The photodynamic effects of hypericin, incorporated into a non-ionic hydrophilic ointment base, were assessed after external application to the skin of patients with herpes communis. The infected dermal surface of treated patients recovered rapidly and the effects lasted in most cases (33).

**Pharmacokinetics**
Single-dose pharmacokinetics of hypericin and pseudohypericin were determined in 12 healthy male volunteers. After a single dose of 300, 900 or 1800 µg extract (equivalent to 250, 750 or 1500 mg hypericin, respectively, and 526, 1578 or 3156 µg pseudohypericin, respectively), plasma levels of the hypericins were measured by high-performance liquid chromatography for up to 3 days. The median plasma levels were 1.5, 4.1 and 14.2 ng/ml for hypericin, and 2.7, 11.7 and 30.6 ng/ml for pseudohypericin, for the three stated doses, respectively. The median half-life of hypericin was
24.8–26.5 hours and 16.3–36.0 hours for pseudohypericin. The median lag-time of absorption was 2.0–2.6 hours for hypericin and 0.3–1.1 hours for pseudohypericin. During long-term dosing (900 mg daily), a steady state was reached after 4 days. The mean maximum plasma level during the steady state was 8.5 ng/ml for hypericin and 5.8 ng/ml for pseudohypericin (108).

A randomized, placebo-controlled clinical trial was performed to evaluate the pharmacokinetics and dermal photosensitivity of hypericin and pseudohypericin in 13 healthy volunteers after administration of a single dose of either a placebo or 900, 1800 or 3600 mg of the extract (equivalent to 0.00, 2.81, 5.62 and 11.25 mg total hypericin [combined hypericin and pseudohypericin], respectively). The maximum total hypericin plasma levels observed at 4 hours after administration were 0, 28, 61 and 159 ng/l, respectively. Before and 4 hours after drug intake, the subjects were exposed to increasing doses of solar-simulated irradiation on small areas of their backs. No dose-related increase in light sensitivity was observed. In the multiple-dose analysis, 50 healthy volunteers received 600 mg extract of the herb three times during 1 day only. A slight increase in solar-simulated irradiation sensitivity was observed (109).

In a randomized, four-way crossover study without controls involving six healthy volunteers, the pharmacokinetics of hyperforin were determined after administration of single doses of 300, 600, 900 or 1200 mg of an alcohol extract containing 5% hyperforin. The maximum plasma level of hyperforin (150 ng/ml) was reached 3.5 hours after administration of 300 mg of the extract. The hyperforin half-life and mean residence time were 9 and 12 hours, respectively. The pharmacokinetics were linear up to 600 mg of the extract. Increasing the dose to 900 or 1200 mg of extract resulted in values for maximum clearance and area under the curve lower than those expected from linear extrapolation of data from the lower doses (110). The pharmacokinetics of hyperforin were studied in nine healthy volunteers, as part of a double-blind, randomized, placebo-controlled study of 54 subjects. The subjects received either a single dose of 900 mg of an alcohol extract containing 5% hyperforin, or 300 mg of an alcohol extract containing 5% hyperforin three times daily for 8 days. No accumulation of hyperforin in the plasma was observed. On the basis of the area under the curve values from the multiple-dose study, the estimated steady-state plasma concentration of hyperforin was approximately 100 ng/ml (110).

**Contraindications**

Herba Hyperici is contraindicated in cases of known allergy to plants of the Clusiaceae family.
Warnings
As with other antidepressant drugs, observation of the therapeutic effects of Herba Hyperici may require 2–4 weeks of therapy. If a significant antidepressant effect is not observed after 6 weeks of treatment, a physician should be consulted.

Precautions

General
Ultraviolet treatments or prolonged exposure to direct sunlight should be avoided when Herba Hyperici is used, as photosensitization may occur in light-sensitive individuals (32). (See Adverse reactions.)

Drug interactions
Although the ingestion of foods containing high concentrations of tyramine such as pickled or smoked foods and cheese, and selective serotonin reuptake inhibitors such as fluoxetine are contraindicated with MAO inhibitors, in vivo data linking Herba Hyperici to MAO inhibition are lacking (111, 112). The combination of Herba Hyperici with other standard antidepressant drugs, such as tricyclic antidepressants or fluoxetine, is not recommended, unless under medical supervision.

There are now numerous reports in the medical literature indicating that Herba Hyperici extracts induce hepatic enzymes that are responsible for drug metabolism and may reduce the serum levels and therapeutic efficacy of drugs (113–117). Coadministration of theophylline with a Herba Hyperici extract lowered the serum level of theophylline in a patient previously stabilized, requiring an increase in the theophylline dose (113). Coadministration of Herba Hyperici and digoxin reduced serum digoxin concentrations after 10 days of treatment (114). A decrease in serum cyclosporin, warfarin and phenprocoumon concentrations was seen in patients after they had additionally taken Herba Hyperici extracts (115). Concomitant use of Herba Hyperici in five patients previously stabilized on serotonin-reuptake inhibitors resulted in symptoms of central serotonin excess (116). The United States Food and Drug Administration has publicized a report concerning a significant drug interaction between Herba Hyperici and indinavir, a protease inhibitor used to treat HIV infections (117). Herba Hyperici substantially reduced indinavir plasma concentrations, due to induction of the cytochrome P450 metabolic pathway. As a consequence, the concomitant use of Herba Hyperici and protease inhibitors or non-nucleoside reverse transcriptase inhibitors is not recommended and may result in suboptimal antiretroviral drug concen-
trations, leading to a loss of virucidal activity and the development of resistance (117).

**Carcinogenesis, mutagenesis, impairment of fertility**

The mutagenicity of hydroalcoholic extracts of Herba Hyperici containing 0.2–0.3% hypericin and 0.35 mg/g quercetin has been studied in various in vitro and in vivo systems (118–121). The in vitro studies were performed using the *Salmonella*/microsome assay, hypoxanthine guanine phosphoribosyl transferase test (up to 4 µl/ml), unscheduled DNA synthesis test (up to 1.37 µl/ml), cell transformation test in Syrian hamster embryo cells (up to 10 µl/ml) and spot test in mice (up to 10 µl/ml). The in vivo tests included the chromosome aberration test with bone marrow cells of Chinese hamsters (10 ml/kg body weight, gastric lavage) and the micronucleus test in rodent bone marrow (2 g/kg body weight, gastric lavage). Although some positive results were observed in vitro in the *Salmonella*/microsome assay (119, 121), all the in vivo tests were negative, indicating that the hydroalcoholic extract was not mutagenic in animals. In a 26-week study, intragastric administration of the hydroalcoholic extract to rats and dogs (900 and 2700 mg/kg body weight) had no effect on fertility, development of the embryo, or pre- or postnatal development (122).

**Other precautions**

No information available on precautions concerning drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Herba Hyperici should not be administered during pregnancy or lactation or to children without medical supervision.

**Adverse reactions**

Phototoxicity has been reported in cattle after ingestion of *H. perforatum* during grazing. However, the doses were estimated to be approximately 30–50 times higher than normal therapeutic doses (123). Photosensitization in light-sensitive individuals has been demonstrated in a controlled clinical trial involving metered doses of hypericin and exposure to ultraviolet A and B irradiation. Patients were treated with 600 mg of a hydroalcoholic extract of the herb (containing 0.24–0.32% total hypericin) three times daily for 15 days. A measurable increase in erythema in light-sensitive individuals was observed after ultraviolet A irradiation. The plasma concentration of hypericin and pseudohypericin in these subjects was double that seen during normal therapeutic treatment of depression (124). A single case of reversible erythema after exposure to ultraviolet B
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has been reported in one patient who had been taking the herb for 3 years (125). A single case of acute neuropathy after exposure to sunlight has been reported in one patient taking the herb (126). Drug-monitoring studies indicate that side-effects of the herb are rare and mild, and include minor gastrointestinal irritations, allergic reactions, tiredness and restlessness. However, these studies did not last longer than 8 weeks (21, 24, 31). Clinical studies have suggested that the use of the herb does not affect general performance or the ability to drive (127, 128).

Dosage forms
Dried crude drug for decoction, powdered drug or extracts in capsules, tablets, tinctures and drops (2, 7, 32). Topical preparations include the oil, infusions, compresses, gels and ointments. Store in a well-closed container, protected from light (10, 11).

Posology
(Unless otherwise indicated)
Daily dosage: 2–4 g crude drug (32). Internal use: standardized tinctures or fluidextracts (23, 98, 100), or standardized hydroethanolic or dried hydromethanolic extracts, up to a daily dose of 900 mg extract (equivalent to 0.2–2.7 mg total hypericin) (19, 21, 22, 27, 31).

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Herba Hyperici


Herba Leonuri

Definition
Herba Leonuri consists of the whole or cut, dried flowering aerial parts of *Leonurus cardiaca* L. (Lamiaceae) (1). According to the USSR Pharmacopoeia, Herba Leonuri consists of the whole or cut, dried aerial parts of *L. cardiaca* L. (*L. cardiaca* L. subsp. *villosum* (Desf.) Jav.) and *L. quinquelobatus* Gilib., collected at the beginning of flowering (2).

Synonyms

Selected vernacular names
Agrimaume, agripalma, agripoume cardiaque, äkta hjärtstilla, arslan kuyruğu, arslonkuiruk, baqlat el amhāt, bonässla, bärenschweif, cardiaca, cardico, cardiaque, coda di leone, common motherwort, common motherwort, common mother-wort, dom-e-shir, echtes Herzgespann, farāsiyūn el qalb, farasyun kalbi, five-lobed bladderwort, herbe battudo, Herzgespann, hjärtstilla, kalomiro, leonuro, lion’s ear, lion’s tail, lääne-südamerohi, Löwenschwanz, melissa salvatica, motherwort, Mutterwurz, nukula, pust’rnik serdechn’i, qafil, roman motherwort, serdetshn’i, shavbalaha, sidrs mātere, talpa gāsttii, throwwort, throw-wort, tsan-ts’ai, wolfstrapp, yabani pirasa, yi-mu-ts,ao (4, 6–15).

Geographical distribution
Indigenous to central and eastern Europe and Scandinavia and Central Asia; also found in Caucasus and western Siberia. It was introduced to North America and has become established in the wild. It is also cultivated (4, 6, 16–21).

Description
A perennial plant, 50–120(200) cm high, short woody rhizome. Stem erect, quadrangular, grooved, hollow, pale green or purplish brown, often
red-violet, may have short hairs on the corners (*L. quinquelobatus* has long prominent hairs on the stem). Leaves decussate, pubescent or glabrous, upper surface green, smooth, lower surface paler and markedly pubescent (veins on the underside of *L. quinquelobatus* leaves are covered by prominent hairs). Leaves, blades broadly ovate to nearly circular in outline, long-petiolated, irregular serrate margin, acute apex, 7–12 cm long; lower leaves 5–7 palmatisect; medium leaves 3-lobed or entire; upper leaves elliptical, ovate base, with two prominent lateral dents, petiole 1–2 cm long (*L. quinquelobatus* has 3-palmatisect or 3-lobed leaves, rarely entire). Inflorescence, long, spike-like, formed by verticillasters of 6–12 small flowers in the axils of the upper leaves. Bracts subulate, short-haired (*L. quinquelobatus* has prominent hairs on the bracts). Calyx green, 5–6 mm long, funnel-shaped, with 5 equal pointed sepals (their triangular apexes are 3–3.5 mm long; two of them are turned down). Corolla 2-lipped, longer than calyx, pink to whitish with purple spots on the 3-lobed lower lip; upper lip entire, hairy on the upper surface (sometimes the upper lip of *L. cardiaca* is glabrous). Stamens 4, under upper lip, stigma 2-lobed. Fruit, triangular nutlet with a tuft of hairs at the tip, brown, 2.5–3 mm long (6, 16, 22–27).

**Plant material of interest: dried aerial parts**

**General appearance**

The stem pieces are hairy, longitudinally striated, quadrangular, hollow, up to about 10 mm wide. They bear decussate, opposite, petiolate leaves and about 6–12 flowers, arranged in sessile whorls forming a long leafy spike. The leaves are ovate-orbicular, palmately 3–5-lobed, rarely 7-lobed, the lobes irregularly dentate. The upper surface of the leaves is green with scattered hairs, the lower surface is paler green, densely pubescent and shows a prominent palmate and reticulate venation. The flowers have a funnel-shaped calyx, 3–5 mm long with stiff, recurved teeth; the corolla is 2-lipped, the upper lip pink and pubescent on the outer surface, the lower lip white with purplish spots; stamens 4, densely pubescent (1).

**Organoletic properties**

Odour: strongly aromatic; taste: bitter (28).

**Microscopic characteristics**

Stem: transverse section shows stem ridged, four-angled with a central hollow; epidermal cells longitudinally elongated with occasional diacytic and anomocytic stomata, and numerous non-glandular trichomes; cover-
Herba Leonuri

ing trichomes, uniseriate, composed of 2–8 cells with slight swellings at the junctions and thick warty walls; glandular trichomes of the typical Lamiaceae type with a short, unicellular stalk and a head composed of a single cell, or less frequently, multicellular and rounded, composed of 4–8 cells; cortex narrow, parenchymatous with collenchyma at the ridges; phloem narrow, thin-walled; xylem lignified with small, spirally and annularly thickened vessels and groups of thick-walled fibres. Leaf: upper epidermal cells of leaf straight-walled with a striated cuticle and scattered large, rounded, diacytic and anomocytic stomata; lower epidermal cells with sinuous walls and more numerous stomata; abundant covering and glandular trichomes on both surfaces, particularly on the lower surface, similar to those occurring on the stem, with both types of glandular trichomes equally numerous. Flower: epidermal cells of the calyx with sinuous anticlinal walls; mesophyll cells containing numerous small cluster crystals of calcium oxalate; inner epidermis of the corolla with very numerous covering trichomes similar to those occurring on the stem and leaves; fibrous layer of the anther; pollen grains spherical, about 25–30 µm in diameter, with 3 pores and 3 furrows and a smooth exine; occasional brown fragments of pericarp with single crystals of calcium oxalate (1, 2, 28, 29).

Powdered plant material
Greenish-grey powder with a strong, aromatic odour and a bitter taste. The powder has the same microscopic characteristics as the entire stem, leaf and flower (see Microscopic characteristics) (28).

General identity tests
Macroscopic and microscopic examinations, luminescence microscopy and thin-layer chromatography for the characteristic constituents, iridoids and flavonoids (1, 2, 5, 28).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (30).

Chemical
No information available.
**Foreign organic matter**
Maximum 2% of brownish or yellowish leaves and maximum 2% other foreign matter (1, 28). Not more than 3% of foreign organic matter. Not more than 46% of stems. Not more than 7% of blackish, brownish and yellowish parts of plant. For cut drug; not more than 17% of fragments having a diameter of more than 7 mm; not more than 16% of fragments having a diameter of less than 0.5 mm (2).

**Total ash**
Not more than 12% (1, 2, 28).

**Acid-insoluble ash**
Ash insoluble in hydrochloric acid not more than 2% (28). Ash insoluble in 10% hydrochloric acid not more than 6% (2).

**Sulfated ash**
No information available.

**Water-soluble extractive**
Not less than 15% (28).

**Alcohol-soluble extractive**
Extractive soluble in 70% ethanol not less than 15% (2).

**Loss on drying**
Not more than 12% (1). Not more than 13% (2).

**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (1). For other pesticides, see the *European pharmacopoeia* (1) and the WHO guidelines on quality control methods for medicinal plant materials (30) and pesticide residues (31).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (30).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (30) for the analysis of radioactive isotopes.

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Other purity tests  
Content of mineral matter not more than 1% (2). Chemical and sulfated ash tests to be established in accordance with national requirements.

Chemical assays  
Contains not less than 0.2% of total flavonoids, expressed as hyperoside (1).

Major chemical constituents  
The major constituents of the aerial parts are flavonoids: O-glycosides of quercetin (including rutin, quercitrin, isoquercitrin, hyperoside), of kaempferol and of apigenin. Also present are the apigenin derivatives genkwanin and quinqueloside, the alkaloids ((–)-stachydrine and leonurine), iridoid glucosides (leonuride, ajugol, galiridoside and reptoside), diterpenoids (leocardin, mixture of 2 clerodane derivatives), cycloleunuripeptides (A, B, C and D), triterpenes (ursolic acid), bitter glycosides, caffeic acid 4-rutinoside and tannins (4, 6, 16–19, 32–39). The structures of the characteristic constituents are presented below.

Medicinal uses  
Uses supported by clinical data  
Positive cardiovascular effects have been reported in open clinical trials (41, 42).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Uses described in pharmacopoeias and well established documents
Herba Leonuri is used against cerebral ischaemia (32). It is also used for treatment of heart palpitations occurring with anxiety attacks or other nervous disorders (6, 43–45).

Uses described in traditional medicine
Traditionally, Herba Leonuri has been used for certain types of heart conditions, simple tachycardia, effort syndrome, and specifically for cardiac symptoms associated with neurosis (28). Herba Leonuri has also been used for urine stimulation, and for removing calculus from kidneys. Used as a remedy for female reproductive disorders; the plant stimulates the muscles of the uterus and is used to treat delayed menstruation, menstrual pain and premenstrual tension (46).

Pharmacology
Experimental pharmacology
Cardiovascular effects
An extract of the dried entire plant has demonstrated antihypertensive activity in rats when administered by intravenous injection at a dose of 50 mg/kg body weight (bw) (47). The effects of aqueous extracts of Herba Leonuri on the contractility of isolated rat aorta were investigated in vitro. Although the aqueous extract (0.3–3 mg/ml) by itself had a limited effect, the extract enhanced phenylephrine-induced contraction of aorta with endothelium. This effect was not seen in studies on the aorta without endothelium. The aqueous extract, like nitro-L-arginine methyl ester, an inhibitor of nitric oxide synthase, significantly inhibited the relaxation induced by acetylcholine in the aorta with endothelium (p < 0.05). Coadministration of the extract with 1 mM of L-arginine reduced the inhibitory effect of the extract on the relaxation of aorta. The vasoconstrictive effect of the extract was not due to leonurine, a constituent of Herba Leonuri, which expressed uterotonic activity. Intravenous injection of the aqueous extract (1.5 mg/kg bw) to rats produced an increase in blood pressure for 5 minutes, similar to that produced by nitro-L-arginine methyl ester (1.35 mg/kg bw). These findings suggest that there is a constituent of Herba Leonuri, which has vasoconstrictive activity in the rat, both in vitro and in vivo, with a similar pharmacological profile to nitro-L-arginine methyl ester (48).

Antioxidant effects
Using antioxidant assays employing 2,2′-azino-bis(3-ethylbenzthiazoline-6-sulfonic acid) and diphenyl-L-picrylhydrazyl in vitro, it was...
demonstrated that in addition to elevating endogenous antioxidant enzyme activity, Herba Leonuri, used traditionally in Chinese herbal medicine for the treatment of cardiovascular disorders, contains a potent antioxidant component capable of effective inhibition of oxidative reactions mediated by the inflammatory oxidants, peroxynitrite, hypochlorous acid and hydroxyl radicals, as well as iron-dependent lipid peroxidation (49).

The antioxidant and cardioprotective effects of an extract of Herba Leonuri on ischaemic myocardium were investigated in rats. A daily dose of the extract (400 mg/kg bw per day) was administered orally starting from 1 week before and continuing until 3 weeks after myocardial infarction. Surviving rats were killed at different times to obtain left ventricles for biochemical assays. The results demonstrated for the first time that Herba Leonuri has antioxidant effects both in vitro and in vivo. The antioxidant effects of the extract are exerted only under the condition of oxidative stress, by selectively preserving the activities of superoxide dismutase and glutathione peroxidase, as well as depressing the formation of malondialdehyde. Its effects of scavenging free radicals and inhibiting the formation of reactive oxygen species probably play a role in protecting the endogenous antioxidant system from oxidative stress in vivo (50).

**Antitumour activity**

Herba Leonuri demonstrated cytotoxicity during in vitro studies on lymphocytic leukaemia (P-388, L-1210), KB cells, human lung carcinoma (A-549), mammary tumour (MCF-7) and human colon tumour cells (HCT-8) (51). Ingestion of the methanol extract of Herba Leonuri in drinking-water at a concentration of 0.5% markedly suppressed the development of mammary cancers in multiparous GR/A mice. The incidence of uterine adenomyosis was also inhibited in mice given an extract of Herba Leonuri. The stimulation by the extract of the excretion of any carcinogenic factors may at least partly contribute to its inhibition of mammary cancers (52).

**Toxicology**

No documented toxicity studies were found, but ursolic acid has been reported to have cytotoxic activity (51). A median lethal dose for the extract of Herba Leonuri in rats of 10.8 g/kg bw by intraperitoneal injection has been recorded (47). In the USA, Herba Leonuri is listed by the US Food and Drug Administration as a “herb of undefined safety” (53).
**Clinical pharmacology**

A 70% ethanol extract of Herba Leonuri was tested in an open clinical study in patients with cardiovascular diseases. An improvement in cardiac activity, and a reduction in blood pressure was observed in 69% of patients (41).

The effect of Herba Leonuri on blood hyperviscosity was investigated in 105 patients. An extract of Herba Leonuri, 10 ml (5 g/ml) in 250 ml of 5% glucose, was given once daily intravenously for 15 days. In 94.5% of patients, improvement was observed. The researchers noted a decrease in blood viscosity and in fibrinogen volume, an increase in the deformability of red blood cells, and a decrease in platelet aggregation (42).

In an open controlled study 121 normal fertile women were given an oral dose of a decoction of Herba Leonuri (30 g dry weight equivalent). An increase in intrauterine pressure in 41.3% of the women was demonstrated. The increase ranged from 150% to more than 300% of spontaneous activity before dosing. Intramuscular injection of ergonovine (positive control) at a dose of 0.2 mg produced a 1% increase in intrauterine pressure. A blind control with water yielded a positive response rate of 2.7%. There were no observable side-effects reported apart from diuresis (54).

The efficacy of several plants (Valeriana, Leonurus, Aralia, Hypericum, Echinopanax, Eleutherococcus, Schizandra, and Panax ginseng) as photoprotectors and photosensitizers was tested by assessing the influence of their extracts on the photochemiluminescence of glycyl-tryptophan solutions. Photosensitization was studied under irradiation with light $\lambda > 280$ nm, as well as with monochromatic light $\lambda = 313$, 365, 405 and 436 nm. All of the plants studied acted as photoprotectors at low concentrations and as photosensitizers at high concentrations. The efficiency of photoprotection or photosensitization of a single dose of plant extracts and their concentration in humans were determined. In order of decreasing effect, the sequence was as follows: Leonurus > Hypericum > Aralia > Schizandra > Echinopanax > Eleutherococcus > Valeriana > Panax ginseng. Photosensitization is attributed to the components of the plant extracts which have strong absorption at high wavelengths (55).

**Adverse reactions**

No information was found.

**Contraindications**

Herba Leonuri should be avoided during pregnancy due to its uterotonic activity, and its ability to affect the menstrual cycle (46, 53). Herba Leon-
uri is also contraindicated in individuals with arterial hypotension and bradycardia (56). If signs of hypersensitivity reactions appear, Herba Leonuri must not be used again (45).

Precautions

**General**
No information was found.

**Drug interactions**
Herba Leonuri strengthens the hypnotic effects of central nervous system depressants, and shows antagonism in relation to analeptic stimulants (21).

**Carcinogenesis, mutagenesis, impairment of fertility**
No information was found.

**Pregnancy**
See Contraindications.

**Nursing mothers**
The use of the plant during breastfeeding should be avoided (53).

**Paediatric use**
No information was found.

**Dosage forms**
Comminuted herb for infusions and other Galenical preparations for internal use.

**Posology**
(Unless otherwise indicated)
The average daily dosage is 2–4.5 g of dried herb or equivalent preparations (28).

*For internal use.* Infusion (2–4.5 g of dried herb in 150 ml boiled water for 10–15 minutes), one tablespoonful three times daily between meals (21). Tincture (1:5 in 45% ethanol) 2–6 ml, three times daily (57). Fluidextract (1:1 in 25% ethanol) 2–6 ml, three times daily (58).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

References
11. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005 (http://www.napralert.org).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Defination
Folium Melissae consists of the dried leaves of *Melissa officinalis* L. (Lamiaceae, Labiatae) (1, 2).

Synonyms

Selected vernacular names
Alahana, appiastro, badarendjabouya, badranjbuyeh, balm, balm mint, bee balm, blue balm, cedronella, citromfülevél, citronelle, citrounado, citrounela, citrounelo, common balm, cure-all, dropsy plant, erva-cidreira-miudade-folha, folia citronellae, franjmeshk, garden-balm, Herzkraut, hhashyshat en-nahl, honey plant, lemon balm, limiera, limouna, limounnet, mallisa, melissa, Melisse, Melissenblätter, Melissenkraut, melisso, melliss, ponciarada, pouncahado, sidrunmeliss, sweet balm, toronjil, toronjil-cidrado, touroudjan, turungan, Zitronenkraut, Zitronenmelisse (4–8).

Geographical distribution
Indigenous to western Asia and the eastern Mediterranean region, and is cultivated in central, eastern and western Europe, and the United States of America (4, 7, 8).

Description
An odorous perennial herb, 0.3–0.9 m high, usually with several stems, lemon-scented on bruising. Stems obtusely quadrangular, furrowed pubescent. Leaves 2–9 cm long and 1–5 cm wide, ovate to obovate-oval, base cuneate truncate or cordate at the base, densely pilose on both surfaces, petiole 0.2–3.5 cm long. Corolla white or pinkish; infundibuliform tube 8–12 mm long; stamens inserted deep in the tube; bracteoles oval-oblong, about 1.5 cm long, pubescent; calyx 5–9 mm long, pubescent outside, pubescent inside (with very short hairs), densely pilose in the middle (4, 8, 9).
Plant material of interest: dried leaves

*General appearance*
Leaves oval, cordate, up to about 8 cm long and 5 cm wide, with more or less long petioles; lamina thin, lower surface has conspicuous, raised, reticulate venation; margins roughly dentate or crenate; upper surface bright green, lower surface lighter in colour (1).

*Organoleptic properties*
Odour: aromatic, lemon-like; taste: aromatic, lemon-like (1).

*Microscopic characteristics*
Dorsoventral epidermal cells with sinuous walls and diacytic stomata on lower surface only; very short, conical, unicellular covering trichomes with a finely striated cuticle occur abundantly, especially over the veins on the lower surface; also uniseriate, multicellular (2–5 cells) covering trichomes, wide at the base and narrowing rapidly toward the tip, with slightly thickened, warty walls; secretory trichomes also very abundant, some small with unicellular stalk and unicellular or bicellular head, others large, of laminaceous type, with unicellular stalk and spherical to ovoid head composed of 8 cells (5).

*Powdered plant material*
Greenish. Fragments of the leaf epidermis with sinuous walls; short, conical, unicellular covering trichomes with a finely striated cuticle; uniseriate, multicellular covering trichomes; 8-celled secretory trichomes of laminaceous type, others with unicellular to tricellular stalks and unicellular or, more rarely, bicellular heads; diacytic stomata, on the lower surface only (1).

*General identity tests*
Macroscopic and microscopic examinations, and thin-layer chromatography for rosmarinic, chlorogenic and caffeic acids (1).

*Purity tests*
*Microbiological*
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (10).
**Folium Melissae**

**Foreign organic matter**
Not more than 2% total foreign matter and not more than 10% of stem fragments with a diameter greater than 1 mm (I).

**Total ash**
Not more than 12% (I).

**Loss on drying**
Not more than 10% (I).

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (11). For other pesticides, see the *European pharmacopoeia* (11), and the WHO guidelines on quality control methods for medicinal plants (10) and pesticide residues (12).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (10).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (10) for the analysis of radioactive isotopes.

**Other purity tests**
Chemical, acid-insoluble ash, sulfated ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 4.0% total hydroxycinnamic acids calculated as rosmarinic acid (I). Quantitative analysis is performed by spectrophotometry at 505 nm (I). Essential oil analysis is carried out according to the method described in the *European pharmacopoeia* (I).

**Major chemical constituents**
The major characteristic constituents are the hydroxycinnamic acids (rosmarinic [up to 6%], p-coumaric, caffeic and chlorogenic acids), and an essential oil (0.02–0.37%) composed of more than 40% monoterpenes and more than 35% sesquiterpenes. The most significant terpenoid com-
ponents are citral (a mixture of the isomers neral and geranial), citronellal, geraniol, nerol, linalool, farnesyl acetate, humulene (α-caryophyllene), β-caryophyllene and eremophilene. Other constituents include flavonoids, tannins and acidic triterpenes (e.g. ursolic and oleanolic acids) (4, 6, 7, 13–15). The structures of the major compound, rosmarinic acid, and terpenoid components are presented below.

![Chemical structures of rosmarinic acid, geranial, neral, geraniol, nerol, and linalool](https://example.com/structures.png)

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Medicinal uses

*Uses supported by clinical data*
Externally, for symptomatic treatment of herpes labialis (16–18).

*Uses described in pharmacopoeias and in traditional systems of medicine*
Orally as a carminative for gastrointestinal disorders, and as a sedative for treatment of nervous disturbances of sleep (5, 15).

*Uses described in folk medicine, not supported by experimental or clinical data*
Treatment of amenorrhoea, asthma, bee stings, coughs, dizziness, dysmenorrhoea, migraine headaches, tachycardia, toothache, tracheobronchitis and urinary incontinence (6, 19).

Pharmacology

*Experimental pharmacology*

**Antiviral activity**
Aqueous extracts of Folium Melissae inhibited the replication in vitro of herpes simplex virus type 2, influenza virus A₂ (Mannheim 57) and vaccinia virus at a concentration of 10% (20). A dried aqueous extract of the leaves inhibited the replication of herpes simplex viruses in vitro at a concentration of 200 µg/ml (18). A condensed tannin isolated from an aqueous extract of the leaves inhibited the replication of influenza virus A₂ and vaccinia virus at a concentration of 200 µg/ml (18).
ous extract of the leaves inhibited haemagglutination induced by Newcastle disease virus or mumps virus; protected eggs and chick cell cultures from infection by Newcastle disease virus; and prevented haemagglutination by Newcastle disease, mumps and parainfluenza viruses 1, 2 and 3, but not by influenza viruses A and B (21). A tannin-free polyphenol fraction of an aqueous extract of the leaves was active against herpes simplex and vaccinia viruses in egg and cell culture systems (22). Aqueous extracts of the leaves have also been reported to have activity against Semliki Forest virus, influenza viruses and myxoviruses in vitro (23, 24).

**Antispasmodic activity**

An ethanol extract of the leaves inhibited histamine- and barium-induced contractions of guinea-pig ileum in vitro (200 µg/ml), while an aqueous extract was inactive (25). A 30% ethanol extract did not inhibit acetylcholine- and histamine-induced contractions in guinea-pig ileum in vitro at concentrations up to 10 µl/ml (26). The essential oil inhibited contractions in guinea-pig ileum, rat duodenum and vas deferens, and rabbit jejunum and aorta in vitro (27, 28). The essential oil also exhibited smooth muscle relaxant activity in guinea-pig tracheal muscle (ED$_{50}$ 22 µg/ml) and in an electrically stimulated ileum myenteric plexus/longitudinal muscle preparation (ED$_{50}$ 7.8 µg/ml) (29).

**Behavioural effects**

Inhalation of the essential oil had a weak tranquillizing effect in mice (30).

**Clinical pharmacology**

An open multicentre study of 115 patients with herpes simplex infections of the skin and transitional mucosa demonstrated that external applications of a 1% lyophilized aqueous extract of Folium Melissae in a cream base reduced the healing time of herpetic lesions from 10–14 days to 6–8 days (18). Treatment with the cream also prolonged the recidivation-free intervals, as compared with other topical virustatic preparations containing idoxuridine and tromantidine hydrochloride (16, 18). A subsequent randomized, double-blind, placebo-controlled study of 116 patients with herpes simplex infections of the skin and transitional mucosa demonstrated a significant reduction in the size of herpetic lesions within 5 days in patients treated with the same cream ($P = 0.01$), as compared with placebo treatment (17, 18).

**Contraindications**

External use: none. Internal use: see Precautions.

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Warnings
No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility
A tincture of Folium Melissae was not mutagenic in vitro (31) and alcohol extracts had antimutagenic activity in vitro (32).

Pregnancy: teratogenic effects
Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

Pregnancy: non-teratogenic effects
Internal use: no information available. Therefore, Folium Melissae should not be administered internally during pregnancy without medical supervision.

Nursing mothers
Internal use: no information available. Therefore, Folium Melissae should not be administered internally during lactation without medical supervision.

Paediatric use
Internal use: no information available. Therefore, Folium Melissae should not be administered internally to children without medical supervision.

Other precautions
No information available on general precautions or precautions concerning drug interactions; or drug and laboratory test interactions; pregnancy.

Adverse reactions
No information available.

Dosage forms
Comminuted crude drug; powder, tea bags, dried and fluidextracts for infusions and other galenical preparations (7, 14, 15). Store in a tightly closed container, protected from light (1). Do not store in plastic containers (7).
Posology
(Unless otherwise indicated)
Daily dosage for oral administration (for gastrointestinal disorders and as a sedative for nervous disturbances of sleep).
Infusion: 1.5–4.5 g crude drug per cup several times daily as needed (15); 45% alcohol extract (1:1): 2–4 ml three times daily (5); tincture (1:5 in 45% alcohol): 2–6 ml three times daily (14).
Daily dosage for topical application (for herpes labialis).
Cream containing 1% of a lyophilized aqueous extract applied 2–4 times daily from the appearance of prodromal signs to a few days after the healing of the lesions, for a maximum of 14 days (14, 18).

References
6. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).


Aetheroleum Menthae Piperitae*

**Definition**
Aetheroleum Menthae Piperitae is the essential oil obtained by steam distillation of the fresh overground parts of *Mentha × piperita* L. (Lamiaceae) (1–4).

**Synonyms**

**Selected vernacular names**
Amentha, american mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nána, ni naa, ni’na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, piperita, pudeena, pum hub, yerba mota (5–7).

**Geographical distribution**
Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (1, 5, 8, 9).

**Description**
A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petiolate, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (3, 8, 10).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
Plant material of interest: essential oil

General appearance
A colourless, pale yellow or pale greenish-yellow liquid (1, 2).

Organoleptic properties
Odour: characteristic, penetrating; taste: characteristic, pungent, followed by a sensation of cold (1, 2).

Microscopic characteristics
Not applicable.

Powdered plant material
Not applicable.

General identity tests
Thin-layer and gas chromatography for characteristic monoterpene profiles (1, 2).

Purity tests

Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (11).

Chemical
Acid value: not more than 1.4 (1, 2).
Relative density: 0.900–0.916 (1–3).
Refractive index: 1.457–1.467 (1–3).
Solvent solubility: miscible with ethanol (96%), ether and methylene chloride (1, 2).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (2). For other pesticides, see the European pharmacopoeia (2), and the WHO guidelines on quality control methods for medicinal plants (11) and pesticide residues (12).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (11).
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (11) for the analysis of radioactive isotopes.

Chemical assays
The monoterpane content determined by gas chromatography should be 1,8-cineole (6–14%), limonene (1–5%), menthone (14–32%), menthofuran (1–9%), isomenthone (2–10%), menthol acetate (3–5%), menthol (30–55%), pulegone (not more than 4.0%) and carvone (not more than 1.0%). The ratio of 1,8-cineole to limonene should be greater than 2.0 (1, 2).

Major chemical constituents
The major constituents are menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (2, 6, 9, 13, 14). The structures of the major monoterpenes, menthol and menthone, are presented below.

Medicinal uses
Uses supported by clinical data
Internally for symptomatic treatment of irritable bowel syndrome (15–20), and digestive disorders such as flatulence and gastritis (21–23). Externally for treatment of myalgia and headache (21, 24–27).

Uses described in pharmacopoeias and in traditional systems of medicine
Internally and externally for the symptomatic treatment of catarrh and coughs (21, 22).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

**Uses described in folk medicine, not supported by experimental or clinical data**

Treatment of dysentery, diabetes, dysmenorrhoea, fevers, jaundice and urinary infections (7).

**Pharmacology**

**Experimental pharmacology**

**Antimicrobial activity**

Aetheroleum Menthae Piperitae inhibited the growth in vitro of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Enterococcus faecalis* and *Escherichia coli* (28–30), but did not affect the growth of *Bacillus cereus*, *Penicillium cyclopium* or *Aspergillus aegyptiacus* (28, 30). The essential oil inhibited the growth in vitro of *Trichophyton equinum* and *T. rubrum* (at a concentration of 0.4 µg/ml) (31), *Aspergillus flavus*, *A. fumigatus* and *A. niger* (32).

**Antispasmodic activity**

The essential oil had smooth muscle relaxant activity in guinea-pig ileum (ED$_{50}$ 26.0 mg/l) and trachea (ED$_{50}$ 87.0 mg/l) in vitro (33), and inhibited electrically induced contractions of guinea-pig ileum (IC$_{50}$ 0.176 mg/ml) in vitro (34). The essential oil decreased both the number and amplitude of spontaneous contractions, and inhibited spasms induced by barium chloride, pilocarpine and physostigmine in isolated segments of rabbit and cat ileum (inhibitory concentrations 0.05 µg/ml) (35). The essential oil (0.5 µmol/l) inhibited smooth muscle contractions of guinea-pig ileum in vitro induced by barium chloride, carbachol, histamine and potassium chloride (36). Both the essential oil and menthol act as calcium antagonists, since they inhibited the influx of calcium ions through smooth muscle of guinea-pig ileum and taenia coli isolated from humans (36–39). The essential oil and menthol inhibited smooth muscle contractions of guinea-pig ileum induced by potassium chloride (IC$_{50}$ 28.1 and 21 µg/ml, respectively) and induced electrically (11.5 and 7.7 µg/ml, respectively) (40). Both also inhibited $^{45}$Ca$^{2+}$ uptake induced by potassium ion-dependent depolarization in brain synaptosomes and retinal neurons, and inhibited specific binding of [³H]nitrendipine to ileal smooth muscle, synaptosomes and retinal neurons (40). The essential oil relaxed carbachol-contracted guinea-pig taenia coli (IC$_{50}$ 22.1 µg/ml), and inhibited spontaneous contractions in isolated guinea-pig colon (IC$_{50}$ 25.9 µg/ml) and rabbit jejunum (IC$_{50}$ 15.2 µg/ml) (41). The essential oil also attenuated contractile responses in guinea-pig taenia coli induced by acetylcholine, histamine, serotonin (5-hydroxytryptamine)
and substance P \((41)\). Contraction of Oddi’s sphincter induced by morphine was reversed after intravenous administration of the essential oil to guinea-pigs \((1.0 \text{ mg/kg body weight})\). However, intravenous injection of the essential oil to guinea-pigs \((25 \text{ mg/kg body weight})\) was found to increase spasms of the sphincter \((42)\). Intragastric administration of the essential oil exhibited cholagogic activity in rats. This activity was attributed to \((-)\)-menthol, a major constituent of the essential oil \((43)\).

**Antifoaming activity**
The essential oil \((0.1\%)\) had antifoaming and carminative activity in vitro; however, the antifoaming effect was less than that observed with a combination of dimethicone and silica \((44)\).

**Toxicology**
Intragastric administration of the essential oil \((100 \text{ mg/kg body weight})\) to rats daily for 28 days induced histopathological changes \((\text{scattered cyst-like spaces})\) in the white matter of the cerebellum. No behavioural or clinical symptoms due to the encephalopathy were observed \((45)\).

**Clinical pharmacology**

**Antispasmodic activity**

**Irritable bowel syndrome**

*Aetheroleum Menthae Piperitae* is a carminative with antispasmodic activity that reduces intracolonic pressure \((22)\). In an open study of 20 patients, an aqueous suspension of peppermint oil \((\text{British Pharmacopoeia Standard})\) injected along the biopsy channel of a colonoscope relieved colonic spasms within 30 seconds, allowing easier passage of the instrument or facilitating polypectomy \((16)\). The essential oil relaxed the oesophageal sphincter when administered orally \((15 \text{ drops [about 0.88 ml] oil in 30 ml water})\), decreasing the pressure differential between the stomach and oesophagus, and allowing reflux to occur \((46)\).

In a double-blind, placebo-controlled, crossover clinical trial, 18 patients with symptoms of irritable bowel syndrome were treated daily with three enteric-coated gelatin capsules, each containing either 0.2 ml essential oil or a placebo for 3 weeks. Patients reported feeling significantly better while taking capsules containing the essential oil than when taking those containing placebo \((P < 0.01)\) and considered the essential oil significantly better than the placebo in relieving abdominal symptoms \((P < 0.005)\) \((19)\). These results were confirmed in a later study \((15)\). A matched-pair, placebo-controlled trial assessed the efficacy of the essential oil in the treatment of 40 patients with symptoms of irritable bowel syndrome. After
14 days of treatment with 1–2 enteric-coated gelatin capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed an increase in intestinal transit time, and subjective improvement in the feeling of fullness, bloating, bowel noises and abdominal pain, as compared with patients who received the placebo (20).

Administration of the essential oil to patients undergoing barium enemas relieved the associated colonic spasms (47, 48). However, two earlier trials failed to confirm the antispasmodic and analgesic activity of the essential oil in the treatment of irritable bowel syndrome (49, 50). A double-blind, placebo-controlled trial assessed the effects of peppermint oil in 34 patients with symptoms of irritable bowel syndrome. After 4 weeks of treatment with two capsules containing either 0.2 ml essential oil or a placebo three times daily, patients treated with the essential oil showed no significant difference in their overall symptoms, as compared with those who received the placebo treatment (49).

A prospective, randomized double-blind, placebo-controlled trial assessed the efficacy and safety of enteric-coated capsules containing 0.2 ml essential oil (one capsule 3–4 times daily for 1 month) for the symptomatic treatment of 110 patients with irritable bowel syndrome. After treatment, 79% of patients in the treatment group and 43% of those in the placebo group experienced alleviation of severe abdominal pain; 83% of the treated group and 32% of the placebo group had reduced abdominal distention and a reduced stool frequency; 73% of the treated group and 31% of the placebo group had fewer bowel noises; and 79% of the treated group and 22% of the placebo group had less flatulence (17).

A review of five randomized, double-blind, placebo-controlled clinical trials assessed the efficacy of the essential oil in the symptomatic treatment of irritable bowel syndrome (18). By measuring the improvement of symptoms, the meta-analysis showed that two of the trials (49, 51) did not show a significant difference between the essential oil and the placebo. However, three of the trials demonstrated significant improvements in symptoms after treatment with the essential oil (15, 19, 52). Although there were methodological flaws in most of the trials analysed, the analysis suggested that there was a significant positive effect of the essential oil ($P < 0.001$) on the symptomatic treatment of irritable bowel syndrome, as compared with the placebo (18).

**Dyspepsia**

A double-blind, placebo-controlled multicentre study involving 45 patients with non-ulcer dyspepsia assessed the change in pain intensity and Clinical Global Impression Scale after treatment with an enteric-coated
capsule containing a combination of the essential oil (90 mg) and caraway oil (50 mg). After 4 weeks of treatment with the essential oil/caraway oil capsules (one capsule three times daily), 63% of patients were free of pain; 89.5% had less pain; and 94.5% showed improvements in the Clinical Global Impression Scale (23). In another study, oral administration of the essential oil (0.2 ml) delayed the gastric emptying time in healthy volunteers and in patients with dyspepsia (53).

**Analgesic activity**

A randomized, double-blind, placebo-controlled, crossover study assessed the efficacy of a combination product of the essential oil (peppermint oil) and Aetheroleum Eucalypti (eucalyptus oil) for headache relief in 32 patients. Five different preparations were used (all in 90% ethanol, to a final weight of 100 g): 10 g peppermint oil and 5 g eucalyptus oil; 10 g peppermint oil and traces of eucalyptus oil; traces of peppermint oil and 5 g eucalyptus oil; and traces of both peppermint oil and eucalyptus oil; or a placebo. The test preparations or placebo were applied topically to large areas of the forehead and temples, and the effects on neurophysiological, psychological and experimental algesimetric parameters were measured. The preparations improved cognitive performance, and induced muscle relaxation and mental relaxation, but had no effect on sensitivity to headache (27). A randomized, double-blind, placebo-controlled study assessed the efficacy of the essential oil in the treatment of 41 patients suffering from chronic tension headache. At each headache episode, patients were treated orally with two capsules of either paracetamol (1 g) or placebo, or external application of 10% essential oil in ethanol, or a placebo solution. Compared with the placebo solution, the 10% essential oil preparation produced a significant ($P < 0.05$) reduction in headache intensity within 15 minutes. Paracetamol was also more effective than the oral placebo but did not differ significantly from topical treatment with the essential oil (54).

**Contraindications**

Preparations of Aetheroleum Menthae Piperitae should not be used internally by patients with inflammation of the gastrointestinal tract or gall bladder, or with impaired liver function (21). Hypersensitivity to the essential oil has been reported (55–57).

**Warnings**

Aetheroleum Menthae Piperitae preparations should not be applied to the face, especially the nose, of infants or young children (21, 22). Keep out of reach of children.
Precautions

General
Patients with achlorhydria (due to medication with histamine H₂ receptor antagonists) should only use enteric-coated preparations (19, 58).

Carcinogenesis, mutagenesis, impairment of fertility
Aetheroleum Menthae Piperitae was not mutagenic in the Salmonella/microsome assay using S. typhimurium strains TA98 and TA1535 (59).

Paediatric use
No information available. Therefore, Aetheroleum Menthae Piperitae should not be administered to children without medical supervision. (See also Contraindications and Warnings.)

Other precautions
No information available on precautions concerning drug interactions; drug and laboratory test interactions; teratogenic and non-teratogenic effects in pregnancy; or nursing mothers. Therefore, Aetheroleum Menthae Piperitae should not be administered during pregnancy or lactation without medical supervision.

Adverse reactions
Following internal administration of Aetheroleum Menthae Piperitae, gastric complaints have been reported in individuals sensitive to the essential oil (21). The use of non-enteric-coated essential oil preparations has occasionally caused heartburn, especially in patients suffering from reflux oesophagitis (58). Skin rashes, headache, heartburn, perianal burning, bradycardia, muscle tremors and ataxia have been reported as rare side-effects, usually associated with overdose (18, 56, 60–65). Recurrent muscle pain has been associated with the ingestion of the essential oil (66). Following external administration of Aetheroleum Menthae Piperitae, skin irritation has been reported (58).

Dosage forms
Essential oil, concentrated peppermint emulsion, peppermint spirit and other galenic preparations (1, 21). Store in a well-closed container, protected from light (1, 2).

Posology
(Unless otherwise indicated)
**Aetheroleum Menthae Piperitae**

**Internal use**
For digestive disorders, daily dosage: 0.2–0.4 ml essential oil three times daily in dilute preparations (58, 67) or suspensions (19). By inhalation: 3–4 drops essential oil in hot water (21). Lozenges: 2–10 mg essential oil per lozenge (58).

For irritable bowel syndrome, daily dosage: 0.2–0.4 ml essential oil three times daily in enteric-coated capsules (21, 58).

**External use**
5–20% essential oil in dilute, semisolid or oily preparations; 5–10% essential oil in aqueous-ethanol; nasal ointments containing 1–5% crude drug (21).

**References**

7. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).


Folium Menthae Piperitae*

Definition
Folium Menthae Piperitae consists of the dried leaves of Mentha × piperita L. (Lamiaceae) (1–3).

Synonyms
Mentha piperita (L.) Huds., M. piperita Stokes, M. balsamea Willd. (1, 4).

Selected vernacular names
Amentha, American mint, balm mint, brandy mint, cabra-caa, curled mint, doun menta piperita, hierbabuena, hortela pimenta, Katzenkraut, lamb mint, la menta, lamint, menta piemonte, mentea peperina, mentha pepe, menthe, menthe anglaise, menthe poivrée, moto yuyo, nâna, ni naa, ni’na el fulfully, pepermin, pepper mint, peppermint, Pfefferminze, Pfefferminzblätter, pipera, pudeena, pum hub, yerba mota (1, 4, 5).

Geographical distribution
Commercially cultivated in eastern and northern Europe and the United States of America, and is found in Africa (1, 3, 6, 7).

Description
A perennial herb, 30–90 cm high. Stems square erect or ascending, branched, the upper portion always quadrangular. Leaves opposite, petio-late, ovate-oblong to oblong-lanceolate, serrate, pointed; dark green on the upper surface. Flowers purplish, occur in thick, terminal, spicoid racemes of verticillasters; each flower shows a tubular calyx with 5 sharp, hairy teeth, a purplish, irregular, 4-cleft corolla, 4 short stamens, a 4-celled ovary and a projecting style ending in a bifid stigma. Fruit consists of 4 ellipsoidal nutlets (1, 7, 8).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
Plant material of interest: dried leaves

General appearance
Green to greenish-brown. Leaves whole, broken or cut; thin, fragile; whole leaf 3–9 cm long and 1–3 cm wide, often crumpled. Lamina oval or lanceolate; apex acuminate; margin sharply dentate; base asymmetrical. Venation pinnate, prominent on the lower surface, with lateral veins leaving the midrib at an angle of about 45°. Lower surface slightly pubescent and secretory trichomes visible under a hand lens as bright yellowish points. Petiole grooved, usually up to 1 mm in diameter and up to 1 cm long (2).

Organoleptic properties
Odour: characteristic, penetrating; taste: characteristic, aromatic (2).

Microscopic characteristics
Upper epidermis composed of large, clear epidermal cells with sinuous, vertical walls and possessing few or no stomata, few glandular trichomes present; palisade parenchyma, comprising a layer of columnar cells rich in chloroplasts; spongy parenchyma, of 4–6 layers of irregularly shaped chlorophyll-containing cells and intercellular air-spaces. Lower epidermis of small epidermal cells with sinuous, vertical walls and numerous diacytic stomata; in the region of veins and midrib, exhibits non-glandular and glandular trichomes as outgrowths; non-glandular trichomes uniseriate, papillose, 1–8-celled; glandular trichomes have 1–2-celled stalk and 1–8-celled glandular head containing the essential oil. Calcium oxalate crystals absent; pollen grains spheroidal and smooth (1, 4, 7, 8).

Powdered plant material
Brownish-green. Fragments of leaf tissue with cells of epidermis having sinuous walls, cuticle striated over the veins, diacytic stomata present predominantly on the lower epidermis; epidermis fragments from near leaf margin with isodiametric cells showing distinct beading and pitting in anticlinal walls; covering trichomes short, conical, unicellular, bicellular or elongated, uniseriate multicellular (3–8 cells) with striated cuticle. Glandular trichomes of 2 types: either with unicellular base with small, rounded, unicellular head 15–25 µm in diameter; or with unicellular base with enlarged, oval multicellular head 55–70 µm in diameter composed of 8 radiating cells; dorsoventral mesophyll fragments with a single palisade layer and 4–6 layers of spongy parenchyma; yellowish crystals of menthol under the cuticle of secretory cells. Calcium oxalate crystals absent (1, 2).

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**General identity tests**
Macroscopic and microscopic examinations, and thin-layer chromatography (1, 2). Gas chromatography of the steam-distilled essential oil (9).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (10).

**Foreign organic matter**
Not more than 5% stems, the diameter of which must be not more than 1.5 mm; not more than 8% leaves showing brown stains due to *Puccinia menthae* (2); not more than 2% other foreign matter (2).

**Total ash**
Not more than 15% according to the *European pharmacopoeia* (2); not more than 12% according to the *African pharmacopoeia* (1).

**Acid-insoluble ash**
Not more than 1.5% (2).

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (2). For other pesticides, see the *European pharmacopoeia* (2), and the WHO guidelines on quality control methods for medicinal plants (10) and pesticide residues (11).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (10).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (10) for the analysis of radioactive isotopes.

**Other purity tests**
Sulfated ash, water-soluble extractive, alcohol-soluble extractive, and loss on drying tests to be established in accordance with national requirements.
Chemical assays
Whole and cut leaves contain not less than 1.2% and 0.9% (v/w) essential oil, respectively, determined as described in the European pharmacopoeia (2).

Major chemical constituents
The major constituent of the leaves is the essential oil (0.5–4%), which contains menthol (30–55%) and menthone (14–32%). Menthol occurs mostly in the free alcohol form, with small quantities as the acetate (3–5%) and valerate esters. Other monoterpenes present include isomenthone (2–10%), 1,8-cineole (6–14%), α-pinene (1.0–1.5%), β-pinene (1–2%), limonene (1–5%), neomenthol (2.5–3.5%) and menthofuran (1–9%) (2, 4, 6, 12, 13).

The structures of the major monoterpenes, menthol and menthone, are presented below.

Medicinal uses
Uses supported by clinical data
None.

Uses described in pharmacopoeias and in traditional systems of medicine
Symptomatic treatment of dyspepsia, flatulence and intestinal colic (1, 3, 14, 15).

Uses described in folk medicine, not supported by experimental or clinical data
As an emmenagogue, vermifuge, lactation enhancer and sedative. Also used to treat bronchitis, bacillary dysentery, diabetes, diarrhoea, dysmenorrhoea, fevers, hypertension, jaundice, nausea, pain, and respiratory and urinary tract infections (5).
Pharmacology

Experimental pharmacology

Antimicrobial activity

Extracts of Folium Menthae Piperitae have antibacterial and antiviral activity in vitro. Addition of ground leaves to the agar medium inhibited the growth of *Salmonella typhimurium*, *Staphylococcus aureus* and *Vibrio parahaemolyticus* at concentrations of 0.1–2.0% (w/v) (16). Aqueous and ethanol extracts of the leaves reduced the number of plaques of the rinderpest virus at concentrations of 4–8 mg/ml (17). Aqueous extracts of the leaves demonstrated activity against the following viruses in egg and cell culture: Newcastle disease, herpes simplex, vaccinia, Semliki Forest and West Nile (18).

Smooth muscle contraction

A 31% ethanol extract of the leaves inhibited both acetylcholine- and histamine-induced smooth muscle contractions in guinea-pig ileum in vitro at a concentration of 10 ml/l (19, 20). The results were similar to those obtained with 0.13 mg atropine (19). An aqueous flavonoid fraction isolated from a leaf extract inhibited barium chloride-induced muscle contractions of guinea-pig ileum in vitro at a concentration corresponding to 0.5 g leaves/ml (21).

Choleretic activity

Injection of a leaf infusion (0.5 ml) or a flavonoid fraction (equivalent to 3.3 g leaves/kg body weight) increased the amount of bile acids in cannulated rats and dogs (dose 0.4 mg/kg body weight) (21, 22). A mixture of flavonoids, isolated from the leaves, had choleretic activity in dogs (2 mg/kg body weight) (23). Flavomentin, a flavonoid isolated from the leaves, stimulated bile secretion and the synthesis of bile acids in dogs (2 mg/kg body weight) (24). Intragastric administration of a 30% ethanol extract of the leaves to rats (1 ml/kg body weight) increased bile flow by 43%. The extract did not induce sedation in mice at doses up to 10 ml/kg body weight (20).

Anti-oedema activity

Topical application of a methanol leaf extract to mice (2.0 mg/ear) inhibited ear oedema induced by 12-O-tetradecanoylphorbol-13-acetate (25).

Analgesic activity

Intragastric administration of a 30% ethanol extract of the leaves inhibited phenylbenzoquinone-induced writhing in mice (ED₅₀ 2.1 ml/kg body weight) (20).
Toxicology
Intragastric administration of a leaf extract (50 g leaves infused with 500 ml hot water for 10 minutes, then spray-dried) to 12 mice (4 g/kg body weight as a single dose) did not result in central nervous system depression, toxic effects or mortality (26).

Clinical pharmacology
None.

Contraindications
No information available.

Warnings
No information available.

Precautions

General
Patients with gallstones should not use Folium Menthae Piperitae unless under medical supervision (15).

Other precautions
No information available on precautions concerning drug interactions; drug and laboratory test interactions; carcinogenesis, mutagenesis, impairment of fertility; teratogenic and non-teratogenic effects in pregnancy; nursing mothers; or paediatric use. Therefore, Folium Menthae Piperitae should not be administered during pregnancy or lactation or to children without medical supervision.

Adverse reactions
No information available.

Dosage forms
Dried leaves (2, 3). Tincture and infusions (6). Store in a well-closed container, protected from light (2).

Posology
(Unless otherwise indicated)
Daily dosage: 1–3 g crude drug three times daily (14, 27). Infusion: pour 150 ml hot water over 1.5–3.0 g (one tablespoon) dried leaves, steep for
10 minutes, strain and drink three times daily between meals (6, 15, 28). Tincture: 2–3 ml (1:5, 45% ethanol) three times daily (14).

References
5. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, February 9, 1998 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Herba Millefolii

Definition
Herba Millefolii consists of the whole or cut, dried flowering tops (1, 2) or aerial parts collected during the flowering season (3, 4) of Achillea millefolium L. (Asteraceae).

Synonyms
Achillea borealis Bong., A. lanulosa Nutt., A. magna auct., A. millefolium ssp. borealis (Bong.) Breitung., A. millefolium ssp. lanulosa (Nutt.) Piper, A. millefolium var. occidentale DC (5).

Selected vernacular names
Achillée, achillenkraut, amelotu, artemisia bastarda, Bauchwehkraut, berbe militaris, biranjasi, bloodwort, bumadaran, carpenter’s grass, carpenter’s weed, chipmunk grass, centofoglie, cickafark, ciento en rama, common yarrow, daun seribu, dog daisy, egel tologch ovs, erba da carpentieri, erba da falegnam, erva d’o marchese, flor de la pluma, gandana, gordoloba, green arrow, herbe au charpentier, herbe de millefeuille, hezarbarg, Jungfrau kraut, Katzenkraut, knight’s milfoil, mil de tama, mil en rama, mil flores, mil hojas, milefolio, milfoil, millefolium, milenrama, nosebleed, old man’s pepper, oum alf ouraka, pharange, saigum, sanguinary, sataraatyoutas, Schafgarbe, Schafgarbenkraut, seiyonokogirisou, seiyonokogirisou, sneezeweed, soldier’s milfoil, straticites, tansy, thou alf ouraka, thousand leaf, thousand leaf grass, thousand seal, thousand weed, trava tysyachelistnik, troneto, umm alf waraqah, western yarrow, wound wort, yarrow, yerba de carpintero, yerba de la muela (2, 6–10).

Geographical distribution
Native to Asia, Europe and North America, now widely distributed and cultivated in the temperate regions of the world (2, 7, 8, 11, 12).

Description
A perennial herb, 30–90 cm in height, with aromatic odour and greyish-green colour from the numerous small hairs; stem angular. Leaves green or
greyish-green, faintly pubescent on the upper surface and more pubescent on the lower surface, 2–3 pinnately divided with linear lobes and a finely pointed whitish tip, alternate, clustered at the base of the stem. Flowering heads (capitula) in a flat-topped corymb (3–5 cm in diameter), small, pedunculate, varying in colour from white to pink, magenta and red; involucral bracts in few rows, the outer somewhat shorter than the inner, with a scarious margin. Outer florets in each capitulum usually 5, female, ligulate with more or less 3-dentate, patent ligules; inner florets hermaphrodite, 5-lobed, with compressed corolla tube and a receptacle scale at the base. Fruit a compressed achene, oblong or obovate, without pappus (1).

Plant material of interest: dried flowering tops and aerial part

General appearance

Flowering tops: Leaves green or greyish-green, faintly pubescent on the upper surface and more pubescent on the lower surface, 2–3 pinnately divided with linear lobes and a finely pointed whitish tip. The capitula are arranged in a corymb at the end of the stem. Each capitulum (3–5 cm in diameter) consists of the receptacle, usually 4 or 5 ligulate ray-florets and 3–20 tubular disc florets. The involucre consists of 3 rows of imbricate lanceolate, pubescent green bracts arranged with a brownish or whitish, membranous margin. The receptacle is slightly convex, and in the axillae of paleae, bears a ligulate ray floret with a 3-lobed, whitish or reddish ligule and tubular disc florets with a radial, 5-lobed, yellowish or light brownish corolla. The pubescent green, partly brown or violet stems are longitudinally furrowed, up to 3 mm thick with a light-coloured medulla (1).

Aerial part: Stems rounded, pubescent, furrowed, usually unbranched, 40 cm or more in length, distinctly woolly, pale green, sometimes purplish. Lanceolate leaves, up to 15 cm in length and 3 cm in width, 2 to 3 pinnate with the ultimate segments linear and subulate, pale greyish-green and covered with long white hairs; lower leaves with a short petiole, upper leaves sessile, often with two or three small axillary leaves at the base. Flowers numerous, in dense terminal corymbs, each capitulum about 3–5 cm in diameter with an ovoid involucre composed of 3 rows of imbricate lanceolate, pubescent green bracts arranged with a brownish or whitish, membranous margin; 4 or 5 white, pink or reddish ligulate ray-florets and 3–20 white or cream tubular disc florets; achenes 2 mm long, shiny, greyish-brown, slightly curved (1, 3, 4).

Organoleptic properties

Odour: slightly aromatic; taste: bitter, faintly aromatic (3, 4, 7).

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Microscopic characteristics

Aerial part: Stem shows epidermal cells axially elongated with occasional anomocytic stomata and a faintly striated cuticle; abundant covering and scattered glandular trichomes; cortex narrow, parenchymatous with several layers of collenchyma in the ridges; numerous vascular bundles, arranged in a ring in transverse section, each with a small group of phloem and a wide cap of thick-walled, lignified pericyclic fibres; parenchymatous cells of outer pith lignified and pitted, those of the central region un lignified and sometimes collapsed in older stems forming a hollow. Leaf cells isobilateral, with palisades composed of 1–3 layers; upper and lower epidermal cells with sinuous anticlinal walls and numerous anomocytic stomata; abundant covering trichomes and scattered glandular trichomes occurring on both epidermises. Flower epidermal cells consisting of bracts, longitudinally elongated, thin-walled, filled with dark brown striated pigment, scattered covering trichomes and occasional stomata; the inner central region composed of elongated cells with lignified and finely pitted walls. Corolla of the ray floret with the epidermis of the ligule composed of wavy-walled cells with rounded papillae; corolla of the disc floret composed of rectangular cells with moderately thickened walls; numerous small cluster crystals of calcium oxalate occur in both ray and disc florets. Pollen grains spherical, 30–35 µm in diameter, with a spiny exine and 3 distinct pores (4).

Powdered plant material

Flowering tops: Green or greyish-green. Fragments of stems, leaves, and bracts bearing rare glandular trichomes with a short stalk and a head formed of 2 rows of 3–5 cells enclosed in a bladder-like membrane and uniseriate covering trichomes consisting of 4–6 small, more or less isodiametric cells at the base and a thick-walled, often somewhat tortuous terminal cell, 400–1000 µm in length; fragments of the ligulate corolla with papillar epidermal cells; small-celled parenchyma from the corolla tubes containing cluster crystals of calcium oxalate; groups of lignified and pitted cells from the bracts; spherical pollen grains, about 30 µm in diameter, with 3 germinal pores and spiny exine; groups of sclerenchymatous fibres and small vessels with spiral or annular thickening, from the stem (1).

Aerial part: Greyish-green powder with epidermal fragments of stem and leaf with abundant covering trichomes and less numerous glandular trichomes, the covering trichomes frequently broken off and occurring scattered; groups of thick-walled, lignified fibres from the pericycle and xylem, those of the xylem sometimes associated with small vessels with spiral or annular thickening; lignified, pitted parenchyma from the pith;
dark brown fragments of the membranous margins of the bracts and groups of lignified and pitted elongated cells from the central region; occasional fragments of the papillose epidermis of the ligulate florets; small-celled parenchyma containing cluster crystals of calcium oxalate; pollen grains with a spiny exine (4).

**General identity tests**
Macroscopic and microscopic examinations (1, 3, 4), and thin-layer chromatography (1).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (13).

**Foreign organic matter**
Flowering tops: not more than 5% of stems with a diameter greater than 3 mm and not more than 2% of other foreign matter (1).
Aerial part: not more than 2% (4).

**Total ash**
Flowering tops: not more than 10.0% (1).
Aerial part: not more than 10% (4).

**Acid-insoluble ash**
Flowering tops: not more than 2.5% (1).
Aerial part: not more than 2.5% (4).

**Water-soluble extractive**
Aerial part: not less than 15.0% (4).

**Loss on drying**
Flowering tops: not more than 12.0% (1).
Aerial part: not more than 13% (3).

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (1). For other pesticides, see the *European pharmacopoeia* (1)
and the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (13) and pesticide residues (14).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (13).

**Radioactive residues**
Where applicable, consult the WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (13).

**Chemical assays**
Flowering tops: not less than 0.2% (v/w) of essential oil calculated on the basis of dried weight; and not less than 0.02% of proazulenes expressed as chamazulene by a combination of steam distillation and spectroscopic analysis (1).

Aerial part: not less than 0.1% (v/w) of essential oil determined by steam distillation (3).

**Major chemical constituents**
Contains 0.2–1.0% of essential oil. Being a chemically polymorphic aggregate plant species, the chemical constitution depends on the number of chromosomes present. Diploid and tetraploid plants contain proazulene sesquiterpenes, which when exposed to heat will be transformed to coloured azulenes, including chamazulene (up to 25%) and achillicin. Other major constituents in tetraploid plants include β-pinene (23%), α-pinene (5%) and caryophyllene (10–22%). Hexaploid plants are azulene sesquiterpene-free, and contain approximately 50% mono- and sesquiterpenes, many of which are in the oxidized form, as well as camphor (18%), sabinene (12%), 1,8-cineol (10%) and β-pinene (9%), among other constituents. Octaploid plants contain approximately 80% oxygen-containing monoterpenes, with linalool being the major constituent. Among the non-essential-oil constituents are flavonoids, coumarins and tannins (6, 7, 9, 11, 15). The structures of representative mono- and sesquiterpenes are presented below.

**Medicinal uses**

*Uses supported by clinical data*
None.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Uses described in pharmacopoeias and well established documents
Orally for loss of appetite, common cold, dyspeptic ailments such as mild spastic discomfort of the gastrointestinal tract, as a choleretic and for the treatment of fevers (6, 12, 16). Externally for skin inflammation and wounds (6).

Externally as a sitz bath for treatment of painful, cramp-like conditions due to menstrual disorders (12).

Uses described in traditional medicine
Orally as an emmenagogue, eyewash, haemostat, laxative, sleep aid, stimulant tonic, and to treat baldness, prostatitis and vertigo (8, 9, 15, 17, 18).

Used externally for the treatment of haemorrhoids, haematoma and burn injuries (19).

Pharmacology
Experimental pharmacology
Note: While the flowering tops of the plant are official in the European pharmacopoeia 2005 (1), much of the research on the pharmacology of this plant has been performed using the aerial parts of the plant, which

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include the flowering tops. These data have been included and designated as coming from studies conducted on the aerial parts, but their direct applicability to the flowering tops needs to be further investigated.

**Antibacterial activity**

A 50% ethanol extract of the flowers inhibited the growth of *Shigella dysenteriae*, but not that of *Escherichia coli* or *Salmonella enteritidis*, in vitro at a concentration of 50 µl/agar plate (20). A methanol extract of the aerial parts inhibited the growth of 18 clinical strains of *Helicobacter pylori* in vitro, with a minimum inhibitory concentration of 50 µg/ml (21).

**Anticonvulsant activity**

Intraperitoneal injection of a 95% ethanol extract of the aerial parts to mice, at a dose of 2.0–4.0 ml/kg body weight (bw), had anticonvulsant activity against supramaximal electroshock- and corazol-induced convulsions, but was not effective against strychnine-induced convulsions (22).

**Anti-inflammatory activity**

In a study in mice, intraperitoneal injection of a fraction from an aqueous extract of the flower heads, at a dose of 40.0 mg/kg bw, inhibited yeast-induced pedal oedema (23). Intragastric administration of an 80% ethanol extract of the aerial parts to rats, at a dose of 100.0 mg/kg bw, inhibited carrageenan-induced pedal oedema by 29% (24). External application of a methanol extract of the aerial parts to mice, at a dose of 1.0 mg/ear, had weak anti-inflammatory effects (25). An aqueous extract of the aerial parts did not inhibit prostaglandin synthesis in microsomes at a concentration of 0.2 mg/ml (26). Santamarin, a sesquiterpene lactone from the crude drug, moderately inhibited the transcription of nuclear factor-kappa-beta, a protein that regulates the transcription of inflammatory mediators such as the cytokines and chemokines, at a concentration of 100 µM (27).

**Antioxidant activity**

Chamazulene, an artefact constituent of the aerial parts, inhibited cell membrane lipid peroxidation induced by Fe²⁺/ascorbate as assessed in the 2-thiobarbituric acid reactive assay. Chamazulene inhibited lipid peroxidation in a concentration- and time-dependent manner, with a median inhibitory concentration of 18 µM. It also inhibited the autoxidation of dimethylsulfoxide (33 mM) by 76% at 25 mM, and had a weak capacity to interact with 2,2-diphenyl-1-picrylhydrazyl (28).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

**Antipyretic activity**
Oral administration of a hot aqueous extract or the juice of the aerial parts of the plant to rabbits, at a dose of 25 and 55 g/kg bw, respectively, reduced body temperature, while the 95% ethanol extract was not active (29).

**Antispasmodic activity**
An aqueous or methanol extract of the aerial parts of the plant (concentration not stated) inhibited contractions of rabbit small intestines in vitro (30).

**Antiviral activity**
A 50% methanol extract of the aerial parts inhibited HIV-1 reverse transcriptase in vitro at a concentration of 10% of the nutrient medium (31). Intraperitoneal administration of a hot-water extract of the dried flowers and leaves of the plant to mice (dose not stated) was active against tick-borne viral encephalitis (32).

**Toxicology**
Intraperitoneal administration of an aqueous extract of the aerial parts to rats had a median lethal dose of 1.5 g/kg bw (33). Intragastric or subcutaneous administration of an aqueous extract of the flowers to mice had a median lethal dose of > 1 g/kg bw (33).

**Clinical pharmacology**
Oral administration of a 70% ethanol extract of the flowers (dose not stated) increased the secretion of gastric juice in healthy volunteers by 178% (16). No further information on this study was available.

**Adverse reactions**
Numerous reports of allergic contact dermatitis have been published (33–39). In clinical testing, product formulations containing 2% of extracts of the crude drug were generally not irritating. In provocative testing, patients reacted to a Compositae mix that contained the crude drug, as well as to the crude drug alone. In clinical testing, a formulation containing 0.1% yarrow extract (propylene glycol and water) was not a sensitizer in a maximization test and alcoholic extracts of aerial parts of *A. millefolium* did not produce a phototoxic response (33).

A 5-year follow-up (1985–1990) of patients who were sensitive to Compositae showed that more than 50% reacted when tested with an ether extract of the plant, indicating cross-sensitivity (35). However, exacerbation of the patch test sites by irradiation with UV light was not ob-
served in any of the tested patients. One guaianolide compound, with a peroxide-bridged cyclopentane ring and an \( \alpha \)-methylene-\( \gamma \)-butyrolactone structure, named \( \alpha \)-peroxyachifolide, has been isolated from the flowers and appears to be responsible for the allergic contact dermatitis (35, 37).

Therefore, direct contact with the crude drug or its preparations may cause hypersensitivity reactions of the skin or mucosa, such as rash, formation of vesicles and pruritus, in sensitive individuals.

**Contraindications**

Hypersensitivity to the plant and other Asteraceae (Compositae) (12, 40, 41). Gastric and duodenal ulcer, occlusion of the bile duct and gallbladder disease (12).

Due to the traditional use of the drug as an emmenagogue, it is contraindicated during pregnancy (9).

**Warnings**

Patients presenting with hypersensitivity or allergic reactions that include the formation of vesicles should stop treatment with Herba Millefolii immediately (40). If signs of hypersensitivity reaction reappear upon further use, the crude drug should not be used again.

**Precautions**

*Carcinogenesis, mutagenesis, impairment of fertility*

A tincture of the crude drug was not mutagenic in the Ames test at a concentration of 160 µl/disc in *Salmonella typhimurium* strains TA98 and TA100. Metabolic activation had no effect on the results (33). An infusion of the aerial parts was tested for genotoxicity in the wing somatic mutation and recombination test (SMART) which makes use of the two recessive wing cell markers, multiple wing hairs (mwh) and flare (flr) on the left arm of chromosome 3 of *Drosophila melanogaster*. Three-day-old larvae, trans-heterozygous for these two markers, were fed the beverage (an infusion of *Achillea millefolium* (20 g/100 ml water) cooled and used immediately for the larval experiments) at different concentrations and for different feeding periods using *Drosophila* instant medium. Somatic mutations or mitotic recombinations induced in the cells of the wing imaginal discs gave rise to mutant single or twin spots on the wing blade of the emerging adult flies showing either the mwh phenotype and/or the flr phenotype. An infusion of *Achillea millefolium* was weakly genotoxic (42).

The results of previous investigations assessing the effect of the crude drug on reproduction have been contradictory. In one study, the addition
of the plant to the feed of rats, at a concentration of 25–50% w/w, sup-
pressed the induction of estrus (43). However, oral administration of an
extract of the leaves to rats did not alter the time of first mating, fertility
or litter size (44). The effect of a 96% ethanol extract (200 mg/kg bw per
day, intraperitoneally, for 20 days) and an 80% ethanol extract (300 mg/
kg bw per day, orally, for 30 days) of the flowers on the spermatogenesis
of Swiss mice was assessed by examining morphological characteristics
with light and electron microscopes. Neither dose caused a significant dif-
fERENCE in body weight gain or in the weight of the testes and seminal
vesicles. The alterations observed were exfoliation of immature germ
cells, germ cell necrosis, and seminiferous tubule vacuolization. Animals
treated with the extracts had an increased number of metaphases in the
germ epithelium that might be due to cytotoxic substances or substances
stimulating cell proliferation (45).

**Pregnancy: Non-teratogenic effects**
See Contraindications.

**Nursing mothers**
Due to the lack of safety data the crude drug should not be used by breast-
feeding mothers.

**Paediatric use**
Due to the lack of safety data the crude drug should not be used in chil-
dren under the age of 12 years.

**Other precautions**
No information was found.

**Dosage forms**
Crude drug, extracts, fluidextract, infusions, succus (pressed juice from
fresh herb) and tinctures.

**Posology**
(Unless otherwise indicated) (12)
Internal: 4.5 g of cut herb (flowering top) per day, or 3.0 g cut flowers for
teas (infusions) and other Galenical preparations; pressed juice of freshly
harvested herb.
Infusion: 1–2 g in 150 ml boiled water for 10–15 minutes, three times dai-
ly between meals.
Succus (pressed juice from fresh herb): 5 ml (1 teaspoon), three times daily between meals.
Fluidextract 1:1 (g/ml): 1–2 ml, three times daily between meals.
Tincture (1:5 g/ml): 5 ml, three times daily between meals.
External: sitz bath: 100 g per 20 litres of warm or hot water (12).

References
9. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network [STN] of Chemical Abstracts Services), 30 June 2005.


**Definition**

Herba Origani consists of the whole or cut dried aerial parts of *Origanum vulgare* L. (Lamiaceae), collected during the flowering phase (1).

*Note:* According to the *European pharmacopoeia*, Origani herba is the dried leaves and flowers separated from the stems of *Origanum onites* L. or *Origanum vulgare* L. subsp. *hirtum* (Link) Ietsw., or a mixture of both species (2).

**Synonyms**


**Selected vernacular names**

Acciughero, aitz belarr, anrar, ào lè găng, ào lè găng cão, avishan kuhi, bantulsi, bergminta, bergmynte, brauner dost, brauner dosten, buklu-tulgezal, ching chieh, common marjoram, dobromysl, dost, doste, dosten, duhov’i tsvet, dushita, dushitsa, dziki majeranek, echter dost, erba acciu-ga, fekete gyopár, frauendost, gemeiner dost, Gewöhnlicher Dost, hana-hakka, harilik pune, herba origani, jakhmbuti, kaslók, kekik otu, klopopnaya trava, kostets, kostolomnaya trava, kung, kungsmynta, lepiodka pospolita, loragiño, majurano fero, marjolaine bâtarde, marazolette, marjolai, marjolaine sauvage, marjolaine sauvage origan, marzangush, materynka, materynka zwichajna, mountain mint, mravinač, mäkimeirami, ngåuh ji, ngou lahk göng, niu zhi, oragan, ordinara origano, oregano, oregánó, oregano, oregánó, orégão, oregâos, orenga, organ, oreganos, organy, origan, origan commun, origan vulgaire, origano, orig-
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anum, ourego, paprastasis raudonėlis, pamajorán obyčajný, pelevoué, pe-nevoué, pot oregano, raudenes, remago, rigan, riegnu, rigon i egër, rijan, rigoni i zakonshëm, satar barri, sathra, sovârf, szurokfű, tavshava, thé rouge, thym de berger, tograihon, tost, vadmajoránna, vild mejram, wild marjoram, wild oregano, wilde marjolein, wilder majoran, winter marjo-ram, wintersweet (3–5, 7–21).

Geographical distribution
The plant is commonly distributed throughout Asia, Europe and northern Africa. It is native to Europe and the Middle East. In the Newly Independent States, it grows in the European areas, also in Caucasus, Central Asia and western Siberia (8, 19, 22–25).

Description
A perennial herbaceous plant, 30–90 cm high. Rhizome, horizontal, creeping. Stems, erect, woody at the base, branched, quadrangular, hairy, often violet or purplish-green. Leaves, opposite, petiolate, ovate, rounded at the base, sub serrate, sometimes toothed, entire-margined or slightly crenate, glabrous or hirsute, translucent punctate, green on both sides, paler underneath, 10–40 mm long, 4–25 mm wide; petiole hairy, about one fourth as long as the leaves. Inflorescence, corymb-like inflorescences at the branch apexes. Flowers, labiate type, generally bisexual, sometimes just female flowers with immature stigmas, zygomorphic, with short peduncle. Bracts elliptical, pointed, longer than calyx, dark purple. Calyx, generally 5-lobed, radial to bilateral, sepals triangular lanceolate, with 13 veins, about 3 mm long, with a hairy ring inside. Corolla, upper lip flat, lower lip has 3 lobes, from pink or purple to white, about 6 mm long. Stamens 4, exserted, didynamous, with double anthers. Pistil, stigma bifid and reflexed. Fruit, nutlets, oval to ovate, in persistent calyx, dry, smooth, dark brown, 0.5–1 mm long (4, 8, 14, 17, 25–29).

Plant material of interest: dried aerial parts
General appearance
The drug consists of flowering leafy stems up to 20 cm long, green or violet in colour (1). The leaves are opposite, petiolate, ovate or ovate-elliptic; the margins are entire or serrate; the apex is acute or obtuse; upper surface green, lower surface paler; 20–40 mm long. Flowers are rare, 3–5 mm long, found as unbroken or broken parts of the corymb. Bracts are dark purple and imbricate. Calyx is tubulous, 5-sepalled, co-
rolla-like, glabrous or lightly hairy, inconspicuous. Corolla of labiate type, white or violet (1, 2).

**Organoleptic properties**
Odour: aromatic; taste: slightly bitter, spicy and astringent (1).

**Microscopic characteristics**
The stem is quadrangular in transverse section, with rectangular epidermal cells; 1-layered collenchyma underlying epidermis and 3-layered one in each corner of the stem. A broken ring of fibres and few stone cells in cortex; cortex cells with brown content in about 3 layers of cells adjoining phloem tissue. Leaf: the cells of leaf epidermis are sinuous (much more so on the underside), with regularly or sometimes irregularly thickened walls. The epidermis is covered by a thin cuticle. Diacytic stomata more frequent on the lower epidermis. Simple and glandular trichomes on both epidermis, preponderant on the lower one. The simple trichomes are curved, pointed, 1–5 celled, rugous. Glandular trichomes with 1–3-cellular stalk and unicellular head. The secretory glands are 8–12-celled, mainly on the lower side of leaves. Petiole with isodiametric or rectangular epidermal cells; simple and glandular trichomes; collenchyma tissue in corners and partly underlying upper and lower epidermis; central vascular bundle. Flower bracts and calyx have similar structure to the leaf but in the calyx there are no hairs on the inner epidermis. The corolla tube has irregular cells in the inner lobe and is regular and papillose towards and at lobes (1, 30–32).

**Powdered plant material**
The powder is green. When examined under a microscope, the covering trichomes are of lamiaceous type or short, unicellular and rarely conical; conical trichomes are shaped like pointed teeth; covering trichomes are thick-walled and contain minute needles. Cuticle of covering trichomes is warty. The epidermis of the leaves have cells with sinuous walls; diacytic stomata; cells of the upper epidermis are beaded; secretory trichomes with 8–12 cells; glandular trichomes are rare, they have a unicellular head and bicellular or tricellular stalk; pollen grains are smooth, spherical and abundant (2).

**General identity tests**
Macroscopic and microscopic examinations (1, 2), and thin-layer chromatography tests for the characteristic volatile oil constituents, thymol and carvacrol (2).
Purity tests

Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (33).

Chemical
No information available.

Foreign organic matter
Not more than 2% (2). Not more than 1%. Not more than 7% fragments of the brownish and blackish herb. Not more than 40% of stems. For cut drug: not more than 10% of fragments of drug having a diameter less than 0.5 mm and not more than 10% of fragments of drug having a diameter more than 7 mm (1).

Total ash
Not more than 15% (2). Not more than 10% (1).

Acid-insoluble ash
Ash insoluble in hydrochloric acid must not be more than 4% (2).

Sulfated ash
No information available.

Water-soluble extractive
No information available.

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 13% (1). Maximum water content, 120 ml/kg, determined on 20.0 g of the powdered drug (2).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (2). For other pesticides, see the European pharmacopoeia (2) and the WHO guidelines on quality control methods for medicinal plant materials (33) and pesticide residues (34).
**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (33).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (33) for the analysis of radioactive isotopes.

**Other purity tests**
The content of mineral matter must not be more than 1% (1). Chemical, sulfated ash, alcohol-soluble extractive and water-soluble extractive tests to be established in accordance with national requirements.

**Chemical assays**
Herba Origani contains not less than 2.5% of volatile oil and a minimum of 1.5% carvacrol and thymol in anhydrous drug. Volatile oil is quantitatively determined by distillation, and the percentage content of phenols is determined by gas chromatography (2). Whole Herba Origani contains not less than 0.1% volatile oil. The cut drug contains not less than 0.08% of volatile oil (1).

**Major chemical constituents**
Herba Origani contains 0.15–1.2% of volatile oil. The chief components of the volatile oil are carvacrol (40–70%), γ-terpinene (8–10%), p-cymene (2.80–10.00%), as well as α-pinene, myrcene, thymol, α-terpinene, estra
gole, eugenol and (E)-β-ocimene, among others. There are also strains that contain thymol, linalool with terpinen-4-ol, linalool, β-caryophyllene, germacrene D and sabinene as the major components. The ethanol-water extract contains flavonoids (naringin, luteolin-7-glucoside, diosmetin-7-glucoside and apigenin-7-glucoside), rosmarinic acid (approximately 5%) and other phenolic esters; tannins are also present (4, 7, 8, 17, 19, 24, 35–38). The structures of the main characteristic constituents are presented below.

![carvacrol](image1)

![thymol](image2)
Medicinal uses

*Uses supported by clinical data*
No information was found.

*Uses described in pharmacopoeias and well established documents*
No information was found.

*Uses described in traditional medicine*
Herba Origani is used to treat cough, colds and bronchial catarrh, and is
used as an expectorant and diaphoretic (39–41). Other uses include the
treatment of bloating, stimulation of bile secretion, of the appetite and of
digestion, and as a sedative and antispasmodic agent (15, 42, 43). Herba
Origani is also used as an emmenagogue in Unani medicine (44), and for
treatment of algomenorrhoea and impotence (45). The herb is used as a
diuretic and as a treatment for kidney infections, kidney stones and poor
renal function resulting from chronic nephritis (22). It is also used to treat
inflammation, arthritis (46), hepatitis (47, 48), and externally for scrofula
and wound healing (49).

Pharmacology

*Experimental pharmacology*

**Antimicrobial activity**
An ethanol extract (80%) of Herba Origani at a concentration of 250 µg/ml/agar plate was active against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella typhi*, *Staphylococcus aureus* and *Streptococcus hemolyticus* in vitro. Using a disc diffusion method, the extract dissolved in dimethyl sulfoxide at a concentration of 4.0 µg/disc, exhibited antibacterial activity against *Bacillus subtilis*. The inhibition halos in the same test (4.0 µg/disc) were: *Klebsiella pneumoniae* and *Proteus mirabilis* 4 mm, *Salmonella typhi* 8 mm, *Staphylococcus aureus* 6 mm, *Streptococcus hemolyticus* 14 mm, and *Escherichia coli* 20 mm. The essential oil of the dried leaf demonstrated antibacterial activity at a concentration of 150.0 ppm against a broth culture of *Lactobacillus plantarum* and *Leuconostoc mesenteroides* (50).

The aqueous ethanol extract (1:1) of the dried entire plant at a concentration of 500 mg/ml/agar plate (dose expressed as dry weight of plant) demonstrated weak antifungal activity against *Aspergillus fumigatus*, *Aspergillus niger*, *Botrytis cinerea*, *Fusarium oxysporum*, *Penicillium digitatum*, *Rhizopus niger*, *Trichophyton mentagrophytes*, and antiyeast activity against *Candida albicans* and *Saccharomyces pastorianus* (51).
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essential oil of the aerial parts of the plant exhibited a strong antifungal effect at a concentration of 100.0 ppm/agar plate against *Gloeosporium albunm, Phytophthora nicotianae, Botrytis cinerea, Helminthosporium teres, Monilia laxa* and *Phytophthora infestans* (52). The essential oil also inhibited the growth of *Cryptococcus neoformans* at a minimum inhibitory concentration of 150 µl/l/agar plate and inhibited the growth of *Candida albicans* by 0.12% (53, 54). The essential oil of the leaf (0.25 and 1 µl/ml/agar plate) inhibited the growth of *Trichophyton rubrum, Trichosporon beigelii* and *Malassezia furfur* (55).

**Antiviral activity**

A 10% aqueous extract of the aerial parts of the plant demonstrated antiviral activity in cell culture against herpes simplex virus (HSV-2), influenza virus A2 (Mannheim 57) and vaccinia virus (56).

**Insecticide activity**

The essential oil of the aerial parts of the plant (concentration 20 µg) caused complete sterility in *Dysdercus koenigii* (57), and topical application of the oil demonstrated insecticidal properties (20 µl of stock solution of origanum oil) against *Drosophila auraria* adults, eggs and larvae (58). The median lethal dose for *Drosophila melanogaster* was determined to be 6.78 µl of stock solution of origanum oil by the somatic mutation and recombination test (59).

**Antiparasitic activity**

The essential oil of the fresh leaves of the plant (1 mg/l) acted as an anti-nematodal agent against *Meloidogyne javanica* (60).

**Anti-inflammatory effects**

The methanol extract of *Origanum* leaf applied externally to mice (20 µl/animal) exhibited anti-inflammatory effects in animals with ear inflammation induced by 12-0-tetradecanoylphorbol-13-acetate (61). Similarly, the external application of a methanol extract of *Origanum* leaf to mice in vivo at a dose of 2 mg/ear inhibited ear inflammation induced by 12-O-tetradecanoylphorbol-13-acetate with an index of inhibition of 27 (62).

**Antioxidant activity**

A tannin fraction and an ethanol-aqueous extract (1:1) of the dried flowering top and leaf of *Origanum vulgare* exhibited strong antioxidant activity in vitro. The free-radical scavenging effect of the tannin fraction on 1,1-diphenyl-2-picrylhydrazyl was estimated to occur at a median effec-
tive dose of 16.2 mg/ml. The median effective dose for the antioxidant activity of the ethanol-aqueous extract was estimated to be 16 mg/ml as assessed by a colorimetric assay (63, 64). In addition, the antioxidant activity of the diethyl ether extract of dried leaves of *Origanum vulgare* (concentration 0.02%) was demonstrated when assayed against corn oil, soybean oil and olive oil (65). The water-soluble active ingredients were isolated, and their structures were determined. Over 70% radical scavenging activity was found for two of them – rosmarinic acid and 4′-O-β-D-glucopyranosyl-3′,4′-dihydroxybenzyl protocatechu – when applied at $2 \times 10^{-5}$ M in the 1,1-diphenyl-2-picrylhydrazyl test (66).

**Antihyperglycaemic activity**
An aqueous extract of dried leaves of *Origanum vulgare* exhibited antihyperglycaemic activity in vivo when administered to rats by the intragastric route at a dose of 20 mg/kg body weight (bw) (46). Commercial samples of *Origanum* leaf (concentration 12.5 mg/ml) exhibited insulin potentiating effects in vitro (67).

**Antimutagenic activity**
The aqueous and methanol extracts of dried and fresh leaves of *Origanum vulgare* exhibited desmutagenic activity in an in vitro model, at a concentration of 10 µg/agar plate of *Salmonella typhimurium* TA98, against 3-amino-1-methyl-5H-pyrido[4,3-b]indole-induced mutagenesis (68). Both the essential oil and carvacrol were shown to strongly inhibit mutagenicity induced by 4-nitro-o-phenylenediamine and 2-aminofluorene in the presence or absence of a metabolic activator, which would suggest a protective effect against cancer (69).

**Toxicology**
In mice, the median lethal dose for an aqueous-ethanol extract (1:1) of the entire plant has been recorded as > 1 g/kg (by intraperitoneal injection) (70). The essential oil of the aerial parts of the plant, at a concentration of 0.01%, inhibited proliferation of rabbit epidermal CA-HEP-2 cells, Vero cells, and cultured HeLa cells (71).

**Clinical pharmacology**
No information was found.

**Adverse reactions**
No information was found.

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Contraindications
If signs of hypersensitivity reactions appear (rash, pruritus, urticaria, swelling of mouth and skin) Herba Origani must not be used again.

Precautions

General
No information was found.

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
Ingestion of strong (concentrated) teas made with Herba Origani may cause uterine contractions. Women should avoid taking the herb during pregnancy and lactation (72).

Nursing mothers
See Pregnancy.

Paediatric use
No information was found.

Drug interactions
No information was found.

Dosage forms
Comminuted herb for infusion.

Posology
(Unless otherwise indicated)
Internal use. As an infusion: one tablespoon of an infusion (10 g of dried herb in 200 ml boiling water for 15–20 minutes) three times daily before meals (73). Tincture: 1 ml of a tincture (10 g of dried herb in 150 ml 70% ethanol) three times daily (74).

External use. As a compress, cataplasm or gargle: add 20–30 g of herb to 200 ml of boiling water for a direct application (75).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

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Herba Pegani harmalae

Definition
Herba Pegani harmalae consists of the dried aerial parts of *Peganum harmala* L. (Zygophyllaceae), collected during the flowering season (1–3). The seeds of *P. harmala* are used in traditional medicine (4–6).

Synonyms
*Peganum multisectum* Maxim. (1).

Selected vernacular names
Adrashman, African rue, armel, aspand, bender tiffin en tamachek, besasa, birz el hharmel, churma, epnubu, esfand, espand, gandaku, garmala ob’knovennaya, gemeine syrische Raute, ghalqat edh dhī’b, haoma, harale, harilik peeganum, harmal, harmala, harmale, harmalkraut, harmal rut-bab, harmel, harmel sahari, harmara, harmaro, hermal, hermale, hermel, Hermalkraut, hermelraute, hharmal, hom, hormol, humoro, hurmul, hurmur, humuro, isband, isbaend-lahouri, isirik, isiriq, isbendlahouri, ispand, ispand lahouri, ispanthan, ispun, kaladana, khokrana, kisankur, lahouri-hurmul, l’harmel, mahmur çić, mariamsakmel, mogilnik, moly, mountain rue, pégane, pegano, peganum, rue, rue sauvage, rue verte, sadhab barri, sadhāb barri, sarmala, sauvage, shimai-aravandi-virati, shimai-azha-vanai-virai, simagoranta, simaiyalavinai, sima-goronti, sime-goranti, sipand, spail-anai, spand, spanda, spani, spélanè, steppenraute, Syrian rue, syrische Raute, ruin weed, ruta della siria, ruta salvatica, sipend, spand, stepnaya ruta, techepak, tukhum-i-isfand, turetskaya kraska, uzarih, vilayati-isband, vilayati-mhendi, wild raute, wild rue, überlik otu (7–21).

Geographical distribution
Native to the Middle East, North Africa and southern Europe, Herba Pegani Harmalae is naturalized in other subtropical regions, including Australia. In the Newly Independent States, it grows in Central Asia, and also in the Caucasus (5, 14, 19, 22).
Description
A perennial plant, 30–100 cm high. Rhizome, woody, large. Root, stout. Stems, numerous, herbaceous, shrubby base, branched, forked-corymbose, glabrous. Leaves, alternate, sessile, ovate outline, 4–10 cm long, 5.8–6.5 cm wide, irregularly finely divided into long narrow lobes of 1–3.5 cm long and 1.5–3 mm wide. Inflorescence, compound monochasial scorpioid cyme. Flowers, terminal and axillary, solitary, actinomorphic, hermaphrodite, white, fragrant, 25–30 mm in diameter; pedicels angular, green, 1–2.5 cm long; petals 5, oblong-elliptic; sepals 5, persistent, narrow, slightly longer than the petals; stamens 10–15, enlarged at the base filaments; ovary globular, trilocular, superior. Fruits, capsules, globular, stalked, erect, 3-valved loculicidal, 6–10 mm in diameter, dull earthy brown colour, reticulate seed coat, strong characteristic odour when crushed, bitter in taste. Seeds, numerous (more than 50), subtriangular, reticulately pitted, 3–4 mm long, dark brown. The herbage begins to develop new shoots in February, flowers appear in April, the plant flowers until October and bears fruits from April to November. The aerial parts are gathered in summer (1, 3, 7, 17, 23–27).

Plant material of interest: dried aerial parts

General appearance
Fragments of young stems, cylindrical, glabrous, 8–80 mm long, up to 8 mm in diameter, yellowish-green. Whole or fragmented leaves, filiform, glabrous, 0.5–20 mm long, yellowish or brownish-green. Flowers large, terminal, and white. The seeds are triangular concavo-convex, dull brown, up to 4 mm long and 1–2 mm broad (14, 22).

Organoleptic properties
Odour: specific, slight, unpleasant; taste (of fruits): very bitter, spicy (4, 28).

Microscopic characteristics
Leaf has two kinds of epidermal cells: large oblong and small isodiametric. Anomocytic stomata surrounded by small epidermal cells. Needle-like calcium oxalate crystals in the mesophyll. Glandular trichomes on the whole upper epidermis of young leaves persisting only at the leaf base at maturity. Trichomes have a stalk of 4–6 cells and a multicellular head. Seed rind is 4-layered. Outer layer of epidermis consists of large, rectangular, radially elongated (the length being two to three times greater than the breadth), thick-walled cells, strongly thickened in the upper corners and with outgrowth of walls starting from the inside. Epidermal cells
Herba Pegani harmalae contain mucilage. Parenchyma layer beneath epidermis is usually formed of 3–4 rows of small air-filled cells; a dark brown layer of disintegrated cells, wavy in appearance; elongated thin-walled cells containing a yellowish brown substance, which gives a positive test for fixed oil. Endosperm made up of polygonal cells with uniformly thickened cellulose cell membranes. The endosperm of seed-lobe area is formed of 7–8 layers of cells and endosperm of rootlet area of 2–3 layers of cells. The germ is slightly bent and consists of 2 equally mature cotyledons, budlet, short hypocotyl and well-marked rootlets with forming root caps (14, 22, 29).

**Powdered plant material**
No information available.

**General identity tests**
Macroscopic and microscopic examinations (24, 28), and thin-layer chromatography to be established in accordance with national requirements. A high-performance liquid chromatography method for the determination of specific alkaloids in the seeds has been developed and validated (30).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (31).

**Chemical**
No information available.

**Foreign organic matter**
Not more than 4% (28). Not more than 2% (24). Maximum 10% fragments of stems longer than 80 mm. Not more than 5% of greyish stems of previous year. Not more than 5% of fragments of drug having a diameter less than 0.315 mm (28).

**Total ash**
Not more than 18% (28). Not more than 10% (24).

**Acid-insoluble ash**
No information available.
Sulfated ash
No information available.

Water-soluble extractive
No information available.

Alcohol-soluble extractive
No information available.

Loss on drying
Not more than 12% (28). Not more than 10% (24).

Pesticide residues
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (32). For other pesticides, see the European pharmacopoeia (32) and the WHO guidelines on quality control methods for medicinal plant materials (31) and pesticide residues (33).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (31).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (31) for the analysis of radioactive isotopes.

Other purity tests
The content of mineral matter is not more than 2% (28). Chemical, acid-insoluble ash, sulfated ash, alcohol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Aerial parts contain not less than 1.5% alkaloids (28). A high-performance liquid chromatography method for the analysis of specific alkaloids in the seeds has been developed and validated (30).

Major chemical constituents
The major constituents of the dried aerial parts are indole alkaloids which dominate during and after flowering when harmine and harmaline pre-
dominate. Other major alkaloids are harmolol (harmol) and peganine. Harmine is present in all parts of the plant. On isolation it forms colourless crystals. The alkaloid (–)-peganine (vasicine) occurs in blossoms and stems. The aerial parts contain 0.77%, leaves 0.3–0.4% and seeds contain 3.5–6% alkaloids (including 60% harmaline and 30% harmine) (22, 30, 34–39). Several other alkaloids (among them dipeginine, dipegoline and tetrahydroharmine), and four flavonoid glycosides (acacetin-7-O-rhamnose, acacetin-7-O-[6′′-O-glucosyl-2′′-O-(3′′-acetyl)rhamnosyl]glucoside, acacetin-7-O-[2′′-O-rhamnosyl-2′′-O-glucosyl]glucoside and the glycoflavone 2′′′-O-rhamnosyl-2′′-O-glucosylcytisoside) have been isolated from the drug (40, 41). Also present are quinazoline alkaloids with a similar structure: vasicinone, peganline, tetrahydroharmann and desoxypasicinone (17) together with saponins, tannins and organic acids (22). The structures of some characteristic constituents are presented below.

![Chemical structures of alkaloids](image)

**Medicinal uses**

**Uses supported by clinical data**

No information was found.

**Uses described in pharmacopoeias and well established documents**

Used in the treatment of different forms of myasthenia, myopathy and atony of the bowels (35).

**Uses described in traditional medicine**

Used for treatment of epilepsy (42), as a central nervous system (CNS)-stimulant, hypnotic and relaxant (43, 44). Also used as an anthelminthic,
diuretic (45), diaphoretic, lactogogue (24, 46), aphrodisiac and antiasthmatic (47). It is also used as a fumigant for treatment of headache, sore throat and inflammation (48), rheumatism (root applied externally) (49, 50), jaundice (51), otitis and cataracts (fresh juice and seeds applied locally) (6, 52). Additional described uses of the plant include treatment of dermatitis, alopecia, use as a depurative and abortifacient (53), and (fumigation) as a mosquito repellent and pediculocide (54).

Pharmacology

**Experimental pharmacology**

**Cardiovascular effects**

A methanol extract of the seeds caused a dose-dependent relaxation, after contraction with noradrenaline (10^{-6} M) and potassium chloride (80 mM), in vascular smooth muscle (rat aorta) in vitro at a median inhibitory concentration of 14.49 ± 1.15 and 5.93 ± 1.26 µg/ml, respectively. The vasodilatory effects were potentiated by isoprenaline (10^{-9} M) (1.08 ± 0.14 µg/ml) and decreased by a nonspecific inhibitor of phosphodiesterase 3-isobutyl-1-methylxanthine (10^{-4} M) (20.81 ± 1.06 µg/ml) (55).

**Cholinergic effects**

An aqueous extract of the seeds (0.5 ml) exhibited a smooth muscle relaxant effect in vitro (guinea-pig ileum, rabbit jejunum and trachea) against acetylcholine- and histamine-induced contractions (56).

**Antinociceptive effects**

The analgesic activity of an ethanol extract of the entire dried plant was tested in vivo in mice using the hot-plate test. An intraperitoneal injection of the extract at a dose of 150 mg/kg body weight (bw) demonstrated analgesic effects against acetic acid-induced writhing (57).

**Hypothermic effect**

Intraperitoneal administration of the total alkaloid extract of the aerial parts of the plant to rats (0.5 ml/kg bw) produced significant and dose-dependent hypothermia. Pretreatment with p-chlorophenylalanine (100 mg/kg/day for 3 days), a serotonin (5-hydroxytryptamine, 5-HT) synthesis inhibitor, or with serotonin antagonist methysergide (2 mg/kg), significantly attenuated the hypothermic effect of the total alkaloids. Propranolol (10 mg/kg), a β-adrenoreceptor antagonist, failed to attenuate the effect, suggesting that β-adrenoreceptors are not involved in the pathway producing hypothermia caused by the alkaloids. Pretreatment with a dopamine receptor antagonist, haloperidol (5 mg/kg, subcutane-
Herba Pegani harmalae

ously and 2 mg/kg, intraperitoneally, 24 and 2 h before the experiment, respectively) significantly attenuated the hypothermic effect of harmala alkaloids. Moreover, pretreatment of rats with haloperidol and methysergide (2 mg/kg, intraperitoneally) completely attenuated the hypothermic effect of the alkaloids. Thus, harmala alkaloids produce a hypothermic effect mainly through endogenous stimulation of the 5-HT\textsubscript{1A} receptor (58).

**Antimicrobial activity**

1-Butanol and aqueous extracts of shade-dried aerial parts (60.0 µg/agar plate) expressed antibacterial activity against *Escherichia coli*. An aqueous extract of the aerial parts was also active against *Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes* and *Candida albicans* (in broth culture). A methanol extract of dried aerial parts of Herba Pegani harmalae (60 µg/agar plate) was active against *Streptococcus pneumoniae* (42) and a 95% ethanol extract of dried entire plant (0.3 mg/ml/agar plate) was active against *Bacillus cereus, Staphylococcus aureus* and *Staphylococcus epidermidis* (59). Furthermore, an 80% ethanol extract of dried aerial parts demonstrated weak antimycobacterial activity at a concentration of 1 mg/ml/agar plate against *Mycobacterium smegmatis* (60).

**Anti-inflammatory effects**

An ethanol extract of the dried aerial parts and seeds of the plant administered subcutaneously to male rats (100 mg/kg bw) exhibited antiinflammatory effects against carrageenan-induced plantar oedema (58% decrease of inflammation) (61).

**Antihyperglycaemic effects**

Intragastric administration of harmala seed powder at a dose of 53.2 mg/kg bw to rats resulted in an antihyperglycaemic effect. Weight increases were observed in animals with streptozotocin-induced diabetes challenged with glucose after having received a daily dose of extract, 53.2 mg/kg bw, for 1 week (62).

**Antiparasitic activity**

A 100% ethanol extract of dried leaf showed weak in vitro antimalarial activity against *Plasmodium falciparum* with a median inhibitory concentration of 46 µg/ml (63). An aqueous extract (concentration 1:200) of the dried leaves of Herba Pegani harmalae exhibited antimalarial activity against *Plasmodium falciparum* FCR-3/Gambia in vitro (64).
Uterine stimulant and abortifacient effects
The methanol extract of the aerial parts of the plant at a dose of approximately 2.5 g/kg/day, offered in food or in drinking suspension to female rats for 30 days, significantly prolonged diestrus by 1 day. At doses of 2, 2.5 and 3.5 g/kg/day, the extract appeared to cause a significant dose-dependent decrease in litter size. No change in the physical and nutritional status of the animals and no other adverse toxicological effects were observed (65).

Effects on male fertility
Intragastric administration of the dried seeds of Herba Pegani harmalae (100 mg/kg bw) to male rats caused a significant ($p < 0.05$) increase in sperm motility and testosterone level, and augmentation of weight of epididymis, prostate, seminal vesicles and testes (66).

Toxicology
The therapeutic and toxic effects in relation to an oral dose of the aqueous extract of Herba Pegani harmalae were studied in Wistar rats. In acute studies, a median lethal dose of 2.70 ± 0.05 g/kg was reported. In chronic studies, oral administration of the extract six times per week at doses of 1, 1.35 and 2 g/kg bw for a 3-month period increased transaminase activity. Histological examination showed liver degeneration and spongiform changes in the central nervous system in rats treated with the 2 g/kg dose, but not in those that received the therapeutic dose of 1 g/kg (67). Subcutaneous administration of the 95% ethanol extract (120 mg/kg) of fresh Herba Pegani harmalae to rats, and intraperitoneal administration of the extract to mice (250 mg/kg bw) resulted in toxic effects including stiffness, trembling, frequent urination, hypothermia, weakness, stimulation of the central nervous system, convulsions and death. A median lethal dose of 500 mg/kg was determined from studies of oral administration of the ethanol extract to mice (68, 69). An analysis of 56 medical records of patients admitted to a toxicological intensive care unit from 1983 to 1998 following the ingestion of medicinal plants in Tunisia was performed. The sex ratio of patients (men/women) was 1:2; the mean age of patients was 26 years. A number of plant species were involved; in 7% of the cases Peganum harmala was associated with toxicity. Poisoning involved the neurological (91%), gastrointestinal (73%) and cardiovascular systems (18%) (70).

Clinical pharmacology
No information was found.
Adverse reactions
No information was found.

Contraindications
The drug is not recommended during pregnancy due to its ability to cause abortion (59). Herba Pegani harmalae is contraindicated for paediatric use and for nursing mothers due to its central nervous system exciting effects (4, 70). It is also contraindicated in patients with peptic ulcer (22).

Precautions
General
The plant is toxic and should be used with caution (5).

Drug interactions
No information was found.

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
A significant increase in the testosterone level in male rats, and a decrease in litter size in female rats has been reported (65, 66).

Pregnancy
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Dosage forms
Comminuted herb for infusion.

Posology
(Unless otherwise indicated)
Internal use. Infusion: one teaspoonful 3–4 times daily. Prepare by placing one teaspoonful of dried herb in 1 cup of boiling water and boiling for 15 minutes on a water bath. Then insist within 2 hours, filter (8).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

External use. Bath: an infusion from two tablespoonfuls of the cut herb added to 500 ml of water per bath (6).

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Folium Plantaginis majoris

Definition
Folium Plantaginis majoris consists of the whole or cut dried leaves of perennial Plantago major L. (Plantaginaceae) collected during the flowering season from both cultivated and wild plants (1).

Synonyms

Selected vernacular names
Arnoglossa, bağ yaprağı, baka zhal by rak, bartang, bazir dam bil, breitwegereich, broadleaf plantain, broad-leaved plantain, büyük sinirliot, büyük sinir out, cart-track plant, celtekas, ceuli, ceuli uncal, chajeoncho, ch’e ch’ien, che qian zi, common plantain, cuckoo’s bread, damarotu, daum sejumbok, daun sendok, daun urat, door-yard plantain, ekur anjing, ezan lezu, gechi oulaghi, Englishman’s foot, filo, filomatol, grand plantain, great plantain, great plantain, grosser Wegerich, grote weegbree, healing-blade, henplant, jghakhot, katir, katta zubturum, kesirotu, ki urat, kuping menjangan, lahariya, lanting, lanting haba, lamb’s-foot, laukahi, lielā ķelmalīe, lisan al-hamal, llanten mayor, llanten, meloh kiloh, mo noi, nipple grass, otoot otootan, pātlaginā, piantaggine grande, piantaggine maggiore, piharatamo, phak kat nam, plantain, plantain commun, plantain majeur, plantate gros, podorozhnik bolshoi, poputnik, pridorozhnik, priputnik, putik, putnik, ratamo, ribgrass, ripple grass, sangka buwah, sangkubah, sangkuwah, sei ohr re, sembung otoot, sinurotu, snakeweed, sobatshi jazyk, suri pandak, suur teeleht, tanagem, tanchagem-maior, tarkuz, tirnagt, torongoat, triputnik, tsirevaja trava, twissat mariam, wayboard, waybread, wegerlich, white-man’s foot (3, 5–24).

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Geographical distribution
Indigenous to the temperate regions of the world (especially Asia and Europe). Naturalized elsewhere in temperate regions. It is found in the Mediterranean and Western Asia. Rarely cultivated, it is normally harvested from the wild (3, 5, 6, 25–29).

Description
Perennial herb, with scapes, up to 30 cm high, short rhizome, fibrous primarily adventitious roots. Caudex short. Basal rosette-like leaves broadly elliptic to ovate, obtuse to rounded at the top, entire or irregularly toothed, strongly parallel-veined (3–9 ribs, usually 5), tapered into long petioles, 4–24 cm long, 2.5–11 cm wide, pubescent when young, remaining pubescent on the principal veins or becoming glabrous at maturity. Stem leaves lacking. Inflorescence of dense, narrow, bracteate spikes. Spikes less than 1 cm thick, 5–30 cm long, green-brown, smooth. Flowers hermaphrodite, anemophilous and/or autogamous. Peduncle glabrous. Bracts concave, ovate-oblong, obtuse, thin-margined, 1.5–4 mm long. Calyx 3 mm long, sepals subequal, distinct, ovate to suborbicular, 2–2.5 mm long, glabrous. Corolla greenish, 4-lobed, the lobes deltoid, less than 1 mm long. Stamens inconspicuous, filaments white, anthers violet to yellowish-brown. Capsules, ovate, 2.5–4 mm long, glabrous, dehiscent at or slightly below middle, the top coming off as a conical lid tipped with the remains of the style. Seeds 5–25, black or brown, 1 mm long, finely veined (6, 8, 27, 28, 30, 31).

Plant material of interest: dried leaves

General appearance
Dried, whole or partly fragmented twisted leaves. The dried leaves are ovate or broadly elliptic, entire or toothed, 3–9 ribbed. The ribs taper into a long petiole and they protrude from the cut edge. The leaves are green or brownish-green, up to 24 cm long (including the length of petiole) and 3–11 cm wide. The fragments of cut drug are irregular; their dimensions (length and width) vary within a 7 mm limit (1).

Organoleptic properties
Odour: slight; taste: slightly bitter (1).

Microscopic characteristics
Examining the surface of the leaf, two epidermises can be distinguished: an upper epidermis (polygonal cells with straight cell walls) and a lower
epidermis (polygonal cells with slightly sinuous cell walls). There are anomocytic stomata on both epidermises, but mainly on the lower one. The epidermal cells occasionally have a striated cuticle. There are rosettes of epidermal cells with attached or detached trichomes of two types: simple and glandular. The simple trichomes are multicellular, smooth, with an enlarged base. The glandular trichomes have a monocellular stalk and a bicellular elongated head, rarely a multicellular stalk and an oval or spherical unicellular head. The length of trichomes varies between 30 and 200 µm (1, 27, 32). In transverse section, there are tannins in the mesophyll cells (33).

**Powdered plant material**
Green or brownish-green. The powder has the same microscopic characteristics as the whole leaf (see Microscopic characteristics). The trichomes may be broken off at the “joints”.

**General identity tests**
Macroscopic and microscopic examinations. Phytochemical reactions for detection of polysaccharides and galacturonic acid (1). Thin-layer chromatography for detection of aucubin. Visualization reagents: phloroglucinol and hydrochloric acid (32), dimethyl benzaldehyde (34), benzidine or anisaldehyde or vanillin-sulfuric acid reagents (35). The specific iridoids can be valuable taxonomic markers (36).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (37).

**Chemical**
No information available.

**Foreign organic matter**
Not more than 1% of foreign organic matter. Not more than 5% of brownish and blackish leaves. Not more than 1% of inflorescences. Not more than 5% of fragments of drug having a diameter less than 1 mm. For cut drug: not more than 10% of fragments having a diameter more than 7 mm; not more than 7% of fragments having a diameter less than 0.5 mm (1).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

**Total ash**
Not more than 20% \( (I) \) or not more than 15% \( (38) \).

**Acid-insoluble ash**
Ash insoluble in 10% hydrochloric acid not more than 6% \( (I) \).

**Sulfated ash**
No information available.

**Water-soluble extractive**
Not less than 30% \( (27) \).

**Alcohol-soluble extractive**
No information available.

**Loss on drying**
Not more than 14% \( (I) \).

**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg \( (39) \). For other pesticides, see the European pharmacopoeia \( (39) \) and the WHO guidelines on quality control methods for medicinal plant materials \( (37) \) and pesticide residues \( (40) \).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials \( (37) \).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials \( (37) \) for the analysis of radioactive isotopes.

**Other purity tests**
The content of mineral matter not more than 1% \( (I) \). Chemical, sulfated ash and alcohol-soluble extractive tests are to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 12% polysaccharides \( (I) \).
Major chemical constituents
Dried leaves contain iridoids as the main constituents: aucubin, 3,4-dihydroaucubin, 6’-O-β-glucosylaucubin, catalpol, plantarenaloside and melittoside. Also mucilage (up to 12%); flavonoids (apigenin, baicalein, scutellarein, baicalin, homoplantaginin, nepetrin, luteolin, hispidulin, plantagoside); carbohydrates (L-fructose, D-glucose, planteose, saccharose, stachyose, D-xylose, sorbitol, tyrosol, mucilage and gum); alkaloids (boschniakine, methyl ester of boschniakinic acid); acids (benzoic, caffeic, chlorogenic, cinnamic, p-coumaric, ferulic, fumaric, gentisic, 4-hydroxybenzoic, neochlorogenic, salicylic, syringic, ursolic, vanillic and oleanolic); amino acids; lipids; proteolytic enzymes; tannins (approximately 4%), saponins; steroids; and vitamins are present (18, 22, 27, 29, 41–47, 91). The carbohydrate component of the plantaglucide polysaccharide isolated from leaves of *P. major* consists of galacturonic acid (27%) and monosaccharides: galactose, glucose, mannose, xylose, arabinose and fucose (48). The structures of some characteristic constituents are presented below.

![aucubin](aucubin.png)  ![catalpol](catalpol.png)  ![β-D-glucopyranosyl](beta-D-glucopyranosyl.png)

Medicinal uses

**Uses supported by clinical data**
No information was found.

**Uses described in pharmacopoeias and well established documents**
*Plantago major* is used internally for catarrh of the respiratory tract, cough, bronchitis, inflammatory alterations of the oral mucosa, phlegm congestion, nephritis, cystitis, urinary retention, dysentery, epistaxis (nosebleed) and excessive diaphoresis (49, 50). It is also used for the treatment of diarrhoea and constipation (22).

**Uses described in traditional medicine**
Fresh leaves of *Plantago major* have been used externally for centuries in many parts of the world as an antiseptic for treatment of skin irritations, erysipelas, abscesses, burns, scrofula and inflammatory reactions of the
skin; for repair of damaged tissue; and to treat fistulae and ulcers (5, 43, 51, 52). It is also used to suppress cough associated with bronchitis, colds and upper respiratory inflammation, and as an analgesic and diuretic agent, in the treatment of kidney stones (53–55). It also has a hepato-protective action (4, 56). Plantago major leaves have been used as a weak antibiotic, astringent (57) and as an immunomodulating (58), antihypertensive (59), hypoglycaemic (60), haemostatic (61), antiallergic, febrifuge and antipruritic agent (62). It is used in the treatment of eye inflammation, and as a vermifuge (63–65). It is commonly prescribed for treatment of cystitis with haematuria and haemorrhoids (38).

**Pharmacology**

*Experimental pharmacology*

**Antiviral, cytotoxic and immunomodulatory activities**

The antiviral activity of an aqueous extract and pure components of *P. major* leaves against herpes viruses (HSV-1 and HSV-2) and adenoviruses (ADV-3, ADV-8 and ADV-11) was studied in vitro. The median effective concentration (EC$_{50}$) for antiviral activity was defined as the concentration that achieved 50% cytoprotection against virus infection. The selectivity index was determined by the ratio of the EC$_{50}$s for cytotoxicity and cytoprotection, as defined above. The results showed that the extract had low sensitivity for herpes virus (66).

The antiviral, cytotoxic and immunomodulatory activities of a hot-water extract of the leaves was investigated in vitro against a series of viruses, namely herpes viruses (HSV-1 and HSV-2), adenoviruses (ADV-3, ADV-8 and ADV-11), and in various human leukaemia, lymphoma and carcinoma cells. The activity was measured using XTT, BrdU and interferon-gamma kits. The results demonstrated that the extract possessed significant inhibitory activity against the proliferation of lymphoma (U937) and carcinoma (bladder, bone, cervix, kidney, lung and stomach) cells and against viral infection (HSV-2 and ADV-11). The extract exhibited both immunostimulant and immunosuppressive activities; at low concentrations (< 50 µg/ml), it enhanced lymphocyte proliferation and secretion of gamma-interferon; however, at a high concentration (> 50 µg/ml), it inhibited these effects. It was concluded that the extract possesses a broad spectrum of antileukemia, anticarcinoma and antiviral activities, as well as activities which modulate cell-mediated immunity. Immunomodulatory activity of a decoction of dried leaves of *P. major* was observed in vitro using the lymphocyte transformation test and stimulation of gamma-interferon production (at concentrations of 12.5 µg/ml and 25 µg/ml, respectively) (67).
Studies using individual components of the *P. major* leaf extracts were conducted on lymphocyte transformation by the BrdU immunoassay. Also studies of secretion of gamma-interferon using an enzyme-linked immunosorbent assay (ELISA) were performed. The results showed that the water-soluble components, namely aucubin, chlorogenic acid, ferulic acid, *p*-coumaric acid and vanillic acid, enhanced the activity of human lymphocyte proliferation and secretion of gamma-interferon. Among the water-insoluble components, with the exception of luteolin, both baikalein and baicalin resulted in an enhancement of the human peripheral blood mononuclear cells. Although oleanolic acid and ursolic acids did not significantly affect the proliferation of peripheral blood mononuclear cells they exhibited a strong stimulation of gamma-interferon secretion. Linalool, a monoterpenoid, showed immunomodulatory activity similar to that of the triterpenes (46).

An endotoxin-free methanol extract from *P. major* leaves, at doses of 50, 100, 250 and 500 µg/ml, increased nitric oxide production by 4.4 ± 1, 6 ± 1, 12 ± 0.4 and 18 ± 0.4-fold, and increased tumour necrosis factor alpha (TNFα) production by 621 ± 31, 721 ± 36, 727 ± 36 and 1056 ± 52 U/ml, respectively in rat peritoneal macrophages. Nitric oxide and TNFα production in untreated macrophages was negligible. In addition, the extract dose-dependently potentiated concanavalin A-induced lymphoproliferation (3- to 12-fold increases), as compared with concanavalin A alone. The regulation of immune parameters induced by the plant extract may be clinically relevant in numerous diseases (68).

**Haematopoietic effects**

Aqueous, methanol, chloroform and hexane extracts of *P. major* leaves were tested for immunostimulant and haematopoietic activities (independent and interdependent) on cultures of *Escherichia coli*, *Bacillus subtilis* and *Candida albicans* and also on CD(1) mice bone marrow and splenocyte cultures (37 °C for 72 hours). Aqueous and methanol extracts at concentrations of 0.4 and 0.2 mg/ml increased the bone marrow cell concentration by 2.70-fold and 3.15-fold, and also increased the spleen cell concentration by 3.38-fold and 6.39-fold, respectively (*p* < 0.001). The data demonstrated in vitro haematopoietic activity of *P. major* (69).

**Antimicrobial activity**

A 50% aqueous–ethanol extract of dried leaves of *P. major* had antibacterial activity against *Shigella dysenteriae* at a concentration of 50 µl/agar plate (70) in vitro. A tincture (1:10) was active against *Bacillus subtilis* (0.1 ml/agar plate), *Escherichia coli* (30 µl/disc), and *Staphylococcus aureus*
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

(30 µl/disc) (52). An ointment from *P. major* leaves expressed antiiyeast activity against *Candida albicans* at a dose of 20.7 µg/g/agar plate (71). The antibacterial effect of a pectin polysaccharide isolated from *P. major* leaves was examined in inbred NIH/OlaHsd and Fox Chase SCID mice, infected with *Streptococcus pneumoniae* serotype 6B. The pectin polysaccharide was administered intraperitoneally (12 µg/animal) either once, three days before challenge, or one to three times, 3–48 hours after challenge. The number of bacteria in blood and the mouse survival rates were recorded. Pre-challenge administration of the polysaccharide and also a lipopolysaccharide (included as a control), provided a dose-dependent protective effect against *S. pneumoniae* serotype 6B infection. However, injection of pectic polysaccharide after establishment of the infection in mice had no effect. These results demonstrate that the pectic polysaccharide fraction from *P. major* protects against pneumococcal infection in mice when administered systemically before challenge, and that the protective effect is due to stimulation of the immune system (72).

**Antiparasite activity**

Weak antigiardiasis activity of a decoction of *Plantago* leaves at a concentration of 60 mg/ml, was observed in vitro in a blinded study using trophozoites of *Giardia duodenalis* incubated with the decoction. The viability of trophozoites was determined using 3-[4,5-dimethylthiazol-2-il]-2,5-diphenyl tetrazolium bromide (MTT), which is reduced to MTT-formazan by the activity of live trophozoites. The reduced MTT was extracted and measured by spectrophotometry at 570 nm. Negative (trophozoites without extract) and positive controls (incubated with tinidazol) were also analysed. Antigiardiasis activity of the decoction as determined by trophozoite mortality was 76 ± 1.2% (73).

**Antinociceptive effects**

The antinociceptive effect of methanolic extracts of *P. major* leaves (400 g/kg body weight (bw)) was studied in mice using the acetic acid-induced writhing inhibition and tail-fl ick tests. Orally administered extract inhibited the nociception to acetic acid-induced writhing with a protection of 50.8–45.8% compared with controls. In the tail-fl ick test, at a dose of 400 mg/kg bw, the extract significantly increased the latency in response of the tail to thermal stimulation. At doses up to 2 g/kg bw, the extracts did not cause any deaths or major signs of acute toxicity (74). Intragastric administration of an aqueous extract of dried leaves of *P. major* inhibited acetic acid-induced writhing in mice at a dose of 1 g/kg bw (65).
Anti-inflammatory activity
The intragastric administration of an aqueous extract of dried leaves of *P. major* at a dose of 1 g/kg bw inhibited carrageenan-induced pleurisy and plantar oedema in rats. A doubling of the dose of the extract (to 2 g/kg bw) inhibited development of croton oil-induced granuloma (65). Ursolic and oleanolic acids were isolated from a hexane extract of dried leaves using bioactivity-directed fractionation. Both substances had anti-inflammatory activity (75).

Histamine release inhibiting activity
An ethanol extract of *P. major* leaves was tested for its ability to inhibit histamine release from RBL-2H3 cells (rat basophilic leukaemia cell line), a tumour analogue of mast cells. The ethanol extract (0.5 mg/ml) inhibited immunoglobulin E-dependent histamine release from RBL-2H3 cells. The inhibitory effect was greater than 80%. The results indicate that the active components of this extract inhibiting mast cell degranulation could be useful in the treatment of asthma (76).

Diuretic activity
Intragastric administration of a decoction of *P. major* leaves to rats, at a dose of 1 g/kg bw, stimulated diuresis (55).

Antitumour effects
A 70% ethanol extract and an aqueous–ethanol (1:1) extract of dried leaves demonstrated anticrustacean activity in the *Artemia salina* assay at a median lethal concentration of 7 µg/ml and a median inhibitory concentration of 4.74 µg/ml, respectively. The ethanol extract also inhibited β-glucuronidase activity at a median inhibitory concentration of 17 µg/ml (77). Fifty-two per cent inhibition of sarcoma 180 (ASC) cell growth was detected in vivo in mice after intraperitoneal injection of 0.2 mg/kg of a 95% ethanol extract for 5 days (78). In a chronic experiment in rats, administration of a polyphenolic complex from *P. major* leaves – plantastine (the route of administration was not mentioned) decreased the effect of an endogenously synthesized carcinogen, nitroso-diethylamine. This carcinogenic compound is synthesized in rats following the long-term administration of amidopyrine and sodium nitrite causing toxic damage to the liver and production of tumours. The number of neoplasms was 33.3% in animals receiving plantastine and 87.5% in rats given the amidopyrine/sodium nitrite combination. Plantastine also decreased the normal level of enzyme activity induced by amidopyrine and sodium nitrite (79). A methanol extract from air-dried and powdered *Plantago* leaves was evalu-
ated for cytotoxic activity against the human cancer cell lines: human renal adenocarcinoma (TK-10), human breast adenocarcinoma (MCF-7) and human melanoma (UACC-62). The sulforhodamine B assay was used in this study to assess growth inhibition. The concentrations of extract (µg/ml) required to inhibit cell growth by 50% were: > 250 (TK-10); 46.5 ± 7.1 (MCF-7) and 46.5 ± 8.2 (UACC-62). The concentrations required to produce total growth inhibition were: > 250 (TK-10); 97.5 ± 1.8 (MCF-7) and 112.5 ± 2.1 (UACC-62), and the concentrations required to cause 50% net cell death were: > 250 (TK-10); 207 ± 18.20 (MCF-7) and 247 ± 12.3 (UACC-62). The results demonstrate that the extract has weak cytotoxic activity with a certain degree of selectivity against the tested cells in culture. The results could justify the traditional use of *P. major* as an antitumour agent (80).

**Wound-healing activity**

The dermal application of the non-hydrolysable chromatographic fraction (10%) from the hexane extract (25%) of dried leaves of *P. major* significantly (*p* < 0.001) accelerated the rate of contraction and epithelialization of excision wounds in rabbits (81).

The interaction between a pectin-type polysaccharide fraction (PTPF), isolated from the leaves of *P. major*, and human complement was tested in vitro using two different haemolytic complement-fixation tests and two ELISA methods for detection of complement-activation products. Serum from 10 human volunteers was used as a complement source. The complement-fixation tests were designed to measure the concentration of the pectin necessary to inhibit haemolysis by 50% (*ICH*<sub>50</sub>). The ELISA tests, for determination of complement-activation products, utilized a fully activated serum as a standard. A greater than 200-fold difference in *ICH*<sub>50</sub> activity of the PTPF pectin was observed in one of the haemolytic tests when the individual serum used as the complement-source was varied. By contrast, the ELISA complement-activation tests showed no significant variation in activity of the PTPF in relation to the complement serum used. The level of antibodies against PTPF detected in the complement sera did not correlate with the *ICH*<sub>50</sub> activity of PTPF. The results indicate that PTPF is a potent complement activator with an activity of the same order of magnitude as that of aggregated human immunoglobulin G. The results might be related to the wound-healing effect of the leaves of *P. major* (82).

**Toxicology**

The median lethal dose (LD<sub>50</sub>) for intragastric administration of an aqueous-ethanol (1:1) extract of *P. major* leaves to mice was determined to be

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11.9 g/kg (77, 83). The somatic mutation and recombination test in *Drosophila melanogaster* was used to evaluate the genotoxic activity of an aqueous extract of *P. major* leaves. Two *Drosophila* crosses were produced: a standard cross and a high-bioactivation cross. Each cross produced two types of descendents. Three-day-old larvae of both types of descendents were treated with undiluted and diluted extract (1:1 and 1:2 in water). The extracts were genotoxic in both crosses, the number of induced frequencies produced were similar in both types of flies. Comparison of the frequencies of wing spots in the descendents indicated that recombination was a major response. The results indicate that, under these experimental conditions, aqueous extracts are genotoxic (recombinogenic) (84). Subchronic toxicity of an aqueous preparation of leaves was tested in 20 NGP male mice, with an average weight of 20.1 g. The extract (2000 mg/kg) was administered once daily on 5 days a week for a total of 40 days. The control group received 0.5 ml of distilled water instead of extract. Signs of subchronic toxicity were recorded on days 2 and 12 of treatment. No significant changes in body weight were observed in mice that received the aqueous extract and control mice. Ocular irritation was tested for in five male New Zealand rabbits, with an average weight of 3.6 kg. The dose used was 200 µl of a preparation (100 mg/ml) of *Plantago major* leaves, instilled into the conjunctiva. The extract caused no significant irritation during the observation period (85). A saline extract of dried leaves of *P. major* was studied for potential genotoxicity in the *Salmonella typhimurium* microsomal activation assay and the alkaline single-cell gel electrophoresis (COMET) assay. The extract (40 µg/agar plate) did not cause a positive response in strains TA98 or TA100 of *Salmonella typhimurium* with or without metabolic activation, but increased values above those of the negative control in the COMET assay. The results indicate that the extract has genotoxic activity in human lymphocytes (86).

**Clinical pharmacology**
No information was found.

**Adverse reactions**
Allergic contact dermatitis in response to *P. major* has been reported (87).

**Contraindications**
In case of hypersensitivity to *P. major* pollen (e.g. contact dermatitis), use should be stopped.
Warnings
No information was found.

Precautions

General
No information was found.

Drug interactions
No information was found.

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found on carcinogenesis or impairment of fertility. Genotoxic activity of the aqueous-ethanolic and saline extracts has been reported under experimental conditions (see Toxicology above).

Pregnancy
The use of the herb is not recommended during pregnancy (see sections on Toxicology and Genotoxicity).

Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Comminuted herb used for infusions and other Galenical preparations for internal use. Juice of the leaves of Plantago major (89).

Posology
(Unless otherwise indicated)
Internal. Granules of dried leaf: 2–4 g three times daily, before meals (38). Infusion: one tablespoon of an infusion (10 g dried leaf in 200 ml boiled water for 15–20 minutes) three times daily before meals (89). Liquid extract: 2–4 ml of a liquid extract from dried leaf (1:1 in 25% ethanol) three
times daily (41). Tincture: 2–4 ml of a tincture of dried leaf (1:5 in 45% ethanol) three times daily (41). Juice of the fresh leaves: one tablespoon three times daily, before meals (28).

External. Cold macerate for use as a rinse, gargle or cataplasm: soak 1.4 g cut herb in 150 ml cold water for 1–2 hours, stirring often. For use as a rinse or gargle: rinse or gargle with cold macerate (soak 1.4 g cut herb in 150 ml cold water for 1–2 hours stirring often) three to four times daily (90).

References
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Folium Plantaginis majoris


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Herba Polygoni avicularis

Definition
Herba Polygoni avicularis consists of the whole or cut dried flowering aerial parts of Polygonum aviculare L. (Polygonaceae) (1, 2).

Synonyms

Selected vernacular names
Allseed nine-joints, armstrong,aviculaire, baekjeol, beggarweed, bian xu, birdgrass, bird knotgrass, bird’s tongue, birdweed, bistorta centinodio, bistorte aviculare, Blutkraut, centinode, centinodia, common knotgrass, common knotweed, coreggiuola, cow grass, crawlgrass, chveulebrivimatitela, devil’s grass, doeji pool, doorweed, eunmadeup, goretspitsii, harilik linnurohi, herba centumnodii, herba sanguinalis, herbe à cochon, herbe aux panaris, herbe de renouée des oiseaux, herbe des St Innocents, hogweed, hou segräs, hundred jointed, knicker, knot-grass, knotgrass herb, knotweed, knot-weed, qu sh toron, laus rasen, madeupnamul, matgrass, maura sûrene, ninety-knot, pig-rush, pigweed, pihatatar, pinkweed, plattsaad, poligono, poligono degli ucelli, porcfu, prostrate knotweed, rdesno ptaci, red robin, renouée des oiseaux, russischer knöterichtee, sanguinaire, sauggrss, saukraut, schweinegrass, schweinekruse, sekedeknä, shabat el ghūl, sparrow tongue, sporiş, sporysz, stonegrass, swine’s grass, swynel grass, tire-goret, trainasse, trampgrass, traniane, tros cot, tunganess, vej-pileurt, vogelknö terich, vogelknöterichkraut, way grass, wegetred, wegetrit, weggras, weg kruast, weidemannscher tee, Zerrgras (4, 6–18).

Geographical distribution
Widespread in the temperate zones throughout the world. A common weed (3, 7, 9, 16, 20).
Description
An annual highly polymorphous plant, small taproot with numerous rootlets. Stems, branched, many prostrate or slightly ascendant, 10–60(100) cm in length, with longitudinal grooves, hairless. Leaves, alternate, petiolate or sessile, oblong to lanceolate or linear, hairless, apex pointed, up to 3 cm long, with pointed and toothed stipules. Ochrea covering the nodes, transparent, silvery, 4–12 mm long, bilobed, later cut into a few narrow strips, 8–10-veined. Flowers, hermaphrodite, entomophile, axillary, solitary or 2–5 fascicled, very small, inconspicuous, greenish-red; peduncle 1–1.5 mm long; calyx with 5 sepals, green with white or pink margins, 1.5–3.5 mm long; 5 petals, 2.5–3.5 mm long; 8 stamens; superior ovary with 3 very short styles and inconspicuous stigmata. Fruits, triangular nutlets, ovate to almost elliptical, as long as the epicalyx or protuberant, striated, flattish or concave faces, dark brown to black, minutely roughened, 2–4 mm long (3, 4, 7, 9, 21–28).

Plant material of interest: dried aerial parts
General appearance
Whole or cut leafy stems up to 40 cm in length. Stem is 0.5–2 mm thick, branched, with nodes, cylindrical or slightly angular and longitudinally striated; bears sessile or shortly petiolate, glabrous entire leaves. Leaves differ widely in shape and size: broad-elliptic, oblong, obovate, lanceolate or nearly linear, up to 3 cm long and 1 cm wide. The sheath-like stipules (ochrea) are lacerate and silvery. The flowers are small and axillary, they have 5 greenish-white perianth segments, the tips of which are often coloured red. The fruits are 2–4 mm long, brown to black triangular nutlets, usually punctate or striate (1, 2).

Organoleptic properties
Odour: slight; taste: slightly astringent (2).

Microscopic characteristics
Cells of upper and lower epidermises have thick, straight, polygonal to sinuous cell walls. Cell walls of upper epidermis occasionally irregularly thickened. Cuticle is longitudinally striated at the leaf edge and on the largest veins. Stomata anisocytic. 1–3 layers of epidermis cells at the leaf margins have strongly thickened cell walls, which have been transformed into papilla-like protuberances. In the mesophyll of the leaves, and in the stems, there are numerous, sometimes very large, clusters of calcium oxalate crystals. There are many sinuous thick-walled fibres, especially on the upper and lower veins, and at the leaf edge.
Powdered plant material
Greenish-brown. Fragments of the leaf epidermis with polygonal to sinuous cell walls and numerous anisocytic stomata; fragments of leaves and stems containing numerous calcium oxalate clusters, some of them very large; groups of thick-walled fibres from the hypodermis of the stem; globular pollen grains with smooth exine and 3 germinal pores; occasional brown fragments of the exocarp composed of cells with thick sinuous walls.

General identity tests
Macroscopic and microscopic examinations, thin-layer chromatography for the presence of characteristic constituents, caffeic acid and chlorogenic acid (1) or flavonoids (29), and colour reaction of cut drug with aluminium chloride for the detection of flavonoids (2) and colour reaction of water extract of pulverized drug with ferric chloride (30).

Using a 675 g/l solution of potassium hydroxide and gently heating, the epidermis of the leaves and a few cells of the mesophyll stain red to reddish-violet when examined using a 0.1 g/l solution of ferric chloride, some leaf fragments stain almost black (1, 2, 7).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (31).

Chemical
No information available.

Foreign organic matter
Not more than 2% of roots and not more than 2% of other foreign matter (1, 2). Brownish and blackish parts of plant, not more than 3%. For cut drug: not more than 10% of fragments of drug having a diameter less than 0.5 mm and not more than 10% of fragments of drug having a diameter more than 7 mm (2). Not more than 3% (30).

Total ash
Not more than 10% (1), 13% (2, 30).

Acid-insoluble ash
Not more than 3% (30).
**Sulfated ash**
No information available.

**Water-soluble extractive**
Not less than 6% (30).

**Alcohol-soluble extractive**
Not less than 16% (30).

**Loss on drying**
Not more than 10% (1) or 13% (2). Not more than 15% (30).

**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (1). For other pesticides, see the *European pharmacopoeia* (1) and the WHO guidelines on quality control methods for medicinal plant materials (31) and pesticide residues (32).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (31).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (31) for the analysis of radioactive isotopes.

**Other purity tests**
The content of mineral matter not more than 2% (2). Chemical and sulfated ash tests to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 0.3% of total flavonoids, expressed as hyperoside (1) or not less than 0.5% of flavonoids, expressed as avicularin (2).

**Major chemical constituents**
The major constituents of the aerial parts are flavonoids (0.1–1%, rarely 2.5–3%); derivatives of kaempferol, quercetin and myricetin, especially avicularin (quercetin-3-O-arabinoside, approximately 0.2%); juglanin (kaempferol-3-O-arabinoside), hyperoside, quercitrin, rhamnetin-3-O-
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galactoside, vitexin, isovitexin and rhamnazin hydrogen sulfate. There is also a lignan glycoside, aviculin, a naphthoquinone (6-methoxyplumbagin), a mucilage, which on hydrolysis produces galacturonic acid, glucose, galactose, arabinose and rhamnose; lignan aviculin; some tannins (rhatan-nin), phenolcarboxylic (e.g. caffeic and chlorogenic) acids, hydroxycou-marins (umbelliferone and scopoletin); tartaric, formic and silicic acid (approximately 1%), a small amount of which is present as water-soluble silicates (4, 7, 8, 19, 20, 33–43). The structures of the main constituents are presented below.

Medicinal uses

*Uses supported by clinical data*

Used for the supportive treatment of gingivitis (44).

*Uses described in pharmacopoeias and well established documents*

Herba Polygoni avicularis is used for the relief of cough and cold symptoms (35). The plant is well known in Chinese medicine where it is used for the treatment of urinary infection with difficult painful urination, as a remedy for heavy menstrual bleeding, for dysentery, snake bites, eczema and vulval itching (29).

*Uses described in traditional medicine*

Herba Polygoni avicularis has been used for lowering blood pressure, and as a haemostatic, anti-rheumatic, antipyretic and hypoglycaemic agent (36, 45–48). It is also used for treatment of intestinal discomfort, to pass kidney stones, to treat varices, as a cholagogue and emmenagogue (49–51). The use of Herba Polygoni avicularis as an insecticide or vermifuge, astringent, antifungal and wound-healing agent has been described (52–54). It is also used for the treatment of weeping eczema (55).
Pharmacology

Experimental pharmacology

Antihepatotoxic activity

The antihepatotoxic activity of a methanol extract of dried Herba Polygoni avicularis was tested in rats. Intraperitoneal administration of the extract as a single dose of 1000 mg/kg body weight (bw) (about 0.2 g per rat) (represented as the amount of crude drug equivalent) inhibited alkaline phosphatase, serum aspartate aminotransferase activity and decreased plasma bilirubin concentrations when hepatotoxicity was induced by α-naphthylisothiocyanate. At a dose of 14.7 mg/kg the extract also inhibited serum alanine amino transaminase activity, induced by α-naphthylisothiocyanate. The extract (200 and 500 mg/kg bw) was hepatoprotective in conditions of carbon tetrachloride-induced hepatotoxicity. Methanol extracts of the crude drug demonstrated hepatoprotective effects by inhibiting lipid peroxide formation induced by adenosine diphosphate + nicotinamide adenine dinucleotide phosphate and carbon tetrachloride in rats at median inhibitory concentrations (MICs) of 21.6 µg/ml and 29.1 µg/ml, respectively (56–58). Intragastric administration of a methanol extract at a dose of 100 mg/kg bw, to male rats, reduced serum aspartate aminotransferase and alanine amino transaminase activities and the hydroxyproline content in the liver. In addition, the extract significantly reduced inflammation and fibrosis of the liver in a bile duct ligation model (59).

A free-radical scavenging effect was observed in vitro with a methanol extract of dried Herba Polygoni avicularis at an MIC of 89 µg/plate (36, 60). Two flavonoids, avicularin and juglanin, were isolated from Herba Polygoni avicularis as the active constituents from the ethanol-acetic fraction by bioassay. Avicularin and, to a lesser extent, juglanin inhibited the lipid peroxidation of rat liver induced by 50% ethanol. Avicularin, the main constituent of the plant, significantly decreased the elevated serum aspartate aminotransferase and lactate dehydrogenase levels in carbon tetrachloride-intoxicated rats, demonstrating hepatoprotective properties. Avicularin also significantly decreased the serum bilirubin level in α-naphthylisothiocyanate-intoxicated rats. These results confirm the hepatoprotective activity of avicularin against chemically induced hepatotoxicity in rats (61).

The protective effects of a methanol extract of Herba Polygoni avicularis against liver fibrosis in rats were studied in a bile duct ligation and scission operation model, for 4 weeks. In rats that had been operated on, the levels of aspartate aminotransferase, alanine amino transaminase, al-
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kaline phosphatase, total bilirubin in serum and hydroxyproline content in liver were dramatically increased. Treatment with the extract in rats that had been operated on reduced the serum aspartate aminotransferase, alanine amino transaminase and alkaline phosphatase levels significantly \( (p < 0.01) \). Liver hydroxyproline content was also reduced to 40% by treatment with the extract as compared with controls \( (p < 0.01) \). The morphological characteristics of fibrotic liver, which appeared in the control group of animals that had been operated on were less marked in the group that had been both operated on and treated with the extract. These results suggest that Herba Polygoni avicularis has an antifibrotic effect in rats \( (59) \).

Antiaggregatory effects
The antiaggregatory effects of vitexin, isovitexin, luteolin, kaempferol-3-arabinoside, rhamnetin-3-galactoside and quercetin-3-galactoside, active constituents isolated from Herba Polygoni avicularis, were tested in vitro, in platelet-rich plasma from blood donors. It was shown that vitexin and rhamnetin-3-galactoside, at a concentration of \( 10^{-5} \) M, inhibited the aggregation of human blood platelets induced by adenosine diphosphate \( (\text{concentration } 10^{-5} \text{ M}) \) and arachidonic acid \( (\text{concentration } 10^{-4} \text{ M}) \), whereas luteolin and kaempferol-3-arabinoside slowed or stimulated aggregation, depending upon the experimental conditions. These findings suggest that constituents tested may influence platelet aggregation by possible interaction with the cyclooxygenase and lipoxygenase pathway of the arachidonic acid cascade in human platelets \( (62, 63) \).

Angiotensin-converting enzyme inhibiting activity
A chromatographic fraction from Herba Polygoni avicularis, containing rhatannin and other tannins, at a concentration of 20 µg/ml, and a methanol-aqueous extract \( (1:1) \) at a concentration of 200 µg/ml, inhibited the activity of angiotensin-converting enzyme isolated from pig kidney in vitro. Both rhatannin and the tannin samples had potent inhibitory effects on angiotensin-converting enzyme with an MIC of 1.1 mg/ml and showed high specificity for this enzyme \( (64, 65) \).

Anti-inflammatory effects
An aqueous extract of oven-dried Herba Polygoni avicularis \( (\text{at a concentration of } 0.25 \text{ mg/ml}) \) inhibited platelet activating factor in cell culture and platelet activating factor-induced neutrophil exocytosis. These findings may suggest a mechanism for the antiinflammatory action of the plant \( (66) \).
Antispasmodic activity
A 95% ethanol extract of Herba Polygoni avicularis had antispasmodic activity against barium-induced contractions at a concentration of 100 µg/ml in the isolated guinea-pig ileum (67). Hexane, ethyl acetate, and n-butanol extracts of Herba Polygoni avicularis were screened for potential vasorelaxant activity using isolated rat aorta. Hexane and n-butanol extracts exhibited distinctive vasorelaxant activity. The activity disappeared on removal of the functional endothelium or following pretreatment of the aortic tissues with N-nitro-L-arginine methyl ester, which is an inhibitor of nitric oxide synthase. These findings suggest that Herba Polygoni avicularis relaxes vascular smooth muscle via an endothelium-dependent nitric oxide mechanism (68).

Insect repellent activity
A 95% ethanol extract of dried Herba Polygoni avicularis, at a concentration of 1 g/l, was tested externally in hamsters as an insect repellent. The extract, at a dose of 2.5 µg/cm², had insect repellent activity against the sand fly, *Lutzomyia longipalpis*, a major vector of leishmaniasis in South America (69).

Toxicology
The LD₅₀ of a 50% ethanol extract of the aerial parts of Polygoni avicularis administered by the intraperitoneal route in rats was determined to be 500 mg/kg bw (70). Tests with a 10% infusion, decoction (1:4), aqueous extract (1:50) and an ethanol extract of the leaves were conducted in mice, cats, rabbits and dogs. The minimal lethal dose for cats and rabbits was determined to be 20 ml/kg for the infusion or decoction, and 2 ml/kg for the aqueous extract, when administered intravenously. For mice, the minimal lethal dose was determined to be 0.2 ml (about 10 ml/kg) for the aqueous extract, when administered intraperitoneally. Intravenous injections lowered blood pressure in cats, rabbits and dogs. The most potent preparations were the aqueous and ethanol extracts (71).

Clinical pharmacology
The effectiveness of a natural extract of *Polygonum aviculare* was assessed in 60 students (18–25 years old). Over a period of 2 weeks they used the extract (1 mg/ml) in an oral rinse twice daily. The O’Leary Plaque Index and the Loe and Silness Gingivitis Index were recorded at baseline in all the subjects. The result showed that the extract decreased gingivitis from day 0 ("xx" height = “11” width = “13” ≥ 1.056) to day 14 ("xx" height = “11” width = “13” ≥ 1.011) (p ≤ 0.05). The researchers concluded that the
extract in the form of an oral rinse can be included in supportive therapy for gingivitis (44).

**Adverse reactions**
No information was found.

**Contraindications**
No information was found.

**Warnings**
No information was found.

**Precautions**

**General**
No information was found.

**Drug interactions**
No information was found.
Should not be used together with an anticoagulant (see Pharmacology).

**Drug and laboratory test interactions**
No information was found.

**Carcinogenesis, mutagenesis, impairment of fertility**
No information was found.

**Pregnancy**
Use during pregnancy is not recommended (see Pharmacology).

**Nursing mothers**
No information was found.

**Paediatric use**
No information was found.

**Dosage forms**
Ground herb for infusions and other Galenical preparations for internal use and for local application (8).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

**Posology**
(Unless otherwise indicated)
Daily dose: 4–6 g of drug; or equivalent preparations (35).
*For internal use.* Infusion: to 3 tablespoons (15 g) of the herb, add 200 ml of boiling water and allow to stand for 15 minutes; divide 75 ml of the infusion into three parts and drink three times daily, 20–40 minutes before meals (72). A cup of the tea is prepared by placing 1.5 g of the chopped drug into cold water, heating to boiling, and straining after 10 minutes, 3–5 times a day (7).

**References**
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)


Folium Salviae

Definition
Folium Salviae consists of the whole or cut dried leaves of *Salvia officinalis* L. (Lamiaceae) (1, 2) collected during the summer from cultivated plants (2).

Synonyms

Selected vernacular names
Aci elma out, adca çayi, aedsalvei, ārstniecības salvija, asfâqs, broad-leafed sage, broad-leaved white sage, cinstes, cinstet, cocean-capresc, common sage, dalmatian sage, dalmatiner-Salbei, dorivor marmarak, dorivor ma-vrak, echte salvei, echter Salbei, Edelsalbei, edler Salbei, elalisphakos, elelisphakos, fischsalbe, garden sage, Garten Salbei, gradinski tshai, grande sauge, green sage, guiāh-e-tchai, herbe cacrée, jaleš, kharnah, konski bosilek, Königssalbei, Königs-Salbei, maryam-goli, maryamīyah, narrow-leaved white sage, petite sauge, sabikraut, Salbei, salbey, sale, salie, salfei, salva, salvetta, salvia fina, salvia grande, salvia officinale, salvia real, salvia salvatrix, salvie, samkurnalo salbi, saudzette, sauge, sauge commune, sauge officinale, save, sawge, Scharlachkraut, scharlei, shalfei lekarstvennyi, shop sage, szalvia, serialu, serlaiu, Rauch-Salbei, red sage, té della grecia, thè de gréce, the de france, tibbi adacayi, true sage, tugensalbe (3, 5–16).

Geographical distribution
Indigenous to the whole Mediterranean region. Cultivated worldwide (3, 5, 6, 17–20).

Description
A perennial subshrub, 25–50(–70) cm high, woody root. Stems wiry, woody at the base, erect, branched, quadrangular, hollow and softly curly-pubescent. Leaves, opposite, simple, petiolate, from oblong-ovate
to lanceolate (sometimes with two small lobes at the base), round or wedge-shaped base, round or subacute apex, crenulate margins, finely wrinkled by a strongly-marked network of veins on both sides, upper and lower surfaces greyish-green, softly hairy and glandular, 2–10 cm long, 0.8–1.5(–4) cm wide. Inflorescences, loose spikes of flower whors. Flowers, bisexual, zygomorphic, 2 cm long, bluish-violet or purplish, sometimes white. Bracts, sessile, ovate-lanceolate, acuminate, membranous, and striated at the base. Peduncles, curly-pubescent, 3–6 mm long. Calyx, campanulate, membranous, striated, downy (especially outside on the veins and the margins of the sepals), bilabiate; the upper lip 3-toothed; the lower bifi d; all the teeth subulate and acuminate, 9–10 mm long. Corolla, 2 or 3 times as long as the calyx, with a large projecting tube, ringed on the inside, and bilabiate; upper lip arched, lower lip tri-lobed, the lateral lobes being reflexed. Pistil, single, superior 4-lobed ovary. The two usually absent upper stamens are sometimes present in very small-sterile hooks. Fruit, 4 nutlets, nearly round, brown, 2.5 mm in diameter (5, 8, 17, 18, 21–26).

**Plant material of interest: dried leaves**

Fresh material may also be used, provided that when dried it complies with the monograph in the *European Pharmacopoeia* (27).

**General appearance**

The lamina of whole leaf is about 2–10 cm long and up to 3 cm wide, oval, oblong-ovate, elliptical to lanceolate; upper surface pubescent, lower surface tomentose, texture soft and velvety. The margin is finely crenulate to smooth. The apex is rounded or subacute and the base is shrunken at the petiole and rounded or cordate. Both surfaces with conspicuous, reticulate venation. The deeply depressed venation on the upper surface is very prominent on the lower surface and shows a dense network of raised veinlets. The upper surface is pale green and finely granular; the lower surface is greyish-green to white and pubescent. Petiole up to about 4 cm. The cut drug consists of small leaf fragments, which, because of the dense tomentum, cling together; the fine pubescence on both surfaces and the reticulate venation on the lower surface are easily recognized (1, 5, 28, 29).

**Organoleptic properties**

Odour: intensely spicy and aromatic; taste: spicy, aromatic, bitter and slightly astringent (2, 5).
Microscopic characteristics
Dorsiventral with a two-layered palisade; epidermal cells are polygonal and thick-walled; upper epidermis with markedly beaded anticlinal walls and a faintly striated cuticle; lower epidermal cells sinuous; diacytic stomata on both epidermises, more frequent on the lower one; abundant covering and glandular trichomes on both epidermises and also on the petiole; covering trichomes long, narrow, uniseriate, with thick walls, 2–6 celled, with a short basal cell, undulating terminal cells tapering to sharply acute apexes; the glandular trichomes of two types: typical labiate type with a unicellular stalk and a radiate eight-celled head containing reddish-brown secretion, or smaller with a one to four-celled uniseriate stalk and a unicellular or bicellular head (1, 2, 5, 25, 29–31).

Powdered plant material
Grey to brownish-green. Numerous articulated and bent trichomes with narrow elongated cells and very thick cell walls at the base as well as fragments of these trichomes; fragments of the upper epidermis with pitted, somewhat polygonal cells; fragments of the lower epidermis with sinuous cells and numerous diacytic stomata; rare single glandular trichomes with a unicellular or bicellular head and a stalk consisting of 1–4 cells; abundant glandular trichomes with a unicellular stalk and a head composed of 8 radiating cells with a raised common cuticle; groups of vascular tissues from the petiole and main veins showing vessels with annular and reticulate thickening (1, 29).

General identity tests
Macroscopic and microscopic examinations, thin-layer chromatography in daylight and under ultraviolet light for the presence of characteristic essential oil constituents, α-thujone, β-thujone and cineole (1, 29) and other characteristic terpenes (5). Thin-layer chromatographic study of the flavonoids (32).

Purity tests
Microbiological
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (33).

Chemical
No information available.
**Foreign organic matter**
Not more than 2% (1) or not more than 3% (2, 32). Not more than 5% of brownish and blackish leaves. Not more than 13% of other parts of plant (flowers and fragments of stems). For cut drug, not more than 10% of fragments of drug having a diameter less than 0.5 mm (2). Leaves of *Salvia triloba* absent (34).

**Total ash**
Not more than 10% (1). Not more than 8% (29). Not more than 12% (2).

**Acid-insoluble ash**
Not more than 2% (29).

**Sulfated ash**
Not more than 12% (34).

**Water-soluble extractive**
Not less than 16% (29).

**Alcohol-soluble extractive**
No information available.

**Loss on drying**
Not more than 14% (2). Not more than 10% (1).

**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (1). For other pesticides, see the *European pharmacopoeia* (1) and the WHO guidelines on quality control methods for medicinal plant materials (33) and pesticide residues (35).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (33).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (33) for the analysis of radioactive isotopes.

**Other purity tests**
Chemical, acid-insoluble ash, water-soluble extractive and alcohol-soluble extractive tests to be established in accordance with national require-
ments. The content of mineral matter not more than 0.5% (2); not more than 3% of foreign matter (29).

Chemical assays
Contains not less than 1.5% (v/w) of essential oil for the whole drug and not less than 1.0% (v/w) of essential oil for the cut drug (1). Not less than 0.8% of essential oil (2). High-performance liquid chromatography method for determination of the thujone content (36). Hexane extract is coloured red by sodium hydroxide (thujone) (37).

Major chemical constituents
Dried leaves contain 1–3.5% essential oil (fresh leaves contain about 3 times less), mostly monoterpenoids of which 18–60% are α-thujone, 3–21% β-thujone, 4.5–24.5% camphor (both (R)-(+) -camphor and (S) (−)-camphor may be found), 5.5–13% cineole, 0–12% humulene, 1–6.5% α-pinene, 1.5–7% camphene, 0.5–3% limonene, up to 1% linalool, and up to 2.5% bornyl acetate. Sesquiterpenoids such as veridiflorol (11%) and humulene (0–12%), a diterpenoid, manool (9%), and a linear aliphatic alcohol 1-octen-3-ol (8.5%) are present among the main constituents of the essential oil. Sage leaves of Dalmatian origin consist mainly of α-thujone and β-thujone (share 20–60%), 1,8-cineole (6–16%) and camphor (14–37%) (3, 5, 7, 23, 27, 36, 38, 39, 40). Also, apianane terpenoids, 3–8% condensed catechin-type tannins (salviatannin); phenolic acids (rosmarinic, chlorogenic, ferulic and gallic acids; caffeic acid monomers, dimers, trimers and tetramers); 1–3% flavonoids (apigenin and luteolin 7-O-glucosides, genkwanin, genkwanin-6-methyl ether, 5-methoxysalvigenin, hispidulin); diterpenes (carnosol, carnosic acid, rosmanol, safficinolide); triterpenes (oleanolic acid, ursolic acid, α-amyrin, β-amyrin (about 5%)); and resin are present (3, 5, 7, 23, 38, 39, 41–51). The structures of the characteristic constituents are presented below.

Medicinal uses
Uses supported by clinical data
The management of mild to moderate Alzheimer disease (52).

Uses described in pharmacopoeias and well established documents
Salvia officinalis is used internally for treatment of influenza, bronchitis, sinusitis, meningitis and neuritis (53). The European Scientific Cooperative on Phytotherapy supports the use of S. officinalis leaves for stomatitis and gingivitis (27). The German Standard Licence for S. officinalis infu-
sion also indicates its use for the supportive treatment of dyspeptic symptoms and gastrointestinal catarrh (5).

Uses described in traditional medicine
Traditionally *S. officinalis* has been used to treat hoarseness and coughs (54, 55). It is also used as a sedative, tonic, and stimulant (56). *Salvia officinalis* has a long history of use as a restorative of lost or declining cognitive functions in Western European systems of traditional medicine (57). *Salvia officinalis* leaves are also used for treatment of haemorrhages, hyperhidrosis, galactorrhoea and dysentery (58–60). In traditional Italian medicine, they are used to treat rheumatism (61, 62). The use of *S. officinalis* for the treatment of menstrual disorders has been reported (63, 64). It is also used to treat acne, hair loss and dandruff, as a vulnerary and an antiseptic (65, 66).

Pharmacology
Experimental pharmacology
Antioxidant activity
A 95% ethanol and an aqueous-ethanol (1:1) extract of dried leaves of *S. officinalis* demonstrated antioxidant activity in vitro at concentrations of 0.01% and 0.025%, respectively, against 2,2’-azobis(2-amidinopropane) dihydrochloride-induced liposome peroxidation (67, 68). A fat-soluble ex-
tract of *S. officinalis* leaves exhibited antioxidant effects against lipid peroxidation in cooked beef homogenate at a concentration of 30 µg/ml (69). Aqueous and aqueous-ethanol (1:1) extracts of the dried leaves increased scavenging of diphenylpicrylhydrazyl radical and superoxide anions at a concentration of 0.025%, as determined by the neotetrazolium method in vitro (70). Acetone, ethanol-acetic acid, and hexane extracts of the dried leaves exhibited antioxidant activity at a concentration of 0.01% when tested on rapeseed and sunflower oils (71). The median effective dose for antioxidant activity of an aqueous-ethanol extract of the dried leaves and a tannin fraction isolated from the dried flowering top and leaves were determined to be 41 mg/ml and 23.1 µg/ml, respectively by a colorimetric assay in vitro (45). The protective effect of *Salvia* against enzyme-dependent and enzyme-independent lipid peroxidation was evaluated. A 50% aqueous-methanol extract of dried leaves was found to be more effective than the positive control, alpha-tocopherol acid succinate. A 50% aqueous-ethanol extract inhibited lipid peroxide formation in brain homogenate in vitro at a median inhibitory concentration of 2.7 µg/ml in enzyme-dependent and 8.98 µg/ml in enzyme-independent systems of lipid peroxidation (72).

In vitro cultures of hepatocytes isolated from rats drinking a *Salvia officinalis* infusion (2 g of dried leaves in 150 ml of water) and challenged with the oxidant *tert*-butyl hydroperoxide (0.75 or 1.0 mM), showed a significantly higher glutathione content and glutathione reductase activity (10%) after 4 hours of culture when compared with rats drinking water without the extract, and subjected to the same treatment. The compounds present in the *S. officinalis* infusion thus improve the liver antioxidant potential (73). An aqueous-ethanol (1:1) extract of the leaves at a concentration of 0.5 µg/ml, expressed cytoprotective activity in a cell culture of mouse fibroblasts under conditions of active oxygen-induced cell damage (68).

**Hepatoprotective action**

The protective effects of an aqueous extract of *S. officinalis* leaves against the hepatotoxic effects of the anti-metabolite azathioprine, which resulted in acute oxidative damage to the liver, were tested. Administration of azathioprine induced oxidative stress through depletion of antioxidants and elevating the level of malondialdehyde in the liver combined with escalation of alanine aminotransferase and aspartate aminotransferase in the serum. Pretreatment with the extract produced a protective effect against azathioprine-induced hepatotoxicity: animals under investigation failed to show necrosis of the liver after azathioprine administration, and also most parts of the livers were histologically normal. In addition, the extract blocked the elevation of the levels of aminotransferase and aspar-
tate aminotransferase in the serum, and reduced the malondialdehyde level in the liver (74).

**Antimicrobial activity**
The antimicrobial activity of a chloroform extract of the dried leaves was tested in vitro. The extract was active against *Staphylococcus aureus*, *Mycobacterium phlei* and *Candida albicans*, at minimum inhibitory concentrations (MICs) of 4.6, 2.3 and > 9.2 g/l/agar plate (grams of dry leaves per litre of culture medium), respectively. The methanol extract of dried leaves also demonstrated antimicrobial activity against *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycobacterium phlei* and *Candida albicans* with MIC values > 18.9 g/l/agar plate (75). An aqueous extract of the leaves exhibited activity against *Escherichia coli* (MIC = 1.3 mg/100 ml/agar plate), *Enterococcus faecalis* (MIC = 10 mg/ml), and *Bacillus subtilis* (MIC = 7.7 mg/ml) (76). The antifungal activity of the ethanol-aqueous extract (1:1) of dried leaves of *S. officinalis* was tested in vitro. At a concentration of 500 mg/ml (dose expressed as dry weight of the plant), the extract was weakly active against *Penicillium digitatum* (77).

**Antiprotozoal, anthelminthic and insecticidal activity**
At a concentration of 10 µg/ml, a methanol extract of the leaves demonstrated nematocidal activity in a cell culture against *Toxocara canis* (78). Acetone, carbon tetrachloride and methanol extracts of dried leaves, at a concentration of 100 mg/l, demonstrated insecticidal activity against *Spodoptera littoralis* (79).

**Anti-inflammatory activity**
In a model of ear inflammation, induced by 12-Ο-tetradecanoylphorbol-13-acetate, the ethyl acetate and hexane extracts of *S. officinalis* leaves demonstrated anti-inflammatory activity when applied externally to mice at a concentration of 20 µl/animal (80). In addition, antioedema activity was observed when a methanol extract of *S. officinalis* leaves was applied externally to mouse ears at a concentration of 2 mg/ear. The methanol extract had an inhibition ratio of 24 in a 12-Ο-tetradecanoylphorbol-13-acetate-induced ear inflammation model (81). The *n*-hexane and the chloroform extracts of the leaves dose-dependently inhibited croton oil-induced ear oedema in mice. The chloroform extracts were the most active. By contrast, the methanol extracts had a very small effect and the essential oil was inactive. The main active principle was identified as ursolic acid, which had a median inhibitory dose of 0.14 µM/cm² and was twice as potent as indomethacin (median inhibitory dose, 0.26 µM/cm²) (82).
This study was an extension of earlier studies by Yasukawa et al. (81) and Okuyama et al. (80).

Cholinergic activity

Studies were carried out to evaluate the cholinergic receptor-binding activity of ethanol extracts prepared from leaves of *S. officinalis*. Plant extracts were screened for their ability to displace [³H]-(N)-nicotine from nicotinic receptors and [³H]-(N)-scopolamine from muscarinic receptors, in homogenates of human cerebral cortical cell membranes. The most potent extracts, prepared from three *Salvia* species had a median inhibitory concentration (IC₅₀) of < 1 mg/ml. The displacement curves of some of these extracts were comparable with that of carbamylcholine chloride, a potent acetylcholine analogue. Choline, a weak nicotinic ligand (IC₅₀, 3 × 10⁻⁴ M) was found in extracts at concentrations of 10⁻⁶ – 10⁻⁵ M. However, at the concentrations studied, choline accounted for only 5% of the displacement activity observed. Although most extracts screened expressed some nicotinic and muscarinic activity, only a few showed dose-dependent receptor activity typical of compounds with genuine cholinergic activity (57). Mnemogenic effects of the ethanol extract from the leaves of *S. officinalis* (50 mg/kg, administered intraperitoneally) were tested in rats. Interactions of the extract with the cholinergic system in memory retention of passive avoidance learning were investigated. Administration of the extract increased memory retention. Stimulation of muscarinic and nicotinic cholinoreceptors by pilocarpine (0.5 and 1 mg/rat) and nicotine (0.1 and 1 µg/rat) potentiated the response of the extract and increased memory retention (F₄,25 = 7.67, p < 0.001) (83).

Neuroprotective effect

The effect of a standardized extract of the leaves of *S. officinalis* and its active ingredient rosmarinic acid on Alzheimer amyloid-β peptide (Aβ)-induced toxic effects in cultured rat pheochromocytoma PC12 cells was evaluated. Incubation of PC12 cells with Aβ (fragment 1-42) for 24 hours caused cell death and this effect was reduced by the extract, and by rosmarinic acid. Rosmarinic acid reduced a number of events induced by Aβ. These included formation of reactive oxygen species, lipid peroxidation, DNA fragmentation, caspase-3 activation, and tau protein hyperphosphorylation. Moreover, rosmarinic acid inhibited p-p38 mitogen-activated protein kinase, but not glycogen synthase kinase-3 activation. These data demonstrated a neuroprotective effect of *Salvia* leaf extract against Aβ-induced toxicity, which could support the use of this plant in the treatment of Alzheimer disease. Rosmarinic acid could contribute, at least in part, to the extract-induced neuroprotective effect (84).
Cardiovascular effects
Following intragastric administration of an ethanol-aqueous extract (1:1) of fresh leaves to rats, hypotensive activity, negative chronotropic effect and diuretic activity were observed. The concentration of the extract was roughly equivalent to 5 g fresh leaf material/kg body weight (bw) of the animal (results were significant at \( p < 0.05 \)) (85, 86).

Antihyperglycaemic activity
The antihyperglycaemic (antidiabetic) activity of an aqueous-ethanol extract of the dried leaves was studied in healthy male mice and in male mice with alloxan-induced diabetes. The extract significantly reduced the blood glucose concentration of fasting normal mice 120 minutes (15.7%) and 240 minutes (30.2%) after intraperitoneal administration (\( p < 0.05 \)). The extract also significantly diminished the hyperglycaemia in mildly diabetic mice after 240 minutes (22.7%). The administration of the extract to animals with severe hyperglycaemia did not cause a significant decrease in blood glucose concentration (87). A dried methanol extract of the leaves of *S. officinalis* (100, 250, 400 and 500 mg/kg) was injected intraperitoneally to rats with streptozocin-induced diabetes. Blood samples were obtained before and after administration of the extract. The results showed that the extract decreased serum glucose in diabetic rats in 3 hours with no effect on insulin release from the pancreas. This effect was not seen in normal rats (83).

Antimutagenic activity
The antimutagenic activity of a terpenoid fraction of the dried leaves was tested in *Escherichia coli* strain K12 in vitro. At a concentration of 20 µg/ml, the terpenoid fraction demonstrated antimutagenic activity against ultraviolet-induced reversion of argE 3 ochre mutations (88). Acetone, ethyl acetate, methylene dichloride and hexane extracts of the dried leaves also expressed antimutagenic effects in vitro (concentration 10 µg/ml) in *Salmonella typhimurium* strain TA98 against 3-amino-1-methyl-5H-pyrido[4,3-b]indole-induced mutagenesis (89). The antimutagenic properties of terpenoid fractions of *S. officinalis* leaves were tested in a mammalian system in vivo by examining the ability of the plant extracts to decrease the frequency of aberrant cells induced by a potent mutagen. Groups of mice were treated with three concentrations of terpenoid fractions. There was no significant difference between the frequency of aberrant cells after treatment with a concentration of 25 µl/kg and after treatment with the negative control (olive oil). However, at a concentration of 50 µl/kg, the frequency of aberrant cells was significantly de-
creased ($X^2_{(1)}$, 4.05; $p < 0.05$). At a concentration of 100 µl/kg the terpenoid fraction was cytotoxic. Mitomycin C, as a potent mutagen, was used for induction of chromosome aberrations. Treatment with terpenoid fractions (25 µl/kg and 50 µl/kg) significantly decreased the frequency of aberrations caused by mitomycin C ($X^2_{(1)}$, 5.42; $p < 0.02$; $X^2_{(1)}$, 14.93; $p < 0.001$, respectively). There was a dose–response relationship in which increasing concentrations of the plant extract caused decreases in the percentage of aberrations. Nontoxic concentrations of *S. officinalis* may be recommended for use as inhibitors of mutagenesis or carcinogenesis (90).

**Toxicology**

The neurotoxicity of thujone has been demonstrated in rats (91). The oral (median lethal dose $LD_{50}$) in the rat has been reported to be 500 mg/kg body weight (bw) (92). Thujone is much more acutely toxic after parenteral administration and the intravenous $LD_{50}$ in rabbits is stated to be 0.031 mg/kg bw (92). The symptoms associated with acute intoxication are epileptiform convulsions with general vasodilatation, hypotension, retardation of the heartbeat and an increase in respiratory amplitude. In rats, intraperitoneal injections of thujone induced electrocortical seizures associated with myoclonic activity and the convulsant and lethal effects occurred at similar doses of 200 mg/kg bw (93). Several studies on the mechanism of the neurotoxicity of $\alpha$-thujone indicate that it is a modulator of the gamma-aminobutyric acid-type A receptor (94). The principal manifestation of intoxication by thujone is epileptiform convulsions in animals and humans. The no-observable effects limit (NOEL) for convulsions in subchronic toxicity studies in female rats was 5 mg/kg bw administered orally (93). The $LD_{50}$ of a methanol extract of the leaves of *S. officinalis* was determined to be 4000 mg/kg (83).

The safety and antioxidant potential of an infusion of *S. officinalis* leaves was assessed in vivo by measuring plasma transaminase, liver glutathione reductase and glutathione-S-transferase activities in mice and rats. Replacing water with the infusion for 14 days did not affect the body weight or food consumption of the rodents. Liver toxicity was not induced by the infusion. However, significant increases of liver glutathione-S-transferase activity were observed in 24% of rats and 10% of mice receiving the infusion (68).

**Clinical pharmacology**

The objective of a multicentre, randomized, placebo-controlled, parallel group study was to assess the efficacy and safety of an *S. officinalis* ex-
tract (1:1 in 45% alcohol) using a fixed dose (60 drops/day), in patients with Alzheimer disease, over a 4-month period. Patients with mild to moderate Alzheimer disease aged between 65 and 80 years ($n = 42$, 18 women) with a score of $\geq 12$ on the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and $\leq 2$ on the Clinical Dementia Rating (CDR) were randomly allocated to either receive a placebo or a fixed dose of $S. \text{officinalis}$ extract. ADAS-cog is a subscale of 11 items that evaluates selected aspects of attention, language, memory, orientation, praxis and reasoning. CDR (sum of the boxes) provides a consensus-based global clinical measure by summing the ratings from six domains: memory, orientation, judgement, problem-solving, community affairs, home and hobbies, and personal care. Over a 16-week period, the primary outcome measure was the change in the ADAS-cog score. Change in CDR (sum of the boxes) was the secondary outcome of the trial. In addition, side-effects were systematically recorded throughout the study using a checklist. The results showed that at 4 months, the extract led to a better outcome for cognitive functions than placebo (ADAS-cog: $F, 4.77; \text{df, 1}; p, 0.03$) (CDR-SB: $F, 10.84; \text{df, 1}; p < 0.003$). There were no significant differences between the two groups in terms of observed side-effects except for agitation, which appeared to be more frequent in the group treated with the placebo ($p = 0.09$). The results of the study indicate that the extract was efficacious in the management of mild to moderate Alzheimer disease (52).

**Adverse reactions**

After prolonged ingestion of ethanol extracts of leaves of $Salvia \text{officinalis}$, epileptiform convulsions can occur (38).

**Contraindications**

In view of the toxicity of the plant due to the thujone and camphor content, extracts should be used with caution and not ingested in large amounts (95). Because of the known toxic properties of thujone, the described abortifacient properties (96), and lack of safety data concerning administration of Folium Salviae and its preparations in children as well as during pregnancy and lactation, it is contraindicated in these patient groups (38, 97).

**Warnings**

Long-term use of essential oil (more than 2 weeks at a time) should be avoided (98).
Precautions

General
Extracts of the herb should be used with caution and should not be ingested in large amounts or over prolonged periods. Caution is required with the use of ethanol preparations of the leaves because of the presence of thujone and camphor (27). If symptoms worsen or persist for longer than 1 week or in any case of unclear symptoms, such as night sweats, increased body temperature or loss of weight, a physician should be consulted (98).

Drug interactions
Salvia officinalis may interfere with existing hypoglycaemic and anticonvulsant therapies, and may increase the sedative effects of simultaneously used drugs, and central effects of alcohol (95). S. officinalis may interfere with absorption of iron and other minerals (98).

Drug and laboratory test interactions
No information was found.

Carcinogenesis, mutagenesis, impairment of fertility
No information was found.

Pregnancy
Use in pregnancy is not recommended (See Contraindications).

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.

Dosage forms
Cut herb for infusions, ethanol extracts and distillates for gargles, rinses and other topical applications, as well as for internal use. In addition, the fresh plants may be pressed to yield a juice (38).

Posology
(Unless otherwise indicated)
Internal. Daily dose: 4 g of drug or equivalent preparations (38). Infusion: one tablespoon of an infusion (4 g of the leaf) in 200 ml of boiling water, three times daily (38, 95). Tincture: 75 drops of a tincture (1:10 in 55% or
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

70% ethanol), three times daily (27, 32). Fluidextract: 1–4 ml (1:1 in 45% ethanol), three times daily (95). Dry extract: 160 mg of dry aqueous extract corresponding to 880 mg of drug, three times daily (27). For gargles and rinses. Infusion: 3 g of herb or 2–3 drops of essential oil in 150 ml of water (27). Tincture: 1:10 in 70% ethanol. Extract: 5 g of ethanol extract in 1 glass water (20).

External. Cataplasm or irrigation: 30 g of cut herb in 200 ml of boiling water for 20 min, applied to affected area (19).

References


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Folium Sennae*

**Definition**
Folium Sennae consists of the dried leaflets of *Cassia senna* L. (Fabaceae).¹

**Synonyms**
Fabaceae are also referred to as Leguminosae.

Although recognized as two distinct species in many pharmacopoeias (1–8), *Cassia acutifolia* Delile and *C. angustifolia* Vahl. are considered botanically to be synonyms of the single species *Cassia senna* L. (9).

**Selected vernacular names**
Alexandria senna, Alexandrian senna, cassia, eshrid, falajin, fan xie ye, filaskon maka, hindisana, illesko, Indian senna, ma khaam khaek, makhaam khaek, mecca senna, msahala, nelaponna, nelatangedu, nilavanka, nilavirai, nubia senna, rinji, sanai, sand hijazi, sanjerehi, sen de alexandria, sen de la india, senna makki, senna, senamikkii, sennae folium, sonamukhi, Tinnevelly senna, true senna (3, 10–14).

**Description**
Low shrubs, up to 1.5 m high, with compound paripinnate leaves, having 3–7 pairs of leaflets, narrow or rounded, pale green to yellowish green. Flowers, tetracyclic, pentameric, and zygomorphic, have quincuncial calyx, a corolla of yellow petals with brown veins, imbricate ascendent prefloration, and a partially staminodial androecium. The fruit is a broadly elliptical, somewhat reniform, flattened, parchment-like, dehiscent pod, 4–7 cm long by 2 cm wide, with 6 to 10 seeds (11, 14, 15).

**Plant material of interest: leaflets**

**General appearance**
Macroscopically, the leaflets are lanceolate or lanceolate-ovate, unequal at the base, with entire margin, acute-mucronate apex and short, stout peti-

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* Adopted from the volume 1 of WHO monographs on selected medicinal plants.
¹ *C. italica* Mill. is listed in the Malian pharmacopoeia.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

oles; sometimes broken; 1.5–5 cm in length and 0.5–1.5 cm in width, bearing a fine pubescence of appressed hairs, more numerous on the lower surface (1–7).

Organoleptic properties
The colour is weak yellow to pale olive (1, 2). The odour is characteristic, and the taste is mucilage-like and then slightly bitter (1, 3).

Microscopic characteristics
Epidermis with polygonal cells containing mucilage; unicellular thick-walled trichomes, length, up to 260 µm, slightly curved at the base, warty; paracytic stomata on both surfaces; under the epidermal cells a single row of palisade layer; cluster crystals of calcium oxalate distributed throughout the lacunose tissue; on the adaxial surface, sclerenchymatous fibres and a gutter-shaped group of similar fibres on the abaxial side containing prismatic crystals of calcium oxalate (1).

Powdered plant material
Light green to greenish yellow. Polygonal epidermal cells showing paracytic stomata. Unicellular trichomes, conical in shape, with warty walls, isolated or attached to fragments of epidermis. Fragments of fibrovascular bundles with a crystal sheath containing calcium oxalate prisms. Cluster crystals isolated or in fragments of parenchyma (2, 3).

Geographical distribution
The plant is indigenous to tropical Africa. It grows wild near the Nile river from Aswan to Kordofan, and in the Arabian peninsula, India and Somalia (15). It is cultivated in India, Pakistan, and the Sudan (11, 12, 14, 15).

General identity tests
Macroscopic, microscopic examinations, and microchemical analysis (1–6), and thin-layer chromatographic analysis for the presence of characteristic sennosides (sennosides A–D) (3–5).

Purity tests
Microbiology
The test for Salmonella spp. in Folium Sennae products should be negative. The maximum acceptable limits of other microorganisms are as follows (16–18). For preparation of decoction: aerobic bacteria—10⁷/g; moulds and yeast—10⁶/g; Escherichia coli—10³/g; other enterobacteria—
preparations for internal use: aerobic bacteria—$10^5$/g; moulds and yeast—$10^4$/g; Escherichia coli—0/g; other enterobacteria—$10^3$/g.

**Foreign organic matter**
Not more than 2.0% of stems (1) and not more than 1.0% of other foreign organic matter (1, 4, 8).

**Total ash**
Not more than 12% (5).

**Acid-insoluble ash**
Not more than 2.0% (1, 8).

**Water-soluble extractive**
Not less than 3% (1).

**Moisture**
Not more than 10% (6).

**Pesticide residues**
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Folium Sennae is not more than 0.05 mg/kg (18). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (16) and guidelines for predicting dietary intake of pesticide residues (19).

**Heavy metals**
Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (16).

**Radioactive residues**
For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (16).

**Other purity tests**
Chemical tests and tests of alcohol-soluble extractive are to be established in accordance with national requirements.

**Chemical assays**
Contains not less than 2.5% of hydroxyanthracene glycosides, calculated as sennoside B (1, 4, 5). Quantitative analysis is performed by
spectrophotometry (1, 4–8) and by high-performance liquid chromatography (20).

Thin-layer chromatography is employed for qualitative analysis for the presence of sennosides A and B (3–5).

**Major chemical constituents**
Folium Sennae contains a family of hydroxyanthracene glycosides, the most plentiful of which are sennosides A and B. There are also small amounts of aloe-emodin and rhein 8-glucosides, mucilage, flavonoids, and naphthalene precursors (15).

![Chemical Structures](image)

**Dosage forms**
Crude plant material, powder, oral infusion, and extracts (liquid or solid) standardized for content of sennosides A and B (15, 21, 22). Package in well-closed containers protected from light and moisture (1–8).
Medicinal uses

*Uses supported by clinical data*
Short-term use in occasional constipation (21–25).

*Uses described in pharmacopoeias and in traditional systems of medicine*
None.

*Uses described in folk medicine, not supported by experimental or clinical data*
As an expectorant, a wound dressing, an antidysenteric, and a carminative agent; and for the treatment of gonorrhoea, skin diseases, dyspepsia, fever, and haemorrhoids (11, 23, 25).

Pharmacology

*Experimental pharmacology*
The effects of *Folium Sennae* are due primarily to the hydroxyanthracene glucosides, especially sennosides A and B. These β-linked glucosides are secretagogues that increase net secretion of fluids and specifically influence colonic motility and enhance colonic transit. They are not absorbed in the upper intestinal tract; they are converted by the bacteria of the large intestine into the active derivatives (rhein-anthrone). The mechanism of action is twofold: (1) effect on the motility of the large intestine (stimulation of peristaltic contractions and inhibition of local contractions), resulting in an accelerated colonic transit, thereby reducing fluid absorption, and (2) an influence on fluid and electrolyte absorption and secretion by the colon (stimulation of mucus and active chloride secretion), increasing fluid secretion (24, 25).

*Clinical pharmacology*
The time of action of senna is usually 8–10 hours, and thus the dose should be taken at night (24). The action of the sennosides augments, without disrupting, the response to the physiological stimuli of food and physical activity (24). The sennosides abolish the severe constipation of patients suffering from severe irritable bowel syndrome (26). In therapeutic doses, the sennosides do not disrupt the usual pattern of defecation times and markedly soften the stool (24). Sennosides significantly increase the rate of colonic transit (27) and increase colonic peristalsis, which in turn increase both faecal weight and dry bacterial mass (24, 28). Due to their colonic specificity, the sennosides are poorly absorbed in the upper gastrointestinal tract (29).
Toxicity
The major symptoms of overdose are griping and severe diarrhoea with consequent losses of fluid and electrolytes. Treatment should be supportive with generous amounts of fluid. Electrolytes, particularly potassium, should be monitored, especially in children and the elderly.

Contraindications
As with other stimulant laxatives, the drug is contraindicated in persons with ileus, intestinal obstruction, and stenosis, atony, undiagnosed abdominal symptoms, inflammatory colonopathies, appendicitis, abdominal pains of unknown cause, severe dehydration states with water and electrolyte depletion, or chronic constipation (21, 30). Folium Sennae should not be used in children under the age of 10 years.

Warnings
Stimulant laxative products should not be used when abdominal pain, nausea, or vomiting are present. Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition (31). Chronic abuse, with diarrhoea and consequent fluid electrolyte losses, may cause dependence and need for increased dosages, disturbance of the water and electrolyte balance (e.g. hypokalaemia), atonic colon with impaired function, albuminuria and haematuria (29, 32).

The use of stimulant laxatives for more than 2 weeks requires medical supervision.
Chronic use may lead to pseudomelanosis coli (harmless).
Hypokalaemia may result in cardiac and neuromuscular dysfunction, especially if cardiac glycosides (digoxin), diuretics, corticosteroids, or liquorice root are taken (29).

Precautions
General
Use for more than 2 weeks requires medical attention (21, 31).

Drug interactions
Decreased intestinal transit time may reduce absorption of orally administered drugs (32, 33).

The increased loss of potassium may potentiate the effects of cardiotonic glycosides (digitalis, strophanthus). Existing hypokalaemia resulting from long-term laxative abuse can also potentiate the effects of antiarrhythmic drugs, such as quinidine, which affect potassium channels to change sinus rhythm. Simultaneous use with other drugs or herbs which
induce hypokalaemia, such as thiazide diuretics, adrenocorticosteroids, or liquorice root, may exacerbate electrolyte imbalance (21, 22).

**Drug and laboratory test interactions**
Urinary discoloration by anthranoid metabolites may lead to false positive test results for urinary urobilinogen, and for estrogens measured by the Kober procedure (32).

**Carcinogenesis, mutagenesis, impairment of fertility**
No in vivo genotoxic effects have been reported to date (34–37). Although chronic abuse of anthranoid-containing laxatives was hypothesized to play a role in colorectal cancer, no causal relationship between anthranoid laxative abuse and colorectal cancer has been demonstrated (38–40).

**Pregnancy: non-teratogenic effects**
Use during pregnancy should be limited to conditions in which changes in diet or fibre laxatives are not effective (41).

**Nursing mothers**
Use during breastfeeding is not recommended owing to insufficient data on the excretion of metabolites in breast milk (21). Small amounts of active metabolites (rhein) are excreted into breast milk, but a laxative effect in breastfed babies has not been reported (21).

**Paediatric use**
Contraindicated for children under 10 years of age (21).

**Other precautions**
No information available on teratogenic effects in pregnancy.

**Adverse reactions**
Senna may cause mild abdominal discomfort such as colic or cramps (21, 22, 33). A single case of hepatitis has been described after chronic abuse (42). Melanosis coli, a condition which is characterized by pigment-loaded macrophages within the submucosa, may occur after long-term use. This condition is clinically harmless and disappears with cessation of treatment (33, 43, 44).

Long-term laxative abuse may lead to electrolyte disturbances (hypokalaemia, hypocalcaemia), metabolic acidosis or alkalosis, malabsorption, weight loss, albuminuria, and haematuria (21, 22, 33). Weakness and orthostatic hypotension may be exacerbated in elderly patients when stimulant
laxatives are repeatedly used (21, 33). Conflicting data exist on other toxic effects such as intestinal-neuronal damage due to long-term misuse (45–54).

**Posology**
The correct individual dose is the smallest required to produce a comfortable, soft-formed motion (21). Powder: 1–2 g of leaf daily at bedtime (11). Adults and children over 10 years: standardized daily dose equivalent to 10–30 mg sennosides (calculated as sennoside B) taken at night.

**References**
10. Farnsworth NR, ed. *NAPRALERT database*. Chicago, University of Illinois at Chicago, IL, March 15, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).


Radix cum Herba Taraxaci

Definition
Radix cum Herba Taraxaci consists of the entire plant of *Taraxacum officinale* Weber ex Wiggers (Asteraceae) (1–3).¹

Synonyms

Selected vernacular names
Ackerzichorie, amargon, blowball, Butterblume, cankerwort, capo di frate, chicoria amarga, cicoria sarvatica, cicouureya de la bonne, cicouureya des prats, dandelion, dent-de-lion, dente di leone, dhudal, diente de leon, dhor-sat al ajouz, dudhi, engraisa-porc, florion d’or, gol ghased, Gemeiner Löwenzahn, gobesag, Irish daisy, hindabaa beri, hokgei, kanphul, kanphuli, kasni sahraai, Kettenblume, khash berri, Kuhblume, lagagna, laiteron, le-chuguilla, lion’s tooth, Löwenzahn, maaritpauncin, marrara, milk gowan, min-deul-re, monk’s head, mourayr, mourre de por, mourre de pouerc, oduvantschiki, paardebloem, patalagagna, peirin, Pfaffendistel, Pfaffenrörhrlein, Pferdeblume, pilli-pilli, piochoublit, piss-a-bed, pissa-chin, pisanliech, pissenlitr, poirin, po-kong-young, porcin, pu gong ying, puffball, pugongying, Pusteblume, ringeblume, salatta merra, sanalotodo, saris berri, seiyo-tanpopo, sofione, srissi, tarakh-chaqoune, tarkhshaquin, tarassaco, taraxaco, telma retaga, Wiesenlattich, witch gowan, yellow gowan (4–10).

Geographical distribution
*Taraxacum officinale* is indigenous to the northern hemisphere (11). *T. mongolicum*, *T. sinicum* and related species are found in the Korean peninsula and China (4, 5).

¹ Adopted from the volume 3 of WHO monographs on selected medicinal plants.
² Taraxacum mongolicum Hand.-Mazz. and *T. sinicum* Kitag. are also recognized in the Pharmacopoeia of the People’s Republic of China (4) and the *Pharmacopoeia of the Republic of Korea* (5).
Description
A perennial herb consisting of an underground, long, straight, tapering, fleshy brown root, which is continued upward as a simple or branched rhizome. From the rhizome arises a rosette of bright-green runcinate leaves and later, from the centre of the rosette, a hollow scape, 6–30 cm high bearing on its summit a broad orange-yellow head of ligulate flowers. Fruits are fusiform, greenish-brown achenes, terminating in a slender stalk crowned by a silky, spreading pappus, and borne on a globular fruiting head (12).

Plant material of interest: dried whole plants

General appearance
A crumpled and rolled mass. Roots conical, frequently curved, tapering, often broken into irregular pieces, externally brown. Root stock with brown or yellowish-white hairs. Leaves basal, frequently crumpled and broken; when whole, oblanceolate, greenish-brown or dark green with a pronounced midrib; apex acute or obtuse; margins lobate or pinnatifid. Pedicels one or more, each with a capitulum; involucre several rows, the inner row relatively long; corolla yellowish-brown or pale yellowish-white (1, 4, 5).

Organoleptic properties
Odour, slight; taste, slightly bitter (1, 11).

Microscopic characteristics
Epidermal cells on both leaf surfaces have sinuous anticlinal walls, cuticle striations distinct or sparsely visible. Both leaf surfaces bear non-glandular hairs with three to nine cells, 17–34 µm in diameter. Stomata, occurring more frequently on the lower surface, anomocytic or anisocytic, with three to six subsidiary cells. Mesophyll contains fine crystals of calcium oxalate. Transverse section of root shows cork with several layers of brown cells. Phloem broad, groups of laticiferous tubes arranged in several interrupted rings. Xylem relatively small, with indistinct rays, vessels large, scattered. Parenchymatous cells contain inulin (1).

Powdered plant material
Greenish yellow. Large root parenchymatous cells, brown reticulate vessels and tracheids and non-lignified fibres. Leaf fragments with sinuous, anticlinal-walled epidermal cells and a few anomocytic stomata. Numerous narrow annular thickened vessels and fragments of brown laticiferous tissues (1).
Radix cum Herba Taraxaci

**General identity tests**
Macroscopic and microscopic examinations (1, 4, 5).

**Purity tests**

*Microbiological*
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (13).

*Foreign organic matter*
Not more than 2% (3).

*Total ash*
Not more than 17% (3).

*Water-soluble extractive*
Not less than 30% (3).

*Loss on drying*
Not more than 11% (3).

*Pesticide residues*
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (14). For other pesticides, see the European pharmacopoeia (14) and the WHO guidelines on quality control methods for medicinal plants (13) and pesticide residues (15).

*Heavy metals*
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (13).

*Radioactive residues*
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (13) for the analysis of radioactive isotopes.

*Other purity tests*
Chemical, acid-insoluble ash, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

*Chemical assays*
To be established in accordance with national requirements.
Major chemical constituents

The characteristic constituents are sesquiterpenes, including the bitter eudesmanolidetetrahydroridentin B and taraxacolide β-D-glucopyranoside; and the germacranolides, taraxinic acid β-D-glucopyranoside and 11,13-dihydrotaraxic acid β-D-glucopyranoside. Also present are the p-hydroxyphenylacetic acid derivative, taraxacolide; the triterpenes, taraxasterol, ψ-taraxasterol and taraxerol; and inulin (2–40%) (4, 10, 11). Representative structures are presented below.

Medicinal uses

Uses supported by clinical data

No information available.

Uses described in pharmacopoeias and well established documents

To stimulate diuresis (2, 5), increase bile flow and stimulate appetite, and for treatment of dyspepsia (2).

Uses described in traditional medicine

As a galactagogue, laxative and tonic. Treatment of boils and sores, diabetes, fever, inflammation of the eye, insomnia, sore throat, lung abscess, jaundice, rheumatism and urinary tract infections (10).
Pharmacology

Experimental pharmacology

Anti-inflammatory and analgesic activity
External applications of 2.0 mg/ear of a methanol extract of the dried leaves to mice reduced ear inflammation induced by 12-O-tetradecanoylphorbol-13-acetate (16). Intragastric administration of 1.0 g/kg body weight (bw) of a 95% ethanol extract of the whole plant to mice inhibited benzoquinone-induced writhing (17). Intraperitoneal administration of 100.0 mg/kg bw of a 95% ethanol extract of the whole plant to mice inhibited carrageenan-induced footpad oedema by 42%, and reduced pain as measured by the hot-plate test and benzoquinone-induced writhing (17). Intragastric administration of 100.0 mg/kg bw of an 80% ethanol extract of the dried roots to rats inhibited carrageenan-induced footpad oedema by 25%, compared with 45% inhibition resulting from administration of 5.0 mg/kg bw of indometacin (18).

Antimicrobial activity
A 95% ethanol extract of the dried aerial parts, 1.0 mg/ml, did not inhibit the growth of Bacillus globifer, B. mycoides, B. subtilis, Escherichia coli, Fusarium solani, Klebsiella pneumoniae, Penicillium notatum, Proteus morgani, Pseudomonas aeruginosa, Salmonella gallinarum, Serratia marcescens, Staphylococcus aureus, Mycobacterium smegmatis or Candida albicans in vitro (19, 20). No antibacterial effects were observed using a 50% ethanol extract of the whole plant, 50 µl/plate, against Escherichia coli, Salmonella enteritidis, Salmonella typhosa, Shigella dysenteriae or Shigella flexneri (21).

Antiulcer activity
Intragastric administration of 2.0 g/kg bw of an aqueous extract of the whole plant to rats protected the animals against ethanol-induced gastric ulceration. A methanol extract, however, was not active (22).

Choleretic activity
Intragastric administration of an aqueous or 95% ethanol extract of the whole plant (dose not specified) to rats increased bile secretion by 40% (23).

Diuretic activity
Intragastric administration of 8.0–50.0 ml/kg bw of a 95% ethanol extract of the whole plant to rats induced diuresis and reduced body weight (24). Intragastric administration of 0.1 ml/kg bw of a 30% ethanol extract of the whole plant to mice induced diuresis (25). However, intragastric administration of 50.0 mg/kg bw of a chloroform, methanol or petroleum
ether extract of the roots to mice did not consistently increase urine output (26).

**Hypoglycaemic activity**
Intragastric administration of a 50% ethanol extract of the whole plant to rats, 250.0 mg/kg bw, or rabbits, 1.0 g/kg bw, reduced blood glucose concentrations (27). However, intragastric administration of 2.0 g/kg bw of the powdered whole plant to rabbits did not reduce blood sugar concentrations in alloxan-induced hyperglycaemia (28). Intragastric administration of 25.0 mg/kg bw of an aqueous extract of the dried root to mice reduced glucose-induced hyperglycaemia (29, 30). However, a decoction or 80% ethanol extract of the dried roots had no effect (30).

**Immunological effects**
Intragastric administration of 3.3 g/kg bw of an aqueous extract of the whole plant to mice daily for 20 days significantly \((P < 0.01)\) decreased cyclophosphamide-induced immune damage (31). Treatment of scalded mice with suppressed immune functions with an aqueous extract of the whole plant (dose and route not specified) stimulated the immune response (32). Nitric oxide synthesis inhibition induced by cadmium in mouse peritoneal macrophages stimulated with recombinant interferon-\(\gamma\) and lipopolysaccharide was counteracted by treatment of the cells with an aqueous extract of the whole plant, 100 \(\mu\)g/ml. The results were mainly dependent on the induction of tumour necrosis factor-\(\alpha\) (TNF-\(\alpha\)) secretion stimulated by the aqueous extract (33). Treatment of primary cultures of rat astrocytes with an aqueous extract of the whole plant, 100.0 \(\mu\)g/ml, inhibited TNF-\(\alpha\) production induced by lipopolysaccharide and substance P. The treatment also decreased the production of interleukin-1 in astrocytes stimulated with lipopolysaccharide and substance P. The study indicated that Radix cum Herba Taraxaci may inhibit TNF-\(\alpha\) production by inhibiting interleukin-1 production, thereby producing anti-inflammatory effects (34). Treatment of mouse peritoneal macrophages with an aqueous extract of the whole plant, 100 \(\mu\)g/ml, after treatment of the cells with recombinant interferon-\(\gamma\), resulted in increased nitric oxide synthesis owing to an increase in the concentration of inducible nitric oxide synthase. The results were dependent on the induction of TNF-\(\alpha\) secretion by Radix cum Herba Taraxaci (35).

**Toxicology**
The intraperitoneal median lethal dose (LD\(_{50}\)) of a 95% ethanol extract of the whole plant in rats was 28.8 mg/kg bw (24). In rats, the maximum tolerated dose of a 50% ethanol extract of the whole plant administered by the
intraperitoneal route was 500.0 mg/kg bw (27). No visible signs of toxicity were observed in rabbits after intragastric administration of the powdered whole plant at doses of 3–6 g/kg bw per day for up to 7 days (36).

Clinical pharmacology
No information available.

Adverse reactions
Allergic reactions including anaphylaxis and pseudoallergic contact dermatitis have been reported (37–40). Cross-reactivity has been reported in individuals with an allergy to the pollen of other members of the Asteraceae (41).

Contraindications
Radix cum Herba Taraxaci is contraindicated in obstruction of the biliary or intestinal tract, and acute gallbladder inflammation. In case of gallbladder disease, Radix cum Herba Taraxacum should only be used under the supervision of a health-care professional (2).

Warnings
May cause stomach hyperacidity, as with all drugs containing amaroids (2).

Precautions
Drug interactions
A decrease in the maximum plasma concentration of ciprofloxacin was observed in rats treated with concomitant oral administration of 2.0 g/kg bw of an aqueous extract of the whole plant and 20.0 mg/kg bw of ciprofloxacin (42).

Carcinogenesis, mutagenesis, impairment of fertility
No effects on fertility were observed in female rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (43).

Pregnancy: teratogenic effects
No teratogenic or embryotoxic effects were observed in the offspring of rabbits or rats after intragastric administration of 1.6 ml/kg bw of a 40% ethanol extract of the whole plant during pregnancy (43).

Other precautions
No information available on general precautions or on precautions concerning drug and laboratory test interactions; non-teratogenic effects in pregnancy; nursing mothers; or paediatric use.
Dosage forms
Dried whole plant, native dry extract, fluid extract and tincture (1, 2). Store in a tightly sealed container away from heat and light.

Posology
(Unless otherwise indicated)
Average daily dose: 3–4 g of cut or powdered whole plant three times; decoction, boil 3–4 g of whole plant in 150 ml of water; infusion, steep 1 tablespoonful of whole plant in 150 ml of water; 0.75–1.0 g of native dry extract 4:1 (w/w); 3–4 ml fluid extract 1:1 (g/ml) (2); 5–10 ml of tincture (1:5 in 45% alcohol) three times (1).

References
10. Farnsworth NR, ed. NAPRALERT database. Chicago, IL, University of Illinois at Chicago, 9 February 2001 production (an online database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
Radix cum Herba Taraxaci


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Herba Thymi*

Definition
Herba Thymi is the dried leaves and flowering tops of *Thymus vulgaris* L. or of *Thymus zygis* L. (Lamiaceae) (1, 2).

Synonyms
Lamiaceae are also known as Labiatae.

Selected vernacular names
Common thyme, farigola, garden thyme, herba timi, herba thymi, mother of thyme, red thyme, rubbed thyme, ten, thick leaf thyme, thym, Thymian, thyme, time, timi, tomillo, za’ater (1, 3–7).

Description
An aromatic perennial sub-shrub, 20–30 cm in height, with ascending, quadrangular, greyish brown to purplish brown lignified and twisted stems bearing oblong-lanceolate to ovate-lanceolate greyish green leaves that are pubescent on the lower surface. The flowers have a pubescent calyx and a bilobate, pinkish or whitish, corolla and are borne in verticillasters. The fruit consists of 4 brown ovoid nutlets (5, 8, 9).

Plant material of interest: dried leaves and flowering tops

*General appearance*

*Thymus vulgaris*
Leaf 4–12 mm long and up to 3 mm wide; it is sessile or has a very short petiole. The lamina is tough, entire, lanceolate to ovate, covered on both surfaces by a grey to greenish grey indumentum; the edges are markedly rolled up towards the abaxial surface. The midrib is depressed on the ad-axial surface and is very prominent on the abaxial surface. The calyx is green, often with violet spots, and is tubular; at the end are 2 lips of which the upper is bent back and has 3 lobes on its end; the lower is longer and

* Adopted from the volume 1 of WHO monographs on selected medicinal plants.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

has 2 hairy teeth. After flowering, the calyx tube is closed by a crown of long, stiff hairs. The corolla, about twice as long as the calyx, is usually brownish in the dry state and is slightly bilabiate (1).

*Thymus zygis*

Leaf 1.7–6.5 mm long and 0.4–1.2 mm wide; it is acicular to linear-lanceolate and the edges are markedly rolled toward the abaxial surface. Both surfaces of the lamina are green to greenish grey and the midrib is sometimes violet; the edges, in particular at the base, have long, white hairs. The dried flowers are very similar to those of *Thymus vulgaris* (1).

**Organoleptic properties**

Odour and taste aromatic (1–3, 5).

**Microscopic characteristics**

In leaf upper epidermis, cells tangentially elongated in transverse section with a thick cuticle and few stomata, somewhat polygonal in surface section with beaded vertical walls and striated cuticle, the stoma being at a right angle to the 2 parallel neighbouring cells. Numerous unicellular, non-glandular hairs up to 30 µm in length with papillose wall and apical cell, straight, or pointed, curved, or hooked. Numerous glandular hairs of two kinds, one with a short stalk embedded in the epidermal layer and a unicellular head, the other with an 8- to 12-celled head and no stalk. Palisade parenchyma of 2 layers of columnar cells containing many chloroplastids; occasionally an interrupted third layer is present. Spongy parenchyma of about 6 layers of irregular-shaped chlorenchyma cells and intercellular air-spaces (5).

**Powdered plant material**

Grey-green to greenish brown powder; leaf fragments, epidermal cells prolonged into unicellular pointed, papillose trichomes, 60 µm long; trichomes of the lower surface uniseriate, 2–3 celled, sharp pointed, up to 300 µm in diameter, numerous labiate trichomes with 8–12 secretory cells up to 80 µm in diameter; broadly elliptical caryophyllaceous stomata. Six- to 8-celled uniseriate trichomes from the calyx up to 400 µm long; pollen grains spherical; pericyclic fibres of the stem (1–3).

**Geographical distribution**

Indigenous to southern Europe. It is a pan-European species that is cultivated in Europe, the United States of America and other parts of the world (2, 3, 5, 10).

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Herba Thymi

General identity tests
Macroscopic and microscopic examinations (1, 5), and chemical and thin-layer chromatography tests for the characteristic volatile oil constituent, thymol [1].

Purity tests

Microbiology
The test for Salmonella spp. in Herba Thymi products should be negative. The maximum acceptable limits of other microorganisms are as follows (11–13). For preparation of infusion: aerobic bacteria—not more than $10^7$/g; fungi—not more than $10^5$/g; Escherichia coli—not more than $10^2$/g. Preparations for oral use: aerobic bacteria—not more than $10^5$/ml; fungi—not more than $10^4$/ml; enterobacteria and certain Gram-negative bacteria—not more than $10^3$/ml; Escherichia coli—0/ml.

Foreign organic matter
Not more than 10% of stem having a diameter up to 1 mm. Leaves with long trichomes at their base and with weakly pubescent other parts not allowed (1). The leaves and flowering tops of Origanum creticum or O. dictamnus are considered adulterants (3, 5). Other foreign organic matter, not more than 2% (2).

Total ash
Not more than 15% (1).

Acid-insoluble ash
Not more than 2.0% (1).

Moisture
Not more than 10% (1).

Pesticide residues
To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Herba Thymi is not more than 0.05 mg/kg (13). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (11) and guidelines for predicting dietary intake of pesticide residues (14).

Heavy metals
Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (11).
Radioactive residues
For analysis of strontium-90, iodine-131, caesium-134, caesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (11).

Other purity tests
Chemical, alcohol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
Herba Thymi contains not less than 1.0% volatile oil (2, 3), and not less than 0.5% phenols. Volatile oil is quantitatively determined by water/steam distillation (1), and the percentage content of phenols expressed as thymol is determined by spectrophotometric analysis (1). Thin-layer chromatographic analysis is used for thymol, carvacrol, and linalool (1, 15).

Major chemical constituents
Herba Thymi contains about 2.5% but not less than 1.0% of volatile oil. The composition of the volatile oil fluctuates depending on the chemotype under consideration. The principal components of Herba Thymi are thymol [1] and carvacrol [2] (up to 64% of oil), along with linalool, p-cymol, cymene, thymene, α-pinene, apigenin, luteolin, and 6-hydroxyluteolin glycosides, as well as di-, tri- and tetramethoxylated flavones, all substituted in the 6-position (for example 5,4′-dihydroxy-6,7-dimethoxyflavone, 5,4′-dihydroxy-6,7,3′-trimethoxyflavone and its 8-methoxylated derivative 5,6,4′-trihydroxy-7,8,3′-trimethoxyflavone) (1, 3–6, 9).

Dosage forms
Dried herb for infusion, extract, and tincture (1).

Medicinal uses
Uses supported by clinical data
None.
Herba Thymi

Uses described in pharmacopoeias and in traditional systems of medicine
Thyme extract has been used orally to treat dyspepsia and other gastrointestinal disturbances; coughs due to colds, bronchitis and pertussis; and laryngitis and tonsillitis (as a gargle). Topical applications of thyme extract have been used in the treatment of minor wounds, the common cold, disorders of the oral cavity, and as an antibacterial agent in oral hygiene (3, 5, 8, 15, 16). Both the essential oil and thymol are ingredients of a number of proprietary drugs including antiseptic and healing ointments, syrups for the treatment of respiratory disorders, and preparations for inhalation. Another species in the genus, *T. serpyllum* L., is used for the same indications (8).

Uses described in folk medicine, not supported by experimental or clinical data
As an emmenagogue, sedative, antiseptic, antipyretic, to control menstruation and cramps, and in the treatment of dermatitis (7).

Pharmacology

Experimental pharmacology

Spasmolytic and antitussive activities
The spasmolytic and antitussive activity of thyme has been most often attributed to the phenolic constituents thymol and carvacrol, which make up a large percentage of the volatile oil (17). Although these compounds have been shown to prevent contractions induced in the ileum and the trachea of the guinea-pig, by histamine, acetylcholine and other reagents, the concentration of phenolics in aqueous preparations of the drug is insufficient to account for this activity (18, 19). Experimental evidence suggests that the in vitro spasmolytic activity of thyme preparations is due to the presence of polymethoxyflavones (10). In vitro studies have shown that flavones and thyme extracts inhibit responses to agonists of specific receptors such as acetylcholine, histamine and l-norepinephrine, as well as agents whose actions do not require specific receptors, such as barium chloride (10). The flavones of thyme were found to act as non-competitive and non-specific antagonists (10); they were also shown to be Ca²⁺ antagonists and musculotropic agents that act directly on smooth muscle (10).

Expectorant and secretomotor activities
Experimental evidence suggests that thyme oil has secretomotoric activity (20). This activity has been associated with a saponin extract from
T. vulgaris (21). Stimulation of ciliary movements in the pharynx mucosa of frogs treated with diluted solutions of thyme oil, thymol or carvacrol has also been reported (22). Furthermore, an increase in mucus secretion of the bronchi after treatment with thyme extracts has been observed (23).

**Antifungal and antibacterial activities**

In vitro studies have shown that both thyme essential oil and thymol have antifungal activity against a number of fungi, including Cryptococcus neoformans, Aspergillus, Saprolegnia, and Zygorhynchus species (24–27). Both the essential oil and thymol had antibacterial activity against Salmonella typhimurium, Staphylococcus aureus, Escherichia coli, and a number of other bacterial species (28, 29). As an antibiotic, thymol is 25 times as effective as phenol, but less toxic (30).

**Contraindications**

Pregnancy and lactation (See Precautions, below).

**Warnings**

No information available.

**Precautions**

**General**

Patients with a known sensitivity to plants in the Lamiaceae (Labiatae) should contact their physician before using thyme preparations. Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (31).

**Carcinogenesis, mutagenesis, impairment of fertility**

Thyme essential oil did not have any mutagenic activity in the Bacillus subtilis rec-assay or the Salmonella/microsome reversion assay (32, 33). Recent investigations suggest that thyme extracts are antimutagenic (34) and that luteolin, a constituent of thyme, is a strong antimutagen against the dietary carcinogen Trp-P-2 (35).

**Pregnancy: non-teratogenic effects**

The safety of Herba Thymi preparations during pregnancy or lactation has not been established. As a precautionary measure, the drug should not be used during pregnancy or lactation except on medical advice. However, widespread use of Herba Thymi has not resulted in any safety concerns.
**Nursing mothers**
See Pregnancy: non-teratogenic effects, above.

**Other precautions**
No information available concerning drug interactions, drug and laboratory test interactions, paediatric use, or teratogenic effects on pregnancy.

**Adverse reactions**
Contact dermatitis has been reported. Patients sensitive to birch pollen or celery may have a cross-sensitivity to thyme (31).

**Posology**
Adults and children from 1 year: 1–2 g of the dried herb or the equivalent amount of fresh herb as an oral infusion several times a day (30, 36); children up to 1 year: 0.5–1 g (36). Fluid extract: dosage calculated according to the dosage of the herb (37). Tincture (1:10, 70% ethanol): 40 drops up to 3 times daily (38). Topical use: a 5% infusion as a gargle or mouth-wash (30, 38).

**References**
7. Farnsworth NR, ed. NAPRALERT database. Chicago, University of Illinois at Chicago, IL, March 15, 1995 production (an on-line database available directly through the University of Illinois at Chicago or through the Scientific and Technical Network (STN) of Chemical Abstracts Services).
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Flos Tiliae

Definition
Flos Tiliae consists of the whole or cut dried inflorescence of wild or cultivated *Tilia cordata* Mill. and *Tilia platyphylllos* Scop. (Tiliaceae) collected during the flowering phase (1).

*Note:* According to the *European Pharmacopoeia*, Flos Tiliae consists of the whole, dried inflorescences of *Tilia cordata* Miller, of *Tilia platyphylllos* Scop., of *Tilia x vulgaris* Heyne or a mixture of these (Tiliaceae) (2). They are usually supplied whole, but the materials used for commercial purposes may be broken up (3).

Synonyms

Selected vernacular names
**Tilia platyphyllos**; bigleaf linden, broad-leaved lime, fleur de tilluel, Frühlinde, Graslinde, Grossblättrige Linde, large-leaved linden, lehmus, lipa, krupnolistnaja, lipa ploskolistnaja, mshvilpotola cachvi, platlapu liepa, sommerlinde, storblading lind, summer linden, suurelehine pärn, tei mare, tei cu frunza mare, tilleul à grandes feuilles (6–15).

**Geographical distribution**
Indigenous throughout Europe. It is common in northern temperate regions of the world and is also cultivated (6, 7, 16–22).

**Description**
*Tilia cordata*. Medium-sized trees, about 20 m high; wide spreading root system; crown, strikingly dense pyramidal when young, becoming rounded when mature; bark grey to brown, ridged and furrowed on older trees. (*T. platyphyllos* is about 30–40 m high, the branches are thicker and less dense.) Buds: lateral buds alternate, no terminal buds, two shiny glabrous bud-scales, reddish-brown or yellowish-brown, up to 6 mm long and 4 mm wide. (*T. platyphyllos* has hairy non-shiny buds, covered by three bud-scales.) Leaves: simple, cordate, oblique or cordate base, finely serrate, dentate or bidentate, palmate; veinlets of third order non-parallel; glabrous and slightly lustrous above, glabrous beneath with axillary tufts of brown hairs, 2–8(12) cm long, 2–6(10) cm wide, dark green above, bluish-green beneath; petiole 2.5–4.5 cm long. Upper branches fertile, lower ones sterile. The leaves of sterile branches are bigger and darker. (*T. platyphyllos* leaves have axillary tufts of white hairs, 5–8(17) cm long, 6–9(19) cm wide, dark green above, pale green beneath, with prominent parallel veinlets of third order.) Inflorescence: 5–15 flowered horizontal or erect cymes, bearing pale greenish-yellow, leaf-like bracts; bract as long as inflorescence, about 6 cm long, 1–1.5 cm wide; petiole 3–7 cm long. (*T. platyphyllos* has 2–7-flowered pendulous cymes, the bracts are shorter than the inflorescence, 5–9 cm long, up to 2.5 cm wide.) Flower: actinomorphic, hermaphrodite, pentamerous; petals greenish-yellow to pale yellow; stamens, about 30, no staminodes; ovary, pubescent, superior, 5-locular with one smooth style, 5 stigmas; scented, geniculate peduncles are between 1.5 and 3 cm long. (*T. platyphyllos* flowers 10–15 days before *T. cordata*.) Fruits: nutlets, spherical, without ribs, thin shelled, 4–6 mm in diameter, brown to tan when mature (*T. platyphyllos* has oval or pear-shaped nutlets, with woody shell and 3–5 ridges, tomentose, cream-coloured, up to 1 cm in diameter) (6, 23–30).
Plant material of interest: dried inflorescences

General appearance
The inflorescence is yellowish-green. The main axis of the inflorescence bears a linguiform bract, membranous, yellowish-green, practically glabrous, the central vein of which is joined to about half its length with the peduncle. Flowers are arranged in clusters of 3–7 on a stalked pendulous cyme (T. platyphyllos) or in clusters of 3–15 on a stalked erect cyme (T. cordata). The diameter of the flowers is between 1 and 1.5 cm. Sepals are easily detached, oblong-ovate, greyish-green, up to 6 mm long; their abaxial surface is usually glabrous, their adaxial surface and their borders are strongly pubescent. The 5 spatulate or ovate, thin petals are yellowish-white, up to 8 mm long. They show fine venation and their borders are only sometimes covered with isolated trichomes. The numerous stamens are free and usually constitute 5 groups. The superior ovary has a pistil with a 5-lobate stigma. The fruits are nutlets, 2 mm in diameter. The cut drug consists of fragments of inflorescences with a diameter 0.5–20 mm (1–3).

Organoleptic properties
Odour: faint aromatic, characteristic; taste: faint, aromatic, sweetish and mucilaginous (1–3).

Microscopic characteristics
The adaxial epidermis of the bract has cells with straight or slightly sinuous anticlinal walls. The abaxial epidermis has cells with wavy-sinuous anticlinal walls and anomocytic stomata. Two types of trichomes occur near the junction of the bract vein with the peduncle: one glandular, with short 1–3-cellular stalk, and oval multicellular head, and the other covering, stellate, with 3–7 long sinuous cells. The mesophyll is spongy, with clusters or prismatic crystals of calcium oxalate. The parenchyma of the sepals, particularly near the veins, has numerous mucilaginous cells and cells containing small calcium oxalate clusters. The adaxial epidermis of sepals has bent, thick-walled covering trichomes, unicellular or stellate with up to 5 cells. The epidermal cells of the petals have straight anticlinal walls with a striated cuticle without stomata. The parenchyma of the petals contains small calcium oxalate clusters (8–16 µm in diameter) and mucilaginous cells. The mucilage stains pink with ruthenium red solution. The pollen grains have a diameter of about 30–40 µm and are oval or slightly angular with 3 germinal pores and a finely granulated exine. The ovary is glabrous or densely covered with trichomes, often very twisted, unicellular with 2–4 branches. The diagnostic features include the sclereids of the bracts and the tufted trichomes of the sepals, as well as the stel-
late trichomes of the ovary (1–3, 31). According to the Österreichisches Arzneibuch (32) and Pharmacopoeia Helvetica VII (33), adulterants can be recognized microscopically by the densely pubescent bracts (e.g. T. americana L. and T. tomentosa Moench), and/or by the flowers having petalaceous staminodes (e.g. T. tomentosa).

**Powdered plant material**

Pale green powder; lower epidermis of bract has sinuous anticlinal walls, striated cuticle, anomocytic stomata, stellate trichomes and glandular trichomes; epidermal cells of petals elongated, straight anticlinal walls; mesophyll with large cells containing mucilage which stains pink with ruthenium red solution; cluster crystals of calcium oxalate; tetragonal pollen grains with finely warty exine (3).

**General identity tests**

Macroscopic and microscopic examinations, thin-layer chromatography for the presence of rutin, hyperoside, caffeic acid and other characteristic constituents (2), and colour reaction of the cut drug with 5% ammonia solution for the detection of flavonoids. If the cut drug is soaked for 3–5 minutes in cold water, the fragments of drug are mucilaginous to the touch (1). The mesophyll has large cells containing mucilage, which stain pink with ruthenium red solution (3).

**Purity tests**

**Microbiological**

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (34).

**Chemical**

To be established according to national requirements. The German pharmacopoeia (35) describes identification by detection of the flavonoids using the Shinoda reaction, and also by separation by thin-layer chromatography (6).

**Foreign organic matter**

Not more than 2% (2, 3). There should be no inflorescences with a bract bearing at the abaxial face stellate, 5–8-rayed trichomes and flowers having an apparent double corolla by transformation of 5 stamens into petal-like staminoids and having a pistil which is not lobular nor indented. Hexamer-
ous flowers occur only occasionally (*T. americana* L., *T. tomentosa* Moench) (2). Not more than 0.3% of organic matter. Not more than 2% of inflorescences with bract or of bracts without inflorescences which have been damaged by insects or harmed by erysiphe. Brownish and blackish fragments of inflorescences, not more than 4%. Not more than 1% of other parts of plant (leaves and branches). Not more than 2% of inflorescences with fruits. For whole drug: not more than 3% of fragments of drug having a diameter less than 3 mm; not more than 15% of fragments of drug spilled from flowers or from inflorescences without bract. For cut drug: not more than 10% of fragments of drug having a diameter less than 0.310 mm (1).

**Total ash**
Not more than 8% (2).

**Acid-insoluble ash**
Not more than 4% of ash insoluble in hydrochloric acid (3).

**Sulfated ash**
Not more than 10% (33).

**Water-soluble extractive**
Not less than 10% (36).

**Alcohol-soluble extractive**
No information available.

**Loss on drying**
Not more than 12% (2). Not more than 13% (1).

**Swelling index**
Not less than 15 (33).

**Pesticide residues**
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (2). For other pesticides, see the *European pharmacopoeia* (2) and the WHO guidelines on quality control methods for medicinal plant materials (34) and pesticide residues (37).

**Heavy metals**
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (34).
Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (34) for the analysis of radioactive isotopes.

Other purity tests
The content of mineral matter should be not more than 0.1% (1). Chemical and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays
To be established in accordance with national requirements.

Major chemical constituents
The major constituents of the dried inflorescences are flavonoids (1–5%): chiefly quercetin glycosides (rutin, hyperoside, quercitrin and 3-glicosyl-7-rhamnose), and kaempferol glucosides (astragalin (kaempferol-3-glucoside), tiliroside (astragalin-6′′-p-coumaroylste), astragalin-3-glucosyl-7-rhamnose, astragalin-3,7-dirhamnose). A complex of mucilage (7–10%, particularly from the bracts, mainly arabino-galactans with some uronic acid units) is present. The mucilage is composed of 5 fractions dominated by D-galactose, L-arabinose, L-rhamnose and uronic acid, with smaller amounts of glucose, mannose and xylose. The essential oil (0.02–0.1%) contains farnesol and its acetate, linalool, geraniol, geranyl acetate, germacrene, 1,8-cineole, eugenol, camphor, carvone, citral, citronellol, limonene, kaur-16-ene and some 70 other identified compounds; which gives the drug its characteristic faint odour, more pronounced in the fresh flowers. The presence of phenolic acids (caffeic, p-coumaric and chlorogenic acids), scopoletin, tannins (approximately 2%, including the procyanidin dimers B-2 and B-4), leucoanthocyanidins, among others, has also been reported (6, 18, 23, 30, 38–46). The structures of the major constituents are presented below.

Medicinal uses
Uses supported by clinical data
No information was found.

Uses described in pharmacopoeias and well established documents
The Commission E approved the internal use of Flos Tiliae for colds and cold-related coughs (45). The use of the flowers as an antispasmodic and diaphoretic agent is indicated (47).
**Uses described in traditional medicine**
Flores Tiliae are used to treat insomnia (48, 49). Traditionally, the flowers have been used for treatment of migraine, hysteria, arteriosclerotic hypertension, circulatory disorders and swelling of the ankle (50–53), cardiovascular and digestive complaints (54). Flos Tiliae are also used in urinary infections, influenza and anxiety (20, 22, 55).

**Pharmacology**

**Experimental pharmacology**

**Action on lymphocyte proliferation**
The aqueous extract of Flos Tiliae (1.5 g dried flowers in 20 ml of water) demonstrated stimulatory effects on lymphocyte proliferation in vitro. The test system consisted of suspensions of lymphoid cells, which were asepti-
cally removed from the lymph nodes of inbred mice; the final concentration of cells in culture was $2 \times 10^6$ cells/ml. The extract was tested at concentrations ranging from 0.5 to 80 µg/ml; control cells were treated with saline solution. The lymphocyte proliferation effect was mimicked by Ro 5-4864, a specific agonist of the peripheral benzodiazepine receptor and by Pk 11195, an agonist/antagonist of the same receptor; these agents were used as reference standards at a concentration of $5 \times 10^{-7}$ M. Maximum stimulation of 170% was observed at a concentration of 20 µg/ml ($p < 0.05$). The synergistic effect of the extract with Ro 5-4864 suggests that the extract exerted its stimulatory action on cell proliferation by acting as a partial agonist on peripheral-type benzodiazepine binding sites (56).

**Antitumour activity**

The antiproliferative action of various extracts: aqueous (1.5 g flowers in 20 ml of water), dichloromethane (9 g flowers in 200 ml of dichloromethane) and ethanol (9 g flowers in 200 ml of ethanol) of *Tilia cordata* flowers on BW 5147 lymphoma cells and non-tumour lymphocytes was investigated. All extracts (at different concentrations) showed a selective action on tumour cells, inducing apoptosis. In the case of normal lymphocytes, these extracts suppressed mitogen-induced proliferation. The aqueous, dichloromethane and ethanol extracts inhibited proliferation of tumour and non-tumour cells in a concentration-dependent manner. From EC$_{50}$ values, the dichloromethane extract proved to be the most active: it showed the greatest inhibition of cell proliferation, as shown by the EC$_{50}$ values for both tumour cells (4.84 µg/ml) and non-tumour cells (14.12 µg/ml) ($p < 0.05$). Scopoletin, the main component in the dichloromethane extract had an antiproliferative action on BW 5147 cells, suggesting that it may be at least partly responsible for the activity displayed by this extract (57).

**Antimicrobial activity**

An aqueous extract of a commercial sample of Flos Tiliae demonstrated weak antibacterial activity in vitro against *Escherichia coli* and *Staphylococcus aureus* at a median inhibitory concentration (MIC) of 1 mg/ml/agar plate; *Staphylococcus aureus* strain Oxford at an MIC of 1.5 mg/ml; and against *Bacillus subtilis* at an MIC of 3.1 mg/ml (58).

A methanol extract of the dried flowers exhibited weak antifungal activity against *Aspergillus niger* in vitro at a concentration of 5 mg/ml/agar plate (60).

A 10% aqueous extract of dried Tiliae flowers demonstrated antiviral activity against influenza virus A2 (Manheim 57) in cell culture (60).
Smooth muscle effects
An aqueous extract of Tiliae flowers at a concentration of 0.08 g/ml produced a biphasic response in vitro, consisting of transient relaxation of rat duodenum followed by a constriction (61).

Toxicology
An infusion of Tiliae flowers (1:10) was assayed for anti-genotoxicity using the somatic mutation and recombinant test in Drosophila melanogaster. The infusion demonstrated desmutagenic activity (100% inhibition) against hydrogen peroxide used as an oxidative genotoxicant. These results could possibly be explained by synergism between phenolic components of the infusion and the hydrogen peroxide due to the known ability of phenols to scavenge reactive oxygen (62).

Clinical pharmacology
Diaphoretic action
The diaphoretic action of Tiliae flowers was investigated in an open controlled clinical trial in patients with uncomplicated catarrhal disease. Fifteen patients with catarrhal disease inhaled water vapour from a preparation made with two sachets of Tiliae flowers in 500 ml of water. Inhalation was maintained for 10 minutes at 40–50 ºC. A control group of 15 patients inhaled vapour from coloured water. Fifteen minutes after inhalation all patients experienced a certain subjective relief with further improvement of their condition in the group that had inhaled the preparation of Tiliae flowers. In the control group improvement was observed only for the first 120 minutes, and after addition of other symptomatic treatment. In the authors’ opinion the inhalation of a preparation of Tiliae flowers had an appreciable diaphoretic effect. As there was no statistical analysis of the data, an objective assessment of this investigation is not possible (63).

Adverse reactions
A case-report of occupational allergy in a 55-year-old woman has appeared in the scientific literature. The woman, a non-smoker, who was working as a cosmetician, had experienced recurrent itching and erythematous papulovesicular lesions on the backs of her hands for around 18 months, and had had a history of sneezing, nasal obstruction and watery eyes for some years when she came into contact with depilatory wax or flowers of Tilia cordata. Clinical examination, as well as routine laboratory parameters, remained normal. Total immunoglobulin E was 13 084 IU/ml and skin-prick tests showed positive reactions to common environmental allergens – grass and tree pollens, and to flowers. Specific immunoglobulin E antibodies for grass
and tree pollens were negative. The results of patch tests with *Tilia* flowers with a standard series and a series of plant allergens were positive. A bronchial challenge test was performed in an inhalation chamber for 30 minutes. In the first stage, the patient was challenged with placebo (potato flour); during the second stage (after 7 days), with depilatory wax that had been thermally activated, and after 14 days with dried flowers. Following such exposures, clinical symptoms of rhinoconjunctivitis appeared, and were observed for 48 hours after the challenges. In addition, increases in eosinophil and basophil proportions in nasal lavage and tear fluids were observed during the late phase of allergic reaction. A diagnosis of occupational allergy was made based on the positive results of the allergy tests, analysis of the clinical status and medical history, and the positive results of specific challenges (64).

Over a 5-year period, 1790 paediatric outpatients were observed for suspected allergic symptoms and 371 children were given a skin prick test to check for responses to aeroallergens. Aeroallergen sensitization due to *Tilia cordata* was observed in 11.4% of the paediatric patients examined (65).

**Contraindications**
If signs of hypersensitivity reaction appear (contact dermatitis or rhinoconjunctivitis), Flos Tiliae must not be used again.

**Warnings**
No information was found.

**Precautions**
**General**
No information was found.

**Drug interactions**
No information was found.

**Drug and laboratory test interactions**
No information was found.

**Carcinogenesis, mutagenesis, impairment of fertility**
No information was found.

**Pregnancy: teratogenic effects**
No information was found.
**Pregnancy: non-teratogenic effects**
No information was found.

**Nursing mothers**
No information was found.

**Paediatric use**
No information was found.

**Dosage forms**
Dried inflorescences with bracts are used for teas and other Galenical preparations for use in gargles, rinses and other topical applications, as well as for internal use (36).

**Posology**
(Unless otherwise indicated)
*Daily dosage for internal use.* Infusion: 2–4 g of dried flowers in 200 ml of boiling water, three times daily (45). Tincture: (1:5) in 45% ethanol, 1–2 ml, three times daily (55). Fluidextract: (1:1) in 25% ethanol, 24 ml, three times daily (55).

*For gargles and rinses.* Infusion: 4–5 tablespoonfuls of dried flowers in two 200-ml glasses (400 ml in total) of boiling water (66).

*Dosage for external use.* Bath: steep 4–5 tablespoonfuls of dried flowers in two 200-ml glasses (400 ml in total) of boiling water for 20 minutes and add to bath (21).

**References**
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)


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64. Krakowiak A et al. Occupational contact dermatitis with rhinoconjunctivitis due to Tilia cordata and colophonium exposure in a cosmetician. Contact Dermatitis, 2004, 51:34.


Radix Urticae*

Definition
Radix Urticae consists of the dried roots and rhizomes of *Urtica dioica* L., *U. urens* L. (Urticaceae), their hybrids or mixtures thereof (1, 2).

Synonyms
*Urtica dioica* L.

*Urtica urens* L.

Selected vernacular names
*Urtica dioica* L.
Brennesselwurzel, common nettle, csalángyökér, gazaneh, grande ortie, greater nettle, grosse Brennessel, Haarnesselwurzel, Hanfnesselwurzel, hhurrayq, Nesselwurzel, nettle root, ortica, ortie, ortiga, pokrzywa, qurrays, racine d’ortie, raiz de ortiga, stinging nettle, tsuknida, zwyczajna (4–6).

*Urtica urens* L.
Dwarf nettle, Eiternessel, kleine Brennessel, lesser nettle, ortica minore, ortica piccola, ortie brulante, petite ortie, sha’reláguz, small nettle (4, 6–9).

Geographical distribution
*Urtica dioica* is indigenous to Africa and western Asia, but is now found in all temperate regions of the world in Africa, North and South America, Asia, Australia and Europe (3, 4, 6, 7, 10).

Owing to the difficulty in botanical differentiation between *Urtica dioica* and *U. urens* in the wild, they are often harvested together. Although both species have a similar distribution, *U. urens* has become less widely distributed due to the reduction of its habitat (3).

* Adopted from the volume 2 of WHO monographs on selected medicinal plants.
Description

_Urtica dioica L._

A herbaceous perennial with erect, green to purplish square stems, 30–150 cm high, with creeping roots; whole plant covered with stinging hairs. Leaves opposite, cordate at the base, oblong or ovate, finely toothed; upper surface dark green and underside paler. Flowers incomplete, small, green, dioecious (plant has either male or female flowers in separate inflorescences) and occur as racemes in axils of upper leaves; male or barren flowers have a perianth of 4 segments and 4 stamens, which are bent inwards at bud stage; female or fertile flowers have similar perianth surrounding a single 1-seeded carpel, bearing 1 style with a brush-like stigma. Fruit an achene (3, 8).

_Urtica urens L._

A herbaceous annual resembling _Urtica dioica_, but is smaller (usually up to 30 cm high), has smaller leaves and flowers are in short, mostly unbranched clusters; male and female flowers appear together in the same raceme. Glabrous except for the stinging hairs (8, 11).

Plant material of interest: dried roots and rhizomes

General appearance

Rhizome cylindrical and tapering, occasionally branched, up to about 6 mm thick at upper end; outer surface yellowish-brown; internodes with deep longitudinal furrows, numerous smooth, very thin and wiry roots arising from the nodes; in the outer part, inner surface creamy-white with a central hollow; fracture fibrous and tough.

Root greyish-brown, irregularly twisted, about 5 mm thick, distinct longitudinal furrows; hollow in cross-section, cut surface white; fracture fibrous and tough (1, 7).

Organoleptic properties

Odourless; taste: faintly aromatic, characteristically bitter (1).

Microscopic characteristics

Rhizome: thin cork composed of brown, thin-walled cells, a few rows of tangentially elongated cortical parenchyma and a pericyclic region with fairly numerous fibres; fibres usually in small groups, sometimes single; individual fibres greatly elongated with very thick, lignified walls; some cells of pericycle and outer part of the secondary phloem contain fairly large cluster crystals of calcium oxalate. Cambial region distinct and continuous, with narrow radial groups of vascular tissues separated by wide
Radix Urticae

medullary rays; secondary phloem mainly parenchymatous, whereas secondary xylem dense and completely lignified; medullary rays in secondary xylem show alternating areas of lignified and unlignified cells; lignified cells have moderately thickened walls and numerous simple pits. Pith composed of rounded, unlignified parenchyma.

Root: very thin cork, narrow phelloderm and secondary phloem and xylem with alternating areas of lignified and unlignified parenchyma in the wide medullary rays, as in the rhizome; a strand of primary xylem in the centre with a few small vessels (I).

**Powdered plant material**
Fibrous and pale beige. Fragments of greatly elongated pericyclic fibres, occurring singly or in groups, with thick and lignified walls, xylem vessels with bordered pits, associated with thick-walled fibres with slit-shaped pits; lignified, moderately thick-walled and pitted parenchyma from the medullary rays of xylem; abundant thin-walled parenchymatous cells, some containing large cluster crystals or scattered crystals of calcium oxalate; fragments of brownish cork (I).

**General identity tests**
Macroscopic and microscopic examinations (I, 2), and thin-layer chromatography for scopoletin and phytosterols (2).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (12).

**Foreign matter**
Not more than 2% (I).

**Total ash**
Not more than 8% (2).

**Acid-insoluble ash**
Not more than 3.5% (1).

**Water-soluble extractive**
Not less than 15% (1).
**Loss on drying**
Not more than 12% (2).

**Pesticide residues**
The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (13). For other pesticides, see the *European pharmacopoeia* (13), and the WHO guidelines on quality control methods for medicinal plants (12), and pesticide residues (14).

**Heavy metals**
For maximum limits and analysis for heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (12).

**Radioactive residues**
Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (12) for the analysis of radioactive isotopes.

**Other purity tests**
Chemical, sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

**Chemical assays**
In addition to thin-layer chromatography for qualitative analysis (2), enzyme-linked immunosorbent assay and high-performance liquid chromatography methods have also been developed to determine the concentration of *Urtica dioica* agglutinin in Radix Urticae (15, 16). However, concentration limits need to be established.

**Major chemical constituents**
A large number of compounds of different polarity and belonging to various chemical classes, including fatty acids, terpenes, phenylpropanes, lignans, coumarins, triterpenes, ceramides, sterols and lectins, have been isolated from Radix Urticae. Among these are oxalic acid, linoleic acid, 14-octacosanol, 13-hydroxy-9-cis, 11-trans-octadecadienoic acid, α-dimorphecolic acid (9-hydroxy-10-trans, 12-cis-octadecadienoic acid), scopoletin, p-hydroxybenzaldehyde, homovanillil alcohol, β-sitosterol, stigmasterol, 24-R-ethyl-5α,6α-diol, campesterol, daucosterol (and related glycosides), secoisolariciresinol-9-O-β-D-glucoside, neooolivil, oleanolic acid, ursolic acid, *Urtica dioica* agglutinin and polysaccharides RP1-RP5 (3–5, 10, 17–21). The structures of the representative constituents are presented below.
Radix Urticae

\[ \text{ceramides} \]

\[ \text{\( \alpha \)-dimorphecolic acid} \]

\[ p\text{-hydroxybenzaldehyde} \]

\[ \text{scopoletin} \]

\[ \text{homovanillyl alcohol} \]

\[ \text{neoolivil and enantiomer} \]
Medicinal uses

Uses supported by clinical data
Symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, urinary retention) resulting from BPH stages I and II, as defined by Alken, in cases where diagnosis of prostate cancer is negative (22–35).

Uses described in pharmacopoeias and traditional systems of medicine
As a diuretic and for the treatment of rheumatism and sciatica (6).

\[
\text{Glc} = \beta-D\text{-glucopyranosyl}
\]

\[
\beta\text{-sitosterol} \quad R = H
\]

\[
daucosterol \quad R = \text{Glc}
\]

\[
\text{oleanolic acid}
\]
Radix Urticae

Uses described in folk medicine, not supported by experimental or clinical data
Treatment of asthma, coughs, dandruff, diabetes, diarrhoea, eczema, fever, gout, haemorrhoids, nose bleeds, scurvy, snakebites and tuberculosis (5, 6). The plant has also been used to stop uterine bleeding after childbirth, increase lactation and promote hair growth, and as a vermifuge (5, 6).

Pharmacology

Experimental pharmacology

Anti-inflammatory activity
An ethanol extract of Radix Urticae inhibited the activity of human leukocyte elastase and reduced the amount of the enzyme released by activated polymorphonuclear granulocytes during the inflammatory response. The extract also inhibited degradation of a peptide substrate in vitro by human leukocyte elastase (IC$_{50}$ 3.6 µg/ml) and bovine elastin (IC$_{50}$ 68 µg/ml) (36). Intragastric administration of a polysaccharide fraction isolated from Radix Urticae to rats (40 mg/kg body weight) suppressed carrageenan-induced footpad oedema for up to 20 h (21, 37). The activity of the polysaccharides was comparable to that of indometacin (10 mg/kg body weight) (21, 37).

Lymphocyte proliferation
A lyophilized aqueous extract (10 µg/ml) and a 40% alcohol extract of the roots (100 µg/ml) stimulated human lymphocyte proliferation in vitro by 63% and 100%, respectively (21, 37). Polysaccharides isolated from an aqueous root extract induced human lymphocyte proliferation in vitro (10–100 µg/ml) (21, 37). An ethyl acetate extract of the roots induced cell differentiation in human promyelocytic leukaemia HL-60 cells in vitro (ED$_{50}$ 4 µg/ml) (38). Urtica dioica agglutinin (500 ng/ml), however, inhibited lymphocyte proliferation and the binding of epidermal growth factor to its receptor on A431 epidermoid cancer cells in vitro (39). The lectin also exhibited immunomodulatory effects on T-lymphocytes in a dose-dependent manner (21, 37). Urtica dioica agglutinin bound to the cell membrane of prostatic hyperplastic cells (40) and inhibited their proliferation (21).

Effect on benign prostatic hyperplasia

Effect on sex hormone-binding globulin
Sex hormone-binding globulin (SHBG) is a blood plasma protein that binds to circulating androgens and estrogens, thereby regulating their free
concentration in plasma. The plasma membrane of the human prostate contains specific SHBG receptors, and SHBG appears to play a role in the development of BPH. A 10% hydroalcoholic extract of the root reduced the binding capacity of SHBG (isolated from human plasma) for 5α-dihydrotestosterone by 67% in vitro (41). An aqueous extract of the root (0.6–10.0 mg/ml) inhibited the binding of 125I-labelled SHBG to human prostate membranes in vitro (42). The lignan, secoisolariciresinol, and a mixture of the isomeric compounds 13-hydroxy-9-cis,11-trans-octadecadienoic acid and 9-hydroxy-10-trans,12-cis-octadecadienoic acid isolated from a methanol root extract, reduced the binding of SHBG to 5α-dihydrotestosterone (18). Secoisolariciresinol and its main intestinal transformation products, (−)-3,4-divanillyltetrahydrofuran and enterofuran, displaced the binding of 5α-dihydrotestosterone to SHBG in vitro by 60%, 95% and 73%, respectively (43).

**Enzymatic activity**

Intragastric administration of a 30% ethanol extract of the root to male mice inhibited the activities of 5α-reductase and aromatase (ED₅₀ 14.7 and 3.58 mg/ml, respectively) (44). However, a hydroalcoholic extract of the root dissolved in dimethyl sulfoxide did not inhibit the activity of 5α-reductase from human prostate cells in vitro (up to 500 µg/ml) (45). A standardized hydroalcoholic extract of the roots (IC₅₀ 338 µg/ml) inhibited aromatase activity in vitro. A heptane-soluble fraction of the extract was the most effective inhibitor (IC₅₀ 9 µg/ml) (36). Both ursolic acid and 14-octacosanol isolated from a methanol extract of the roots inhibited the activity of aromatase in vitro (46). 9-Hydroxy-10-trans,12-cis-octadecadienoic acid isolated from the roots inhibited the activity of aromatase in vitro (19). Butanol, ether, ethyl acetate and hexane extracts of the roots inhibited the activity of sodium- and potassium-adenosine triphosphatase isolated from prostatic hyperplastic cells by 27.6–81.5% (47). In addition, steroidal components of the roots, stigmast-4-en-3-one, stigmasterol and campesterol (1 µmol/l to 1 mmol/l), inhibited sodium- and potassium-adenosine triphosphatase activity by 23–67% (47).

**Effect on prostate growth**

Intragastric administration of a hexane extract of the roots (1.28 g daily) to castrated rats did not inhibit prostate growth stimulated by testosterone or dihydrotestosterone (45). Intraperitoneal administration of a hydroalcoholic extract of the roots (20 mg/kg body weight) suppressed testosterone-stimulated increases in prostate weight and prostatic ornithine decarboxylase activity in castrated rats (48). Daily oral administra-
tion of a hydroalcoholic extract of the root to dogs with BPH (30 mg/kg body weight) decreased prostate volume by 30% after 100 days of treatment (49).

The effect of various root extracts was assessed after implantation of the fetal urogenital sinus into the prostate gland of adult mice. Intragastric administration of a butanol, cyclohexane or ethyl acetate extract of the root (0.25 ml/daily for 3 weeks) had no effect on the development of BPH in mice. However, intragastric administration of the same dose of a 20% methanol extract of the root reduced the development of BPH by 51.4% (50).

Toxicology
The LD$_{50}$ of an aqueous extract or infusion of the roots after intravenous administration to rats was 1721 mg/kg body weight and 1929 mg/kg body weight, respectively. Oral administration of an infusion of the roots to rats was well tolerated at doses up to 1310 mg/kg body weight (3).

Clinical pharmacology

Benign prostatic hyperplasia

Placebo-controlled clinical trials
Three double-blind, placebo-controlled clinical trials have assessed the efficacy of oral administration of Radix Urticae for the symptomatic treatment of lower urinary tract disorders resulting from BPH (24, 27, 35). One study assessed the efficacy of a 20% methanol extract of the roots in 50 men with BPH stages I and II (35). A significant increase in urine volume (by 43.7%; $P = 0.027$) and a significant decrease in serum levels of SHBG ($P = 0.0005$) was observed in patients treated with 600 mg extract daily for 9 weeks. A modest increase in maximum urinary flow of 8% was also observed in the treated group; however, it was not significant (35). Another study assessed the efficacy of a 20% methanol extract in 40 men with BPH. Treatment with 1200 mg extract daily for 6 weeks decreased the frequency of micturition and serum levels of SHBG (27). The third study assessed the efficacy of a methanol extract in the treatment of 32 men with BPH stage I (24). A 4–14% increase in average urinary flow and a 40–53% decrease in postvoid residual volume were observed in patients treated with 600 mg extract daily for 4–6 weeks (24).

Clinical trials without controls
Numerous clinical trials without controls have assessed the efficacy of oral administration of various Radix Urticae extracts (20% methanol or
30–45% ethanol) for the symptomatic treatment of lower urinary tract disorders (nocturia, polyuria, dysuria, urine retention) resulting from BPH (22, 23, 25, 26, 28–32, 34, 51, 52). One trial assessed the efficacy of a 40% ethanol extract of the roots in 67 men with BPH. Treatment with 5 ml daily for 6 months decreased nocturia and postvoid residual volume, but did not reduce prostate enlargement (23). In another trial, a 20% methanol extract of the roots was assessed in 89 men with BPH. Treatment with 600 mg daily decreased the postvoid residual volume in 75% of patients after 3–24 months (25). In a study of 26 men with BPH stage I or II, a decrease in prostate volume was observed in 54% of patients, and a decrease in postvoid residual volume was observed in 75% of patients, after treatment with 1200 mg methanol extract daily for 3–24 weeks (26). Ten men with BPH were treated with 30–150 drops of a 45% ethanol extract of the root daily for 30 days. After treatment, the postvoid residual volume decreased by 66% (29). In a study of 39 men with BPH stages I–III, an improvement in urinary flow, and a reduction in postvoid residual volume, nocturia and polyuria were seen in 95% of patients after 6 months of treatment with a 20% methanol extract (600–1200 mg daily) (51). Twenty-seven men with BPH stages I and II were treated with a 20% methanol extract of the roots for 3.5 months. Postvoid residual volume decreased significantly in 75% of patients ($P < 0.001$), and maximum urinary flow increased significantly in 50% of patients ($P < 0.002$) (52).

Three large-scale multicentre studies involving 14 033 men with BPH assessed the efficacy of a 20% methanol extract (28, 31, 32). In one study, a decrease in nocturia and polyuria was seen in 91% of patients after 6 months of treatment (28). In another study, a 50% decrease in nocturia was observed in patients treated with 1200 mg extract daily for 10 weeks (31). In the third study, significant improvements in both urinary flow and postvoid residual volume were observed in 4480 patients treated with 600–1200 mg extract daily for 20 weeks ($P < 0.01$) (32).

**Effects on prostate morphology**

Three studies without controls examined the effect of various methanol extracts of *Radix Urticae* on prostate morphology. Prostate cells were obtained from patients with BPH by needle biopsy, and were analysed for morphological changes before and after treatment. In two of the studies, cells were taken from the patients at various intervals during treatment (53, 54). In the third study, cells were obtained once from the patients, and treatment with the extract was carried out in vitro (55). In the first study, 31 men with BPH stages I and II were treated orally with 1200 mg of a
20% methanol root extract daily for 20 weeks. Prostate cells were analysed every 4 weeks by fluorescent microscopy. After 4–16 weeks of treatment, an increase in nuclear volume, as well as hydropic swelling and vacuolization of the cytoplasm, were observed (53). In the second study, prostate cells from four men with BPH stage I were examined by electron microscopy. After 6 months of oral treatment with a 20% methanol extract (1200 mg daily), a reduction in the activity of smooth muscle cells and an increase in the secretory activity of glandular epithelial cells were observed (54). In the third study, prostate glandular epithelial cells from 33 patients with BPH were analysed by fluorescent microscopy following incubation of the cells in vitro with a 20% methanol extract of the root. Treatment with the extract caused an increase in nuclear volume, loosening of chromatin and hydropic swelling of the cytoplasm. In addition, the number of homogeneous secretory granules was reduced, indicating a reduction in the biological activity of these cells (55).

Contraindications
Radix Urticae is contraindicated in cases of known allergy to plants of the Urticaceae family. Owing to its effects on androgen and estrogen metabolism, the use of Radix Urticae during pregnancy and lactation and in children under the age of 12 years is contraindicated.

Warnings
Radix Urticae relieves the symptoms associated with BPH but does not have an effect on the size of the prostate. If symptoms worsen or do not improve, or in cases of blood in the urine or acute urinary retention, contact a physician.

Precautions

Pregnancy: teratogenic effects
See Contraindications.

Pregnancy: non-teratogenic effects
See Contraindications.

Nursing mothers
See Contraindications.

Paediatric use
See Contraindications.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Other precautions
No information available on general precautions or precautions concerning drug interactions; drug and laboratory test interactions; or carcinogenesis, mutagenesis and impairment of fertility.

Adverse reactions
Clinical studies have shown that extracts of Radix Urticae are well tolerated in humans. A few cases of minor transient gastrointestinal side-effects, such as diarrhoea, gastric pain and nausea (32, 35), and allergic skin reactions (32), have been reported.

Dosage forms
Crude drug for infusion; hydroalcoholic extracts (4, 56). Store in a well-closed container, protected from light and humidity (2, 13).

Posology
(Unless otherwise indicated)
Daily dosage: 4–6 g crude drug or equivalent preparations as an infusion (4, 56); 600–1200 mg dried 20% methanol extract (5:1) (22, 25, 27, 31, 32); 1.5–7.5 ml 45% ethanol extract (1:1) (29); 5 ml 40% ethanol extract (1:5) (17, 23).

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Radix Urticae

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Styli cum stigmatis Zeae maydis

Definition
Styli cum stigmatis Zeae maydis consists of the whole or cut dried styles and stigmas of cultivated annual Zea mays L. (Poaceae/Gramineae) harvested during the ripening period (1).

Synonyms

Selected vernacular names
Able, aburow, adakple, akple, artho, avari, avati, bada iringu, bajri, baomaimi, bap ngo, barajuar, bekalo, bhutta, blaifo, blarama, blikple, borona, buta, chhale, cholam, cholum, conac, corn, corn silk, cucuruz, durakhizan, durahshami, ekidid, fiso, froment des Indes, froment d’Inde, frumentone, garouilhe, garoullet, gaudumemekkah, goinjol, gorajonra, graine de turquet, grano siciliano, granoturco, gurulujonra, hausa, hintaherunu, hupfu, Indian corn, jagung, jaorai, jaori, jaorikhurdani, jawdra, jondra, jonra, jorna, junala, junri, kamh irrum, kandaja, kao pót, kao sâli, katsabotsos, katsakandevelohaly, katsamanga, katzaha, katzabazaha, keto, khalavan, khandaruz, khao koane, khao phot, khoshahemakki, khot, kitka, kon, kpkle, kpliedzi, kukri, kukurudza, kukuruz, kukuruza, kukurüza, kukurydza, kuthi, lamari, le mais, lua ngo, ma khau li, maeo, Mais, mâis, maissi, maiz, maiz, maize, silicone, maisgriffl, mahakaya, mahindi, maidis stigmata, mak, makai, maka, makaya, maki, makkajari, makkajowari, makkasholam, makakazonnal, makkei, makki, mbemba, mbila, mealias, mkekjejola, mel, melicatto, meliga, milie, milho, millaral, millargou, misir, mokajanna, mukni, mungari, musukojola, nammanmo, ngo, okchokseoye, okmi, oksusoo, pâpušoi, paut, phoat, poone, popusoiu, porum, potshatka, psheno turetskoeput, pyaungbu, sako, sampantastha, sana, shikhalu, sila, sila nivava lagi, simindi, stigmata maydis, stigmates de maïs, tomorokpshi, trigo de las indias, trigo de-turquia, tsako, tsakotsako, tuerkische korn, tuerkisher weizen, turkey corn, turkey wheat, upfu, watsikple, weizen türkischer, welschkorn, zaburro, zara del peru, zea, zurratulmakakah, zonallo, zondillo, yavanala, yumi, yumixu, yu shu shu (4–19).
Geographical distribution
Indigenous to Central America, it is now cultivated worldwide as green fodder or as a cereal crop (2, 5, 20–23).

Description
A robust monoecious annual plant, up to 3 m in height. Roots, fasciculate; often with prop roots from the lower nodes. Stems, erect, culm-internodes solid, smooth. Leaves, alternate, with sheathing base, ciliate ligule about 5 mm long, broadly linear or lanceolate blade, upper surface hairy, lower surface hairless, acuminate, parallel-veined, 25–100 cm long, 2–10 cm wide. Flowers, unisexual. Inflorescences, terminal panicle of male flowers, and spadix of female flowers. Male inflorescence (tassel) is a terminal large spreading panicle, about 30 cm long, formed by spike-like racemes of staminate spikelets. The spikelets are in pairs, one sessile, the other pedicelled, 8–12 mm long, awnless, 2-flowered, florets both male; glumes papery, equal, enclosing florets. Female inflorescence (spadicles or ears) variable in size and shape, borne on short branch with several short internodes with a papery sheath at each node, these form the husk and enclose the thick central axis (cob) on which the spikelets are arranged in 8–16(30) longitudinal rows; spikelets in pairs, 2-flowered, both sessile, awnless, the lower floret small, rarely female, the upper one female; glumes broad, rounded or notched at apex, fleshy towards base; styles projecting from apex of ear and look like tufts of hair, at first green, later red or yellow. Fruit, caryopsis with adherent pericarp; exposed between gaping lemma and palea at maturity; variable as to size, shape and colour (usually yellow but can be whitish or darker, almost black) (2, 5, 24–27).

Plant material of interest: dried styles and stigmas
General appearance
Slender, yellowish or brownish, filamentous styles, 5–20 cm long, exhibiting slender bifid stigmas 0.5–3.0 mm long. Viewed with a hand lens, they appear flattened and ribbon-like, or grooved and curled up, with spreading trichomes (1, 28, 29). In the cut form, the drug is made up of 5–10-mm long filamentous, channelled pieces of stigmata, pale yellowish or brownish red in colour (5). According to the USSR pharmacopoeia, the cut drug is composed of fragments of styles and stigmas having a length less than 7 mm, they are brownish, brownish red or light yellow in colour (1).

Organoleptic properties
Odour: slight, faint, characteristic; taste: insipid, slightly mucilaginous, somewhat sweetish (1, 5, 28, 29).
**Microscopic characteristics**
Epidermal cells rectangular, often extended into multicellular trichomes 200–800 µm long, the basal portion consisting of 2–5 cells and the upper portion usually unicellular; multicellular and multiseriate trichomes, some of which are bluntly toothed; purplish red parenchymatous cells containing red colouring matter; two vascular bundles containing narrow tracheids with spiral or annular thickening (1, 5, 28, 29).

**Powdered plant material**
Yellow powder with a slight odour and an insipid taste; rectangular epidermal cells often extending into multicellular trichomes; fragments of trichomes; parenchymatous cells with red contents (28).

**General identity tests**
Macroscopic and microscopic examinations (1).

**Purity tests**

**Microbiological**
Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plant materials (30).

**Chemical**
No information available.

**Foreign organic matter**
Not more than 0.5% of organic matter (1). Brownish styles and stigmas or their fragments, not more than 3%. For cut drug: not more than 5% of fragments of drug having a length more than 7 mm and not more than 1% of fragments of drug having a length and diameter less than 0.2 mm (1).

**Total ash**
Not more than 8% (29) or not more than 7% (1).

**Acid-insoluble ash**
Not more than 2% of ash insoluble in concentrated hydrochloric acid (29) or not more than 2.5% of ash insoluble in 10% hydrochloric acid (1).

**Sulfated ash**
No information available.
WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS)

Water-soluble extractive
Not less than 10% (28, 29).

Alcohol-soluble extractive
Not less than 15% (1).

Loss on drying
Not more than 13% (1).

Pesticide residues
The recommended maximum sum limit of aldrin and dieldrin is not more than 0.05 mg/kg (31). For other pesticides, see the European pharmacopoeia (31) and the WHO guidelines on quality control methods for medicinal plant materials (30) and pesticide residues (32).

Heavy metals
For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plant materials (30).

Radioactive residues
Where applicable, consult the WHO guidelines on quality control methods for medicinal plant materials (30) for the analysis of radioactive isotopes.

Other purity tests
Content of mineral matter, not more than 0.5% (1). Foreign matter, not more than 2% (29). Chemical and sulfated ash tests are to be established in accordance with national requirements.

Chemical assays
The high-performance liquid chromatography method for the determination of maysin (33).

Major chemical constituents
The major constituents of the dried styles and stigmas are flavonoids especially 6-C-glycosylflavones; the major one is maysin. Among the flavonoids, a glycoside of luteolin, with small amounts of the corresponding 6-C-glycosyl analogues of apigenin and chrysoeriol; maysin-3′-methyl ether; rutin; anthocyanidins and flavan-4-ols (luteoforol, apiforol) are present. The flavone C-glycosides (chrysoeriol 6-C-β-fucopyranoside and chrysoeriol 6-C-β-boivinopyranosyl-7-O-β-glucopyranoside) have
been isolated. There is also fixed oil (approximately 2%, including pantothenic and linoleic acids); essential oil (approximately 0.2%, containing carvacrol, α-terpineol, menthol and thymol); saponins (2–3%); tannin-like polyphenols (approximately 12%, probably chiefly proanthocyanidins); alkaloids (0.05%), steroids (stigmasterol and sitosterol); vitamin K₁, mucilage (relatively rich in potassium salts); minerals (notably approximately 2.7% of potassium); and carotenoids (2, 5, 16, 17, 34–47). The structures of the characteristic constituents are presented below.

**Medsical uses**

*Uses supported by clinical data*

The stigmas and styles of *Zea mays* are used for the supportive treatment of chronic nephritis (48).
Uses described in pharmacopoeias and well established documents
The stigmas and styles of *Zea mays* are used for the treatment of cholangitis, hepatitis and cholecystitis (43), and of acute and chronic cystitis and urethritis (36). Also used in the treatment of heart disease (as a diuretic), hypertension, rheumatism and diabetes mellitus (49).

Uses described in traditional medicine
The stigmas and styles of *Zea mays* have been used externally in Mayan, Incan and American traditional medicine to treat bruises, swellings, sores, boils, erysipelas, dermatitis and external inflammations (22, 50, 51). Their internal uses in the treatment of gout, gastritis, bile congestion, alcoholism, prostatitis, benign prostatic hyperplasia, nocturnal enuresis and whooping cough have been described (52, 53). They are also used as a sedative and laxative (54–58). Research in China and the former USSR countries indicates that the stigmas and styles of *Zea mays* lower blood pressure and reduce blood-clotting time (21, 59). The stigmas and styles of *Zea mays* are also used in the treatment of cystitis and urethritis (60).

Pharmacology

Experimental pharmacology

Diuretic effect
Oral administration of a methanol extract of the styles and stigmas of *Zea mays* at a dose of 0.6 g/animal had diuretic effects in rats (61). A 50% ethanol-aqueous extract of fresh styles given by intragastric administration to rats at a dose of 40 ml/kg had diuretic action (62). When an infusion of dried stigmas of *Zea mays* was administered to rats at a concentration of 2 g/l (dry weight of stigmas) in drinking-water, a diuretic effect and decreased urinary magnesium and phosphate concentrations were observed. These effects were seen in animals fed a standard diet, but not in those receiving a high-protein or carbohydrate diet (63).

The effects of an aqueous extract of the styles and stigmas of *Zea mays* on the urinary excretion of water, sodium ions (Na⁺), potassium ions (K⁺) and uric acid were studied in water-loaded rats (2.5 ml/100 g bw) by continuous urine collection. Excretion of K⁺ was observed in rats given an intragastric dose of 350 mg/kg (100.42–120.28 µEq/5 h/100 g bw), and of 500 mg/kg bw (94.97–134.32 µEq/5 h/100 g; p < 0.01). The higher dose resulted in diuresis as well (1.98–2.41 ml/5 h/100 g bw; p < 0.05). The effects of the 500 mg/kg bw dose of the extract on urine volume, Na⁺, K⁺, uric acid excretions, and glomerular function, were measured by creatinine and lithium ion (Li⁺) clearance, in water-loaded rats (5 ml/100 g bw). Creatinine (294.6–241.7 µl/
min/100 g bw; \( p < 0.05 \) and the Na\(^+\) filtered load (41.9–34.3, \( p < 0.05 \)) decreased, and creatinine and Li clearances and Na\(^+\) excretion were unchanged, while K\(^+\) excretion (0.10–0.22 µEq/min/100 g bw; \( p < 0.001 \)) increased. Thus, at a water-loading of 2.5 ml/100 g bw, the extract increased diuresis at a dose of 500 mg/kg, and increased excretion of K\(^+\) at doses of 350 and 500 mg/kg. At a water-loading of 5 ml/100 g bw, excretion of K\(^+\) increased at a dose of 500 mg/kg, but glomerular filtration decreased (64).

**Prevention of diabetic complications**

The aldehyde group of reducing sugar and amino residues in protein react and result in the formation of aggregates (advanced glycation end-products) such as N-ε-(carboxymethyl) lysine. Formation of these aggregates in the human body through glycation is associated with the induction of diabetic complications. Accumulation of N-ε-(carboxymethyl) lysine in the kidneys of subjects with diabetes has been reported. The inhibition of N-ε-(carboxymethyl) lysine accumulation by the flavone C-glucoside, chrysoeriol 6-C-β-fucopyranoside, isolated from the style of *Zea mays*, was calculated to be 80.7% (46). The same glycation inhibiting action was later shown for the corresponding 6-boivinoside. Similar derivatives of chrysoeriol, but with one more sugar attached, were inactive. Of the purines and pyrimidines present in *Zea mays*, only guanosine was found to be a glycation inhibitor (65).

The efficacy of a water extract of styles of *Zea mays* on diabetic nephropathy evoked by intravenous injection of streptozocin (40 mg/kg) was investigated in rats randomly allocated either to a control group (non-diabetic rats, \( n = 5 \)), a non-treated group of diabetic rats (\( n = 9 \)), or a group of treated diabetic rats (\( n = 8 \)). The treated groups were given tap water containing an extract of dry styles at a concentration of 0.15% (w/v) (about 0.2 g/day), while the animals in the control and non-treated groups were given ordinary tap water. The rats were allowed free access to their water for 12 weeks. At 12 weeks, urine was collected for 24 hours using a metabolic cage, followed by the collection of a blood sample and a kidney sample after killing the animals. Plasma glucose, haemoglobin, fructosamine, creatinine, urinary creatinine, urinary albumin excretion and other clinical parameters were also measured. Creatinine clearance was calculated per 100 g of body weight. The difference in body weight observed between the non-treated diabetic rats and the control rats was significant (\( p < 0.01 \)). The plasma glucose levels in the non-treated diabetic rats were significantly higher than in the control animals (\( p < 0.01 \)); however, there was no difference in the plasma glucose, fructosamine or haemoglobin levels between treated diabetic rats and non-treated diabetic rats. The ratios of kidney weight to body weight were significantly higher in non-treated diabetic rats.
than in the control rats ($p < 0.01$). Creatinine clearance in the treated diabetic rats was significantly lower than in the non-treated diabetic rats ($p < 0.05$). There was no significant difference in urinary albumin excretion between non-treated diabetic rats and treated diabetic rats. It was concluded that a water extract of the style of *Zea mays* prevented glomerular hyperfiltration and suppressed the progression of diabetic glomerular sclerosis in rats with streptozocin-induced diabetes (66).

**Haematological effects**

A methanol extract of dried styles expressed strong platelet aggregation-inhibiting activity with a median inhibitory concentration (IC$_{50}$) of 0.3 µg/ml by adenosine diphosphate (ADP), collagen, and arachidonic acid-induced platelet aggregation. The ethyl acetate extract of dried styles inhibited platelet aggregation induced by arachidonic acid (IC$_{50}$ = 0.2 mg/ml), collagen (IC$_{50}$ = 0.2 mg/ml), ADP (IC$_{50}$ = 0.5 mg/ml), and platelet aggregating factor (IC$_{50}$ = 0.7 mg/ml) (67, 68). In cell culture, a chloroform extract of the dried stigmas of *Zea mays* inhibited the tumour necrosis factor-alpha (TNF$\alpha$)-induced adhesion of endothelial cells to monocytic cells with a median effective dose (ED$_{50}$) of 70 µg/ml. Similar results were reported for bacterial lipopolysaccharide-induced cell adhesion with an ED$_{50}$ of 82 µg/ml. The results obtained were significant at the $p < 0.01$ level. A 100% ethanol extract of the stigmas of *Zea mays* has also been reported to possess intercellular cell adhesion molecule-1-inhibitory activity against bacterial lipopolysaccharide-induced intercellular cell adhesion molecule-1-expression with an ED$_{50}$ of 50 µg/ml. The same effect with an ED$_{50}$ of 38 µg/ml was detected in an EAHY926 cell culture against TNF$\alpha$-induced intercellular cell adhesion molecule-1-expression (69).

**Haemodynamic effects**

A hot aqueous extract of fresh stigmas produced a negative chronotropic and hypotensive effect in dogs anaesthetized with pentobarbital for up to 80 seconds by intravenous injection at a dose of 1.37–22 mg/kg (70). An aqueous-ethanol (1:1) extract of fresh styles (five parts of fresh plant material in 100 parts of water/ethanol) administered by gastric intubation to conscious rats at a dose of 40 ml/kg had a hypotensive effect (71).

**Antibacterial, anticrustacean and anti-complementary activity**

A 100% (non-diluted) ethanol extract of shade-dried stigmas of *Zea mays* (concentration 2.5 mg/disc) inhibited the growth of *Staphylococcus aureus* and *Candida albicans* in vitro, and exhibited an anticrustacean activity against *Artemia salina* (median lethal dose, 128 µg/ml) (72). A hot aque-
ous extract of dried stigmas of *Zea mays* (concentration 250 µg/ml) revealed an anti-complementary activity in a culture of cells from human serum (73).

**Antioxidant activity**

A methanol extract of the stigmas of *Zea mays* at various concentrations (0.2–4 mg/sample) inhibited lipid peroxide formation in liposomes, induced by the Fe²⁺/ascorbate system, and measured spectrophotometrically by a thiobarbituric acid assay (74).

**Antitumour activity**

Intraperitoneal administration of an aqueous extract of dried stigmas and styles at a dose of 150 mg/kg on days 5, 6 and 7 after the start of the experiment revealed antitumour activity in the Ehrlich-carcinoma ascites model in mice (75).

**Toxicology**

A number of haematological factors in rats were altered by intragastric administration of an aqueous extract of the stigmas of *Zea mays* at doses of 50 and 100 mg/kg, but the effects at these dose levels were not considered significantly toxic (76). A 100% (non-diluted) ethanol extract of shade-dried stigmas of *Zea mays* (at a concentration of 70 µg/ml) expressed mutagenic activity in vitro on *Salmonella typhimurium* T1530 (72). The toxicity of a methanol-insoluble fraction of an aqueous extract of dried stigmas of *Zea mays* in rabbits was reported to be low. The effective intravenous dose for a diuretic action was documented as 1.5 mg/kg bw, and the LD₅₀ as 250 mg/kg in rabbits (78). Stigmas of *Zea mays* contain an unidentified toxic principle described as being a cyanogenic compound (78). In the course of a study of the possible diuretic activity of a dried aqueous extract of the style and stigma of *Zea mays* (the main effect observed was an increased loss of sodium, potassium and chloride ions), the LD₅₀ of the extract for male rats was 14.5 g/kg bw (79).

**Clinical pharmacology**

The diuretic effect of styles and stigmas of *Zea mays* has been tested in an open non-randomized clinical trial. Thirty patients with various cardiovascular diseases with accompanying fluid retention received an infusion of dried styles and stigmas (30 g in 200 ml of water), at a dose of one tablespoonful six times daily for 4–5 days. An increase in diuresis was observed in 65% of the patients. Observations in patients with other conditions have shown that the same dosage regime led to an increase in diuresis of about 36% in patients with chronic nephritis and of 32% in
patients with exudative pleuritis. Thus, the diuretic effect seems to be greatest in patients with cardiovascular diseases (48).

**Adverse reactions**

Allergic reactions including contact dermatitis and urticaria have been documented for the styles and stigmas of *Zea mays* (36).

**Contraindications**

Styli cum stigmatis *Zeae maydis* is contraindicated in patients with loss of appetite and a low body mass or, in view of the ability of this drug to decrease clotting time, those with high coagulability of blood (76, 80). It is not recommended for irrigation therapy (hydro-colon therapy) in patients with oedema due to impaired heart or kidney function (70). If signs of hypersensitivity reactions appear (contact dermatitis and urticaria) the styles and/or stigmas of *Zea mays* must not be used again.

**Warnings**

No information was found.

**Precautions**

**General**

Prolonged use may result in hypokalaemia because of the diuretic action (36).

**Drug interactions**

No information was found.

**Drug and laboratory test interactions**

No information was found.

**Carcinogenesis, mutagenesis, impairment of fertility**

No information was found on carcinogenesis or impairment of fertility. A mutagenic effect has been reported for an ethanol extract (see Toxicology).

**Pregnancy: teratogenic effects**

No information was found.

**Pregnancy: non-teratogenic effects**

Styles and/or stigmas of *Zea mays* have been reported to stimulate uterine contractions in rabbits. Styles and/or stigmas should therefore not be taken during pregnancy without consultation with a physician (36).
Nursing mothers
No information was found.

Paediatric use
No information was found.

Dosage forms
Dried styles and/or stigmas used for infusion and other Galenical preparations for topical applications, as well as for internal use (60).

Posology
(Unless otherwise indicated)
For internal use. Daily dosage of dried styles and/or stigmas, 4–8 g or infusion (4–8 g in 200 ml of boiling water), one tablespoon three times daily (36). Tincture (1:5) in 25% ethanol, 5–15 ml three times daily (60). Liquid extract of stigmas (1:1) in 25% ethanol, 4–8 ml three times daily (60).
For external use: Cataplasm or bath, 4–5 tablespoons of stigmas in 400 ml (two glasses) of boiling water for 20 minutes applied to affected area or added to the bath water (44).

References
Annex

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Selected WHO publications of related interest

Information on medicinal plants:

WHO monographs on selected medicinal plants, Volume 4

WHO monographs on selected medicinal plants, Volume 3

WHO monographs on selected medicinal plants, Volume 2
(ISBN 92 4 154537 2), 2002

WHO monographs on selected medicinal plants, Volume 1
(ISBN 92 4 154517 8), 1999

Quality assurance and control of herbal medicines:

WHO Guidelines on good agricultural and collection practices (GACP) for medicinal plants
(ISBN 92 4 154627 1), 2003

WHO good agricultural and collection practices (GACP) monograph on Artemisia annua L.

Quality control methods for medicinal plant materials
(ISBN 92 4 154510 0), 1998

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms

WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues
(ISBN 978 92 4 159444 8), 2007

WHO guidelines for good manufacturing practices (GMP) for herbal medicines

Regulation, evaluation and safety monitoring of herbal medicines:

Summary report of the global survey on national policy on traditional medicine and complementary/alternative medicine and regulation of herbal medicines
(ISBN 92 4 159323 7), 2005

WHO guidelines on safety monitoring and pharmacovigilance of herbal medicines
(ISBN 92 4 159221 4), 2004

General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine

Consumer information:

WHO guidelines on development of consumer information on proper use of traditional medicine and complementary/alternative medicine
(ISBN 92 4 159170 6), 2004

Further information on WHO technical documents in the field of traditional medicine including those listed above, can be found at the address below:
http://apps.who.int/medicinedocs/en/cl/CL10/
Despite the increasing use of herbal medicines, there is still a significant lack of research data in this field, so that the WHO monographs are playing an increasingly important role.

In order to meet demands of the Newly Independent States (NIS) to regulate herbal medicines and to ensure safety, efficacy and quality of herbal medicines, WHO has provided technical guidance and worked with the national health authorities of interested NIS and Countries of Central and Eastern Europe (CCEE) to develop monographs on commonly-used medicinal plants in the NIS.

The NIS monographs include comprehensive scientific information on the safety, efficacy and quality of medicinal plants. The format of the NIS monographs is the same as of the WHO monographs on medicinal plants. Each monograph follows a standard format, with information presented in two parts, followed by a reference list. The first part presents pharmacopoeial summaries for quality assurance, while the second part includes sections on medicinal uses, pharmacology, safety issues and dosage forms.

The monographs may serve as an authoritative source of information for national drug regulatory authorities, since they have been fully involved in the development of the monographs. However, it should also be emphasized that the descriptions included in the section on medicinal uses should not be taken as implying WHO’s official endorsement or approval and also not intended to replace any national monographs or national pharmacopoeia of medicinal plants. They merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of information exchange.