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# 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, biranjasif, 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 carpentierir, erba da falegnam, erva d'o marchese, flor de la pluma, gandana, gordoloba, green arrow, herbe au charpentier, herbe de millefeuille, hezarbarg, Jungfrauakraut, 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, sataratyoutas, Schafgarbe, Schafgarbenkraut, seiyoukokogiriso, seiyoukokogirisou, sneezeweed, soldier's milfoil, stratictes, 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; involucre 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).

### ***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 unligified 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  $\mu\text{m}$  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  $\mu\text{m}$  in length; fragments of the ligulate corolla with papillary 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  $\mu\text{m}$  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  $\beta$ -pinene (23%),  $\alpha$ -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  $\beta$ -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.

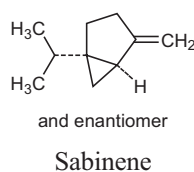
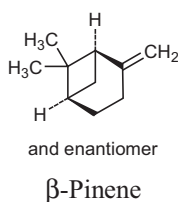
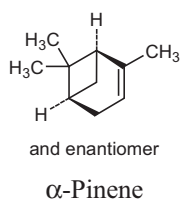
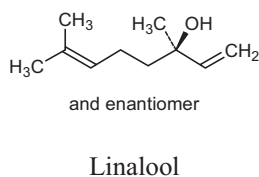
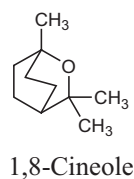
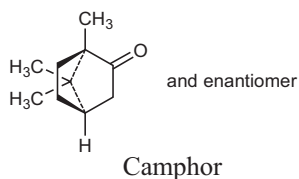
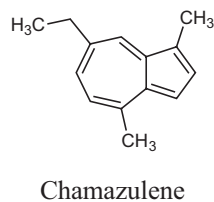
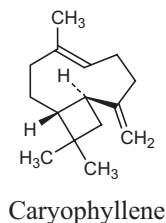
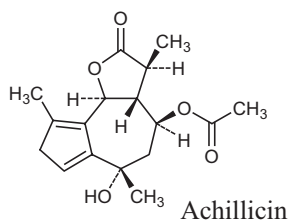
## **Medicinal uses**

### ***Uses supported by clinical data***

None.

### ***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 choleric 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 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 Fe<sup>2+</sup>/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).

### **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 observed 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, suppressed 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 breastfeeding mothers.

***Paediatric use***

Due to the lack of safety data the crude drug should not be used in children 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 daily 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).

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