Radix Valerianae

Definition

Radix Valerianae consists of the subterranean parts of *Valeriana officinalis* L. *(sensu lato)* (Valerianaceae)[1] including the rhizomes, roots, and stolons, carefully dried at a temperature below 40 °C (*1–6*).

Synonyms

Valeriana alternifolia Ledeb., *Valeriana excelsa* Poir., *Valeriana sylvestris* Grosch. (*1*).

Selected vernacular names

All heal, akar pulepandak, amantilla, balderbrackenwurzel, baldrian, Baldrianwurzel, cat's love, cat's valerian, fragrant valerian, garden heliotrope, great wild valerian, ka-no-ko-so, Katzenwurzel, kesso root, kissokon, kuanyexiccao, luj, nard, ntiv, racine de valeriane, St. George's herb, setwall, txham laaj, valerian fragrant, valerian, valeriana, valeriana extranjera, valeriana rhizome, valeriane, vandal root, waliryana, wild valerian (*8–11*).

Descriptions

A tall perennial herb whose underground portion consists of a vertical rhizome bearing numerous rootlets and one or more stolons. The aerial portion consists of a cylindrical hollow, channelled stem attaining 2 m in height, branched in the terminal region, bearing opposite exstipulate, pinnatisect, cauline leaves with clasping petioles. The inflorescence consists of racemes of cymes whose flowers are small, white, or pink. The fruits are oblong-ovate, 4-ridged, single-seeded achenes (*1*, *9*).

Valeriana officinalis (*sensu lato*) is an extremely polymorphous complex of subspecies. The basic type is diploid, $2n = 14$, (*V. officinalis*) and other subspecies have very similar characteristics: *V. officinalis* ssp. *collina* (Wallr.) Nyman

[1] Approximately 200 *Valeriana* species are available, but only a few are or were used medicinally, such as *V. fauriei* Briquet (Japanese Valerian) (*7*), *V. wallichii* DC (Indian Valerian) and *V. edulis* Nutt ex. Torr. & Gray (*8*). In commerce, *V. edulis* Nutt. ex Torr. & Gray is known as "Valeriana mexicana". Plants bearing this common name should not be confused with *V. mexicana* DC., which is in fact *V. sorbifolia* H.B.K. var. *mexicana* (DC) F.G. Mey.

($2n = 28$) has leaves with 15–27 folioles, all of the same width, and *V. officinalis* ssp. *sambucifolia* (Mikan f.) Celak, *V. excelsa* Poiret ($2n = 56$) has leaves with 5–9 folioles, with the apical one clearly larger than the others. In contrast to the other subspecies, the rhizome of the latter is clearly stoloniferous (epigenous and hypnogenous stolons). *V. repens* Host. (equivalent to *V. procurrens* Wallr.) could be considered a fourth species, according to the Flora Europaea. Often appended to this species are taxonomic groups of uncertain status and limited distribution (e.g. *V. salina* Pleigel or *V. versifolia* Brügger) (*12*).

Plant material of interest: dried roots, rhizomes and stolons

General appearance

Rhizome, erect, entire or usually cut into 2–4 longitudinal pieces, 2–5 cm long, 1–3 cm thick; externally, dull yellowish brown or dark brown, sometimes crowned by the remains of stem bases and scale leaves, and bears occasional, short, horizontal branches (stolons), and numerous rootlets or their circular scars; fracture, short and horny. Internally, whitish, with an irregular outline, occasionally hollow and exhibiting a comparatively narrow ark traversed, here and there, by root-traces, and separated by a dark line, the cambium, from a ring, small xylem bundles surrounding a central pith. Roots, numerous, slender, cylindrical, usually plump; 2–12 cm but mostly 8–10 cm long, 0.5–2 mm in diameter; externally, greyish brown to brownish yellow, longitudinally striated, with fibrous lateral rootlets; brittle; internally, showing a wide bark and a narrow central stele (*1*, *9*).

Organoleptic properties

Odour, characteristic, penetrating valeric acid-like, becoming stronger on aging; taste, sweetish initially, becoming camphoraceous and somewhat bitter (*1–5*, *9*).

Microscopic characteristics

Rhizome, with epidermis of polygonal cells, having the outer walls slightly thickened; cork, immediately below the epidermis, of up to 7 layers of slightly suberized, brownish, large polygonal cells; cortex, parenchymatous with rather thick-walled parenchyma, containing numerous starch granules and traversed by numerous root-traces; endodermis of a single layer of tangentially elongated cells containing globules of volatile oil; pericycle, parenchymatous; vascular bundles, collateral, in a ring and surrounding a very large parenchymatous pith, containing starch granules and occasional scattered groups of sclereids with thick pitted walls and narrow lumen; xylem, with slender, annular, spiral, and pitted vessels, in small numbers. Branches similar to rhizome but with a prominent endodermis and a well-defined ring of vascular bundles, showing secondary thickening.

Root, with piliferous layer, of papillosed cells, some developed into root hairs; exodermis, or a single layer of quadrangular to polygonal cells, with suberized walls, and containing globules of volatile oil; cortex, parenchymatous, with numerous starch granules, the outermost cells containing globules of volatile oil; endodermis, of 1 layer of cells with thickened radial walls; primary xylem, of 3–11 arches surrounding a small central parenchymatous pith containing starch granules, 5–15 μm in diameter, sometimes showing a cleft or stellate hilum; the compound granules, with 2–6 components, up to 20 μm in diameter. Older roots show a pith of starch-bearing parenchyma, vascular bundles with secondary thickening and a periderm originating in the piliferous layer (*1*, *4*, *9*, *13*).

Powdered plant material

Light brown and characterized by numerous fragments of parenchyma with round or elongated cells and containing starch granules, 5–15 μm in diameter, sometimes showing a cleft or stellate hilum, the compound granules, with 2–6 components, up to 20 μm in diameter; cells containing light brown resin; rectangular sclereids with pitted walls, 5–15 μm thick; xylem, isolated or in noncompact bundles, 10–50 μm in diameter; some absorbing root hairs and cork fragments are also present (*4*).

Geographical distribution

Valeriana officinalis (*sensu lato*) is an extremely polymorphous complex of subspecies with natural populations dispersed throughout temperate and sub-polar Eurasian zones. The species is common in damp woods, ditches, and along streams in Europe, and is cultivated as a medicinal plant, especially in Belgium, England, eastern Europe, France, Germany, the Netherlands, the Russian Federation, and the United States of America (*1*, *9*, *10*, *12*).

General identity tests

Macroscopic, microscopic, organoleptic, and microchemical examination (*1–6*, *9*, *13*); and by thin-layer chromatography for the presence of valerenic acid, acetoxyvalerenic acid, valtrate, and isovaltrate (*1–5*).

Purity tests

Microbiology

The test for *Salmonella* spp. in Radix Valerianae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*14–16*). 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 10^5/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.

Foreign organic matter

Not more than 5% (*1*).

Acid-insoluble ash

Not more than 7% (*1–5*).

Dilute ethanol-soluble extractive

Not less than 15% (*2–5*).

Pesticide residues

To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin for Radix Valerianae is not more than 0.05 mg/kg (*16*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*14*) 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 (*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 purity tests

Chemical, moisture, total ash and water-soluble extractive tests are to be established in accordance with national standards.

Chemical assays

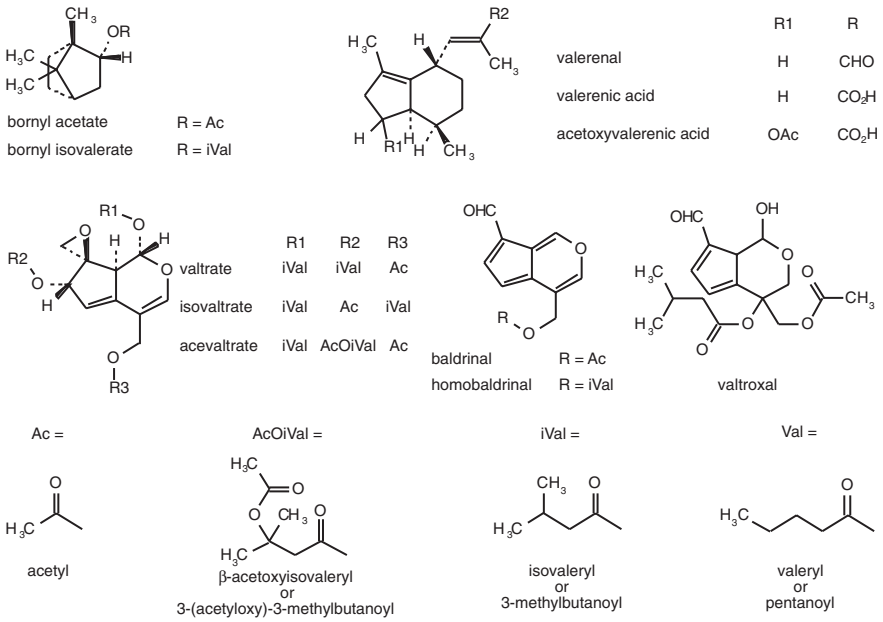
Contains not less than 0.5% v/w of essential oil (*3–5*), quantitatively determined by distillation (*2–5*). Content of individual constituents including valepotriates, valerenic acids and valerenal, determined by high-performance liquid (*18, 19*) or gas–liquid (*20*) chromatographic methods.

Major chemical constituents

The chemical composition of Radix Valerianae varies greatly depending on the subspecies, variety, age of the plant, growing conditions, and type and age of the extract. The volatile oil (ranges 0.2–2.8%) contains bornyl acetate and

bornyl isovalerate as the principal components. Other significant constituents include β-caryophyllene, valeranone, valerenal, valerenic acid, and other sesquiterpenoids and monoterpenes (*12*, *21*). The co-occurrence of three cyclopentane-sesquiterpenoids (valerenic acid, acetoxyvalerenic acid, and valerenal) is confined to *V. officinalis* and permits its distinction from *V. edulis* and *V. wallichii* (*12*). The various subspecies of *V. officinalis* have different compositions of volatile oil and, for example, average bornyl acetate content varies from 35% in *V. officinalis* ssp. *pratensis* to 0.45% in *V. officinalis* ssp. *illyrica* (*12*).

A second important group of constituents (0.05–0.67% range) is a series of non-glycosidic bicyclic iridoid monoterpene epoxy-esters known as the valepotriates. The major valepotriates are valtrate and isovaltrate (which usually represent more than 90% of the valepotriate content). Smaller amounts of dihydrovaltrate, isovaleroxy-hydroxydihydrovaltrate, 1-acevaltrate or others are present (*8*, *12*). The valepotriates are rather unstable owing to their epoxide structure, and losses occur fairly rapidly on storage or processing, especially if the drug is not carefully dried. Principal degradation products are baldrinal, homobaldrinal, and valtroxal (*8*).



Dosage forms

Internal use as the expressed juice, tincture, extracts, and other galenical preparations (*8*, *22*). External use as a bath additive (*22*). Store in tightly closed containers, in a cool dry place, protected from light (*1–6*).

Medicinal uses

Uses supported by clinical data

As a mild sedative and sleep-promoting agent (*8*, *12*, *22–25*). The drug is often used as a milder alternative or a possible substitute for stronger synthetic sedatives, such as the benzodiazepines, in the treatment of states of nervous excitation and anxiety-induced sleep disturbances (*22–25*).

Uses described in pharmacopoeias and in traditional systems of medicine

As a digestive aid, and an adjuvant in spasmolytic states of smooth muscle and gastrointestinal pains of nervous origin (*8*, *12*). When associated with papaverine, belladonna, and other spasmolytics, Radix Valerianae has been shown to be useful as an adjuvant in spastic states of smooth muscle such as spastic colitis (*8*).

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

To treat epilepsy, gum sores, headaches, nausea, sluggish liver, urinary tract disorders, vaginal yeast infections, and throat inflammations; and as an emmenagogue, antiperspirant, antidote to poisons, diuretic, anodyne, and a decoction for colds (*5*, *8*).

Pharmacology

Experimental pharmacology

The sedative activity of *V. officinalis* has been demonstrated both *in vitro* and *in vivo*. *In vitro* studies have demonstrated the binding of valerian extracts to GABA (γ-aminobutyric acid) receptors, adenosine receptors and the barbiturate and benzodiazepine receptors (*8*, *26*). Both hydroalcoholic and aqueous total extracts show affinity for the GABA-A receptors, but there is no clear correlation between any of the known chemical components isolated from Radix Valerianae and GABA-A binding activity (*8*). Aqueous extracts of the roots of *V. officinalis* inhibit re-uptake and stimulate the release of radiolabelled GABA in the synaptosomes isolated from rat brain cortex (*27*, *28*). This activity may increase the extracellular concentration of GABA in the synaptic cleft, and thereby enhance the biochemical and behavioural effects of GABA (*8*, *27*). Interestingly, GABA has been found in extracts of *V. officinalis* and appears to be responsible for this activity (*29*). The valtrates, and in particular dihydrovaltrate, also show some affinity for both the barbiturate receptors and the peripheral benzodiazepine receptors (*8*).

In vivo studies suggest that the sedative properties of the drug may be due to high concentrations of glutamine in the extracts (*29*). Glutamine is able to cross the blood–brain barrier, where it is taken up by nerve terminals and subse-

quently metabolized to GABA (*29*). The addition of exogenous glutamine stimulates GABA synthesis in synaptosomes and rat brain slices (*29*).

The spasmolytic activity of the valepotriates is principally due to valtrate or dihydrovaltrate (*30*). These agents act on centres of the central nervous system and through direct relaxation of smooth muscle (*31*), apparently by modulating Ca^{2+} entry into the cells or by binding to smooth muscle (*8*, *32*).

Clinical pharmacology

A number of clinical investigations have demonstrated the effectiveness of Radix Valerianae as a sleep aid and minor sedative (*8*, *22–25*). In a double-blind study, valerian (450 mg or 900 mg of an aqueous root extract) significantly decreased sleep latency as compared with a placebo (*23*). The higher dose of valerian did not further decrease sleep latency (*23*). Additional clinical studies have demonstrated that an aqueous extract of valerian root significantly increased sleep quality, in poor and irregular sleepers, but it had no effect on night awakenings or dream recall (*24*). The use of Radix Valerianae appears to increase slow-wave sleep in patients with low baseline values, without altering rapid eye movement (REM) sleep (*24*).

While extracts of the drug have been clearly shown to depress central nervous system activity, the identity of the active constituents still remains controversial. Neither the valepotriates, nor the sesquiterpenes valerenic acid and valeranone, nor the volatile oil alone can account for the overall sedative activity of the plant (*8*, *33*). It has been suggested that the baldrinals, degradation products of the valepotriates, may be responsible (*26*). Currently, it is still not known whether the activity of Radix Valerianae extracts resides in one compound, a group of compounds, or some unknown compound, or is due to a synergistic effect.

Contraindications

Radix Valerianae should not be used during pregnancy or lactation (*31*, *34*).

Warnings

No information available.

Precautions

General

May cause drowsiness. Those affected should not drive or operate machinery. Although no interaction between valerian and alcohol has been demonstrated clinically, as a precautionary measure patients should avoid consuming alcoholic beverages or other sedatives in conjunction with Radix Valerianae (*31*).

Carcinogenesis, mutagenesis, impairment of fertility

Some concern has been expressed over the cytotoxicity of the valepotriates. Cytotoxicity has been demonstrated *in vitro* but not *in vivo*, even in doses of 1350 mg/kg (*35*). Some of the valepotriates demonstrate alkylating activity *in vitro*. However, because the compounds decompose rapidly in the stored drug, there is no cause for concern (*35*). The valepotriates are also poorly absorbed and are rapidly metabolized to the baldrinals (*26*), which have better sedating effects. *In vitro*, the baldrinals are less toxic than the valepotriates, but *in vivo* they are more cytotoxic because they are more readily absorbed by the intestine. Baldrinals have been detected at levels up to 0.988 mg/dose in commercial preparations standardized with respect to the concentration of valepotriates and may be of cytotoxic concern (*36*).

Pregnancy: teratogenic effects

Prolonged oral administration of valepotriates did not produce any teratogenic effects (*8*, *37*).

Pregnancy: non-teratogenic effects

The safety of Radix Valerianae during pregnancy has not been established; therefore it should not be administered during pregnancy.

Nursing mothers

Excretion of Radix Valerianae into breast milk and its effects on the newborn infant have not been established; therefore it should not be administered during lactation.

Paediatric use

Radix Valerianae preparations should not be used for children less than 12 years of age without medical supervision (*34*).

Other precautions

No information on general precautions or drug interactions or drug and laboratory test interactions was found.

Adverse reactions

Minor side-effects have been associated with chronic use of Radix Valerianae and include headaches, excitability, uneasiness, and insomnia. Very large doses may cause bradycardia and arrhythmias, and decrease intestinal motility (*38*). The recommended first aid is gastric lavage, charcoal powder, and sodium sulfate (*38*). Doses up to 20 times the recommended therapeutic dose have been reported to cause only mild symptoms which resolved within 24 h (*38*). Four cases of liver damage have been associated with use of preparations containing

Radix Valerianae (*39*). However, in all cases the patients were taking a combination herbal product containing four different plant species and thus a causal relationship to the intake of valerian is extremely doubtful.

Posology

Dried root and rhizome, 2–3 g drug per cup by oral infusion, 1–5 times per day, up to a total of 10 g and preparations correspondingly (*6*, *22*). Tincture (1:5, 70% ethanol), 0.5–1 teaspoon (1–3 ml), once to several times a day. External use, 100 g drug for a full bath (*22*).

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