American Herbal Pharmacopoeia™
and Therapeutic Compendium

Valerian Root
Valeriana officinalis

Analytical, Quality Control,
and Therapeutic Monograph

A | H | P

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Statement of Nonendorsement
The reporting on the use of proprietary products reflects studies conducted with these preparations and is not meant to be an endorsement of these products.

NOMENCLATURE

Botanical Nomenclature

Valeriana officinalis L., *s.l.*

Botanical Family

Valerianaceae

Definition

Valerian consists of the fragments or whole fresh or dried rhizomes, roots, and stolons of *Valeriana officinalis* L., *s.l.* The whole botanical contains not less than 0.5% (*V*/w) essential oil as determined on a dry weight basis. Powdered material contains not less than 0.3% (*V*/w) essential oil as determined on a dry weight basis.

Common Names

United States:	Valerian
France:	Valeriane
Germany:	Baldrian
Italy:	Amantilla
United Kingdom:	Valerian

HISTORY

The name valerian is said to be derived either from Valerius, who was reported to have first utilized its medicinal properties, or from the Latin term *valere*, meaning health or well-being (Grieve 1976). It has been used medicinally for at least 2000 years. Dioscorides (ca. AD 40-80) wrote of several species of valerian (*phu*), and Galen (ca. AD 131-208) reported on its sedative effects (Pickering 1879). The name valerian was first used around the 9th and 10th centuries and was an entry in the domestic books of home remedies as early as the 11th century. The names valerian, amantilla, and fu were all used synonymously in the Alphita, a medieval vocabulary of the schools of Salernum (Flückiger and Hanbury 1879). It was first used as a treatment for epilepsy in the late 16th century reportedly by Fabius Columna, who related a personal cure, but subsequently was also reported to have relapsed. Fifty years later, additional reports of its effectiveness in three cases of epilepsy were reported by Dominicus Panarolus. Numerous reports by a wide variety of writers followed, and valerian subsequently became routinely used for the treatment of various nervous disorders (Benigni and others 1971; Hobbs 1989). Respected American medical botanist William Woodville reported that various European authorities ascribed antispasmodic, anthelmintic, diuretic, diaphoretic, and emmenagogue actions to valerian and related its usefulness for hysteria. However, Woodville himself did not consider it to be as effectual as proclaimed by other writers, an opinion reportedly supported by the *Edinburgh Dispensary* (Woodville 1810).

Photograph © 1999 Martin Wall Photography, Pleasant Garden, NC. Location Gaia Herbs, Brevard, NC

Valerian was widely used by Eclectic physicians. John King, in his highly acclaimed *American Dispensatory*, cited valerian as being an aromatic stimulant and reported some unique indications, including its use for rheumatism, low grade fevers, and as an aphrodisiac, as well as its use in hysteria (King 1866). John Finley Ellingwood in *Systematic Treatise on Materia Medica and Therapeutics* considered valerian to be a nervine and sedative for the treatment of hysteria, epilepsy, and menopausal nervous anxiety (Ellingwood and Lloyd 1900). John Milton Scudder in *Specific Medications* (Scudder 1903) cites valerian as having activity as a cerebral stimulant, analgesic, and sedative useful in nervous irritability, specifically when the condition is a result of "enfeebled cerebral circulation".

Valerian was included in many editions of the *United States Dispensatory* which reported on its effect on the nervous system and its ability to produce drowsiness and sleep (Wood and Bache 1849). It was also listed in official compendia throughout the world, including the *British Pharmacopœia* in 1867 (British Pharmacopœia 1867),

the *United States Pharmacopeia* from 1820-1936 (Hobbs 1989), and the *United States National Formulary* until 1946.

Various species of valerian continue to be included in the pharmacopoeiae of many nations such as Belgium, France, Germany, Italy, Switzerland, and the United Kingdom, and a valerian monograph has been accepted by the United States Pharmacopeial Convention for inclusion in the *National Formulary* (Pharmacopeial Forum 1998). Its widespread use as a sedative and antispasmodic in the United States continues. Valerian preparations appear to be the most likely candidates to use as safe and effective, nonaddictive alternatives to conventional sleep medications.

IDENTIFICATION

Botanical Identification (Figures 1–2)

Valeriana officinalis L. Herbacious perennial, rhizomatous. **Stem:** Solitary, hollow, 15-150 cm. **Leaf:** Basal and cauline, opposite, oddly once pinnately lobed, lobes 11-21 lanceolate, entire or dentate, basal leaves petiolate, cauline leaves subsessile to clasping. **Inflorescence:** Compound cyme, terminal or axillary, many pale pink to white, strongly scented flowers. **Flower:** Calyx 5-lobed, lobes inconspicuous in flower, becoming elongate and pappus-like in fruit, corolla funnel-form, slightly saccate at the base, 5-lobed, tube 4 mm, lobes 1 mm, stamens 3, filaments attached to corolla tube alternate to corolla lobes, ovary inferior, tri-loculate, uni-ovulate, only 1 locule fertile, stigma tripartite. **Fruit:** Achene crowned by persistent calyx, lanceolate-oblong, 4.5-5 mm, hairy or glabrous.

Populations of *V. officinalis* range in ploidy level from diploid to tetraploid or octaploid. British *V. officinalis* is usually octaploid, and central European supplies are tetraploid. There are three subspecies of *V. officinalis:* ssp. *officinalis,* ssp. *collina* (Wallr.) Nyman, and ssp. *sambucifolia* (Mikan fil.) Celak. All three of these subspecies, as well as the other European species of valerian, *V. repens* Host, have been considered acceptable source material for medicinal preparations (Frohne and Jensen 1992; Steinegger and Hänsel 1992; Titz and others 1982, 1983).

Distribution: Damp or dry meadows, scrub, woods. Most of Europe, rare in the south, cultivated and naturalized in North America (Bailey and Bailey 1976; Cronquist 1981; Gleason and Cronquist 1963; Hickman 1993).

Macroscopic Identification (Figures 3–8)

Various chemotypes will have slightly different characteristics. When dried, the whole rhizome is up to 50 mm long and up to 30 mm in diameter, obconical to cylindrical, with an elongated or compressed base. It has a yellowish-brown to dark brown exterior with a circular stem and leaf scars. The rhizome contains numerous thick, light to dark brown rootlets which are located around a thin ligneous cord. The root is longitudinally wrinkled and approximately 100 mm long and 1-3 mm in diameter, almost cylindrical and almost the same color as the rhizome. In longitudinal section, the pith exhibits a central cavity transversed by septa. The stolons are 20-50 mm long, pale yellowish-grey with prominent nodes separated by longitudinally striated internodes. It is commonly sliced in half for ease of cleaning. The rootlets, which contain the majority of the essential oil, are brittle and break in short, horny fractures and are whitish or yellowish internally (European Pharmacopoeia 1998). **Aroma:** When dried properly, *V. officinalis* L., *s.l.* has only a very faint characteristic, valeric acid-like aroma which becomes stronger as it ages. Improperly dried or old material possesses a strong and characteristic odor due to the enzymatic hydrolysis of esters of the valepotriates (isovaleric acid and hydroxyvaleric acid). **Taste:** Mildly sweet and camphoraceous with a slightly bitter and spicy aftertaste (Reynolds 1993; Steinegger and Hänsel 1992).

Powder: Should be light brown or tan in color. However, due to improper drying, it is often dark brown.

Figure 1a *Valeriana officinalis*
Photograph © 1999 Roy Upton

Figure 1b *Valeriana officinalis*
Photograph courtesy of Bioforce of Switzerland

Figure 2 Field of organically cultivated *Valeriana officinalis*
Photograph © 1999 Martin Wall Photography, Pleasant Garden, NC. Location Gaia Herbs, Brevard, NC

Figure 3   Fresh organically cultivated *Valeriana officinalis* var *anthos*

Sample courtesy of Pacific Botanicals, Grants Pass, Oregon

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™

Figure 4   Dry organically cultivated *Valeriana officinalis* var *anthos*

Sample courtesy of Pacific Botanicals, Grants Pass, Oregon

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™

Figure 5   Fresh organically cultivated *Valeriana officinalis*

Sample courtesy of Pacific Botanicals, Grants Pass, Oregon

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™

Figure 6   Dry organically cultivated *Valeriana officinalis*

Sample courtesy of Pacific Botanicals, Grants Pass, Oregon

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™

Figure 7a   Properly dried (note light tan color) and cut organically cultivated *Valeriana officinalis*

Sample courtesy of Pacific Botanicals, Grants Pass, Oregon

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™

Figure 7b   Improperly dried (note dark brown color) and cut *Valeriana officinalis*

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™


Figure 8   Dry Indian valerian *Valeriana wallichi*

Sample courtesy of Nature Care Ayurvedic Products, Guilderland, NY

Photograph Joanne Thompson © 1999 American Herbal Pharmacopoeia™

Microscopic Identification (Figures 9–10)

Examine under a microscope using chloral hydrate solution. Starch grains are numerous, up to 20 μm in diameter, mainly 2-4 compound with cleft or radiate hilum, packed into parenchymatous cells of cortex and pith which are large elongated cells with slightly thickened walls. Sclereids from the rhizome are small with thick walls, narrow branched lumen, and numerous pits. Those from the base of the stem are larger with only slightly thickened walls. Piliferous layer shows cicatrices or occasionally attached unicellular root hairs and associated hypodermis of elongated cells. Vessels with reticulate thickening or bordered pits; fibers occasional, lignified with simple pits. Lignified cells of tegumentary tissue from rhizome with brown granular contents; fragments of endodermis show sinuous walls. Calcium oxalate absent.

Note: It is difficult to differentiate between pulverized *V. officinalis, V. wallichi,* and *V. edulis* (Woerdenbag and others 1997).
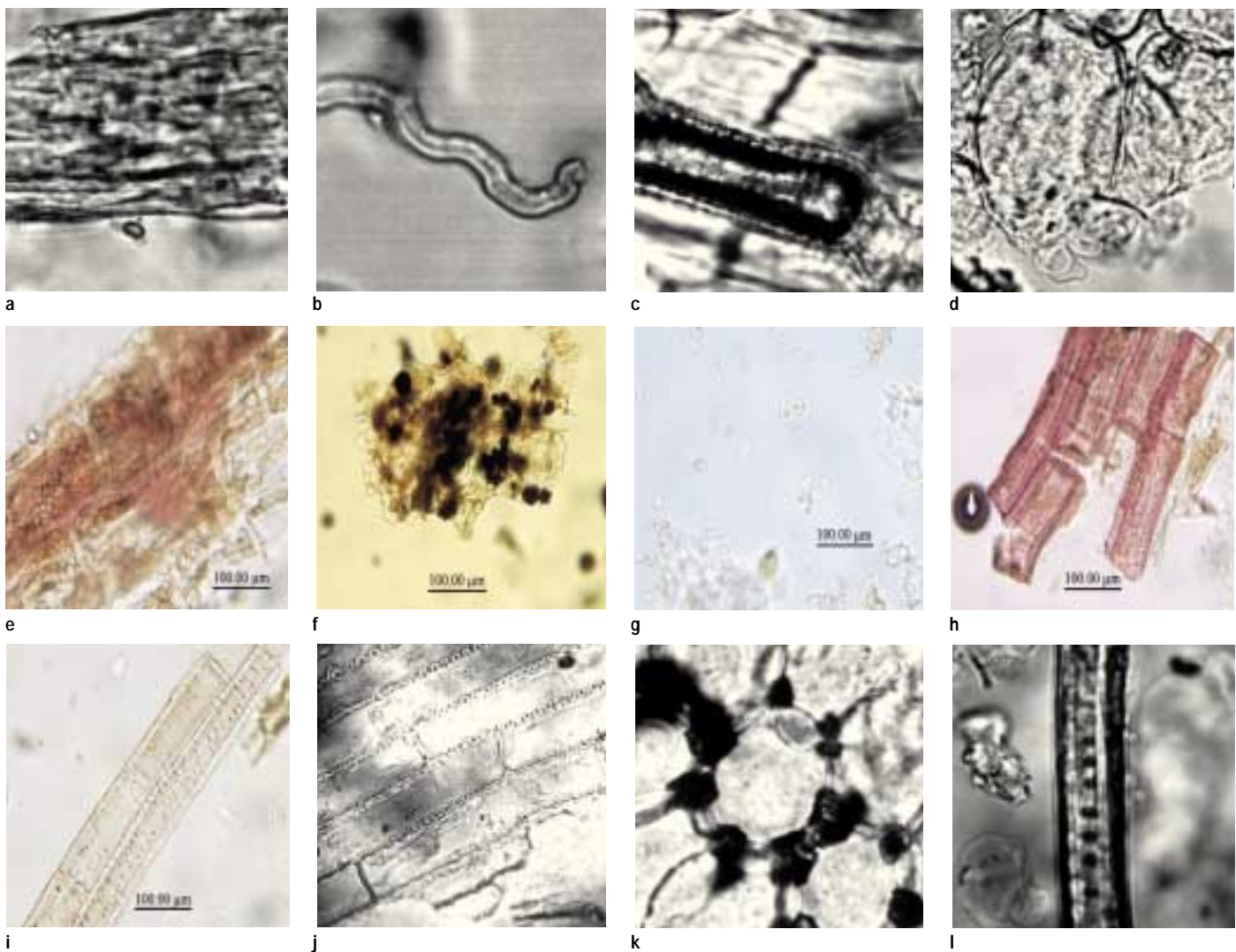
Figure 9 **Microscopic images of *Valeriana officinalis***

a. Piliferous layer of the root showing some root hair scars (magnification 400X). **b.** Root hair (magnification 400X). **c.** Sclereids from the stem base (magnification 800X). **d.** Parenchymatous cells of cortex or pith (transectional view; magnification 400X). **e.** Cortical parenchyma (longitudinal view; objective 40X; magnification 400X). **f.** Parenchyma with starch granules (objective 40X; magnification 400X). **g.** Starch grains (objective 40X; magnification 400X). **h.** Epidermal cells (objective 40X; magnification 400X). **i.** Epidermal tissue (objective 40X; magnification 400X). **j.** Endodermis of root with sinuous tangential walls (magnification 400X). **k.** Tegumentary tissue from rhizome showing brown contents (magnification 400X). **l.** Narrow, thick-walled fiber (magnification 400X).

Microscopic images courtesy of Botanicals International, Long Beach, CA and Alkemists Pharmaceuticals, Costa Mesa, CA
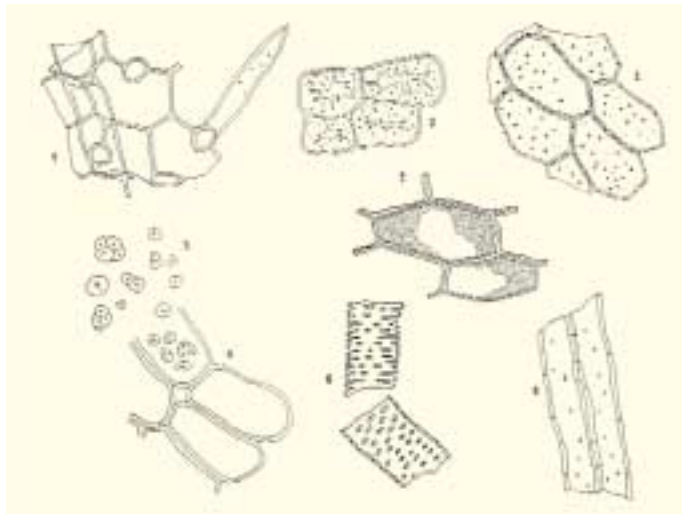
Figure 10 Microscopic characteristics of *Valeriana officinalis*

1. Piliferous layer showing cicatrices and attached root hair.
2. Sclereids from rhizome.
3. Sclereids from base of stem.
4. Parenchyma.
5. Starch grains.
6. Fragment of vessels.
7. Tegumentary tissue showing brown contents.
8. Fibers from stem base.

COMMERCIAL SOURCES & HANDLING

Valerian is cultivated in Britain, Belgium, Eastern Europe, France, Germany, Holland, Japan, the Netherlands, North America, and Russia (Evans 1996; Steinegger and Hänsel 1992). The majority of standardized extract products and crude cut and sifted material on the domestic market are prepared from European supplies. A large number of liquid extracts are prepared from domestically cultivated material. Many species other than *V. officinalis* are reported to be traded as medicinal valerian. These include *V. edulis* Nutt. ex Torr. & A. Gray, *V. coreana* Briq.k, *V. stubendorfi* Kreyer ex Kom., *V. amurensis* P. Smirn. ex Kom., *V. hardwickii* Wall., *V. exaltata* Mikan, and *V. wallichi* DC. syn. *V. jatamansi* Jones* (Leung and Foster 1996; Steinegger and Hänsel 1992). The most frequently used North American species include *V. sitchensis* Bong and *V. edulis* Nutt.* = *V. edulis* Nutt. ex Torr. & Gray ssp. *procera* (Kunth). Other species reported to be used locally include *V. arizonica* Gray, *V. capitata* Pall ex Link., *V. diocia* L., and *V. scouleri* Rydb. Detailed chemical analyses of most American species are lacking. A limited number of assays of material cultivated in the Pacific Northwest show varying levels of essential oil ranging from 0.4% to 1.3%. Valerenic acid and valepotriates have been found to be present in fresh and dry samples of *V. sitchensis* Bong (Anonymous 1996; Förster and others 1984). *V. sitchensis* Bong exhibits a strong pungency when fresh.

High quality material is reported to contain from 1.0% to 1.5% essential oil, ≥ 30% extractable matter, and ≥ 0.5% valerenic acid (Bos 1997).

* V. wallichi DC. and V. edulis Nutt. reportedly are lacking in valerenic acid and its derivatives (Bos 1997).

Collection

The majority of valerian in trade comes from cultivated material. Harvest times will vary geographically. The composition of the essential oil varies greatly among different populations of the same subspecies (Corsi and others 1984) and even between the same population of plants from year to year (Hazelhoff and others 1979). Essential oil content also varies with genotypes, harvest times, growing conditions, age of root, drying techniques, and method of analysis. It has been reported that valerian harvested in higher elevations, grown in dryer regions, or those cultivated in phosphate-rich soil yields relatively high levels of essential oil (Bos and others 1998a).

Older literature reports that valerian should be harvested in the fall, between August and September, preferably in the second year of growth (Violon and others 1983; Youngken 1930). Analyses of material cultivated in the Netherlands report that the majority of constituents, including the essential oil and valerenic acid, was highest in roots harvested in the first year of growth with essential oil being highest in September and November (1.2% to 2.1%). The next highest level of essential oil was reported for material harvested in March (0.9% to 1.6%). Valerenic acid and its derivatives were found to be highest in February and March (0.7% to 0.9%) followed by material harvested in September (0.5% to 0.7%) and then in January (0.3% to 0.4%).

From a commercial standpoint, it is more cost effective to harvest the roots in the same year the plants are sown than in the second year (Bos and others 1998a).

Cultivation

Sowing seeds has been reported to be preferred over planting of seedlings. Best results were achieved by flat field planting at row spacings of 50 cm and a seed rate of 3 kg/ha (Mheen 1996). Cutting off the flowering tops before the plant has set seed causes the rhizome to develop more fully. Wagner reports that harvest should take place in the morning during relatively cool weather (Wagner and others 1972), a general recommendation for roots rich in essential oils.

Drying

For maximum preservation of the essential oils, valerian should be dried at 40 °C with a flow rate of 0.05 kg/sec/m² (Elbanowska and others 1975). Alternatively, drying at room temperature (20 °C) for approximately 10 days, shade drying at approximately 45 °C, low temperature vacuum-drying, and freeze-drying are also reported to be appropriate drying techniques (Benigni and others 1971; Bos 1997). When dried at 50 °C as compared with drying at 20 °C, there is a 50% decrease in essential oil content. No differences in content of valerenic acid and its derivatives are observed between these two methods (Bos 1997).

Careless or prolonged drying produces a darker color in the roots and results in the hydrolysis of the isovalerianic esters and the liberation of isovaleric and hydroxy-isovaleric acid. This produces the characteristic valerianic aroma (Samuelsson 1992). Properly dried valerian will produce this same aroma over time.

Handling

The essential oil is located in the hypodermis of the rhizome in large thin-walled cells. Because of this, care must be taken not to damage these cells during handling. Excess washing of the roots can result in a significant reduction of extractive matter (Bos 1997). Because of the sensitivity of volatile oils to heat, it is necessary to minimize the amount of time generated in the grinding or powdering process by doing small lots at a time, with frequent interruptions in run times, or by utilizing a cryogenic grinder.

Storage

Store in closed containers protected from light, air, and moisture. Hydroxyvalerenic acid, a decomposition product of acetoxyvalerenic acid, is formed when the herb is stored at too high humidity (Woerdenbag and others 1997).

Improper storage conditions can cause significant deterioration of the material. Although the essential oil is relatively stable, it can evaporate with excessive exposure to air. The essential oil can degrade quickly in powdered material. In powdered root, the essential oil content can decrease by 50% within 6 months.

Valepotriates are sensitive to humidity, temperatures above 40 °C, and acid mediums (pH < 3) and are generally not detected in commercial products after 60 days (Houghton 1988; Lutowski and Turowska 1973).

Adulterants

Other species of valerian. Wichtl and Bisset cite that an unidentified *Apiaceae* species may be found in valerian trade (Wichtl and Bisset 1994). Adulteration of valerian in the American market is not common.

Preparations

A variety of valerian root preparations are in commerce with various manufacturers preparing their products according to their own specifications utilizing fresh and/or dried material. The following guidelines are provided in the literature.

Valerian Infusion

Hot Infusion: 2-3 g of valerian steeped in 225 mL of boiled water for 10-15 minutes in covered vessel (Bradley 1992).

Cold Infusion: 2-3 g of valerian soaked in 225 mL of cold water for 6-8 hours (Osol and others 1947).

In a limited number of analyses, teas prepared from *V. officinalis* were found to contain valerenic acid and its derivatives and very low levels or no valepotriates (Bos 1997).

Valerian Tincture

Valerian tinctures are official in the Dutch, German, and Swiss pharmacopoeiae, prepared either by maceration or percolation at a concentration of 1 part herb to 5 parts water-alcohol menstruum (70% ethanol *V/V*). **Characteristics:** Dark brown liquid with a strong characteristic valerian smell and taste.

The German pharmacopoeia requires the finished tincture to yield a minimum of 3% (w/w) dry residue as determined on 3.00 g tincture as described in the monograph for tinctures. The Swiss pharmacopoeia requires the finished tincture to yield 0.06% essential oil. **Storage:** Store in tightly closed containers protected from light.

Note: Valerenic acid derivatives begin to be extracted at alcohol concentrations above 30% and are relatively constant above 50%. Valepotriates are only extractable at alcohol concentrations above 70%.

Valerian Fluid Extract

Prepared either by maceration or percolation at a concentration of 1 part herb to 1 part water-alcohol menstruum (70% ethanol *V/V*) (Bos 1997). **Characteristics:** Dark brown liquid with a strong characteristic valerian smell and taste. **Storage:** Store in tightly closed containers protected from light.

Valerian Root Dried Extract According to the German Pharmacopoeia (Deutsches Arzneibuch 10 1993)

Prepared from the chopped roots of valerian and 70% ethanol (*V/V*) as described in the valerian extract monograph. The relationship of the drug to the extract is between 4:1 and 7:1. **Characteristics**: Brown, hygroscopic, powder or pulverized mass with intense characteristic aroma. **Loss of Moisture on Drying:** At most 5%. **Storage:** Protect from moisture and light.

C ONSTITUENTS

The roots of *V. officinalis* contain several compounds with demonstrable pharmacological activity. These include the essential oil and its sesquiterpenoids (valerenic acid), epoxy iridoid esters (valepotriates) and their decomposition products such as baldrinal and homobaldrinal, amino acids (arginine, GABA, glutamine, tyrosine), and alkaloids. Valerian also possesses small amounts of phenolic acids and flavonoids, valerosidatum, chlorogenic acid, caffeic acid, choline, β-sitosterol, fatty acids, and various minerals.

Essential Oil (0.1% to 0.6%)

The essential oil content and composition of valerian varies significantly. Most pharmacopoeial standards require that valerian contain a minimum of 0.5% essential oil based on dry weight. Very few studies have been conducted on fresh material with the most recent published report finding approximately 0.25% essential oil (Hendriks and others 1981).

The essential oil contains mono- and sesquiterpene hydrocarbons with the main constituents being bornyl acetate, valerianol, valeranone, cryptofauronol, and valerenal, depending on the chemovar. The sesquiterpenes have three types of structures based on kessane, valeranone, and valerenic acid skeletons. Valerenic acid and its derivatives (acetoxyvalerenic acid and hydroxyvalerenic acid) have been reported to be characteristic of *V. officinalis* and its subspecies (Hänsel and Schulz 1982). However, species other than those considered as part of the aggregate have also been

found to contain valerenic acid and its derivatives (Bos 1997).

More than 150 compounds have been reported in the essential oil, including acyclic, monocyclic, and bicyclic hydrocarbons as well as oxygen-containing derivatives such as alcohols, aldehydes, ketones, phenols, oxides, and esters (Bos 1997). Bornyl acetate and isovalerate have been reported to be the primary components of the essential oil of *V. officinalis* ssp. *officinalis* (Morazzoni and Bombardelli 1995). Other primary compounds include valerianol, valeranone, cryptofauronol, or valerenal. Other secondary compounds include isoborneol, borneol, isobornyl acetate, isobornyl isovalerate, isoeugenyl-isovalerate, valeranone (ca. 0.005% to 40%), terpinolene, α-pinene (6.76%), camphene (ca. 16%), β-pinene (ca. 6.5%), β-caryopyllene, limonene (1% to 2%), carveyl acetate (ca. 5%), and dihydrocarveyl acetate (1% to 2%) (Hazelhoff and others 1979; Long 1987; Violon and others 1984).

Epoxy Iridoid Esters (Valepotriates)

Valepotriates are triesters of a terpenoid, trihydric alcohol. This alcohol has the structure of an iridoid cyclopenta-(c)-pyran with an attached epoxide ring. Numerous acid residues are found.

Valepotriate concentrations range from as little as 0.5% to 2% in European *V. officinalis* species (Hänsel and Schulz 1982), up to 8% in South American *V. edulis* Nutt. (Marekov and others 1983), and as high as 14.5% in *V. thalictroides* Graebn. Valtrate makes up approximately 80% to 90% of total valepotriates with the remainder consisting of acevaltrate, didrovaltrate, and isovaleroxyhydroxydidrovaltrate (IVHD valtrate) (Samuelsson 1992; Stahl and Schild 1971). Valepotriates degrade rapidly, especially in acidic solutions. When carefully dried, *V. officinalis* contains at least 0.8% valepotriates (Samuelsson 1992). Most European supplies contain an average of 0.4% to 0.6% valepotriates (Steinegger and Hänsel 1992). *V. officinalis* seldom contains more than 1.2% (w/w) (Houghton 1988).

Alkaloids

The dried root contains 0.05% to 0.1% alkaloids, including valerianine (0.002% in fresh roots), valerine, chatinine (0.01% in fresh roots) (Drobot'ko and others 1958; Franck and others 1970, isovaleramide, pyrryl-α-methylketone (Balandrin and others 1996), dipyridylmethylketone, actinidine (0.03%) (Johnson and Waller 1971; Torssell and Wahlberg 1967), pinoresinol, l-hydroxypinoresinol, and pinoresinol-β-D-glucoside (Bodesheim and Hölzl 1995).
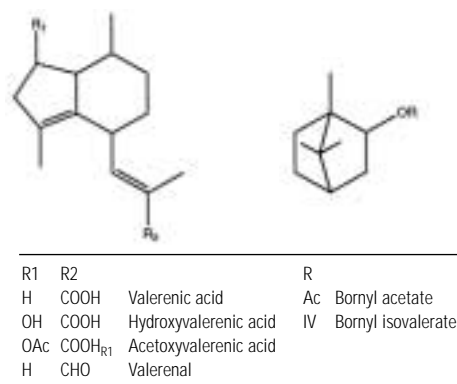
ANALYTICAL

Analysis of valerian has primarily focused on the essential oil, valerenic acid, and valepotriates. In the United States, the essential oil and valerenic acid are commonly used as marker compounds for qualitative and quantitative analysis of valerian root and valerian products. The following methods have been adopted.
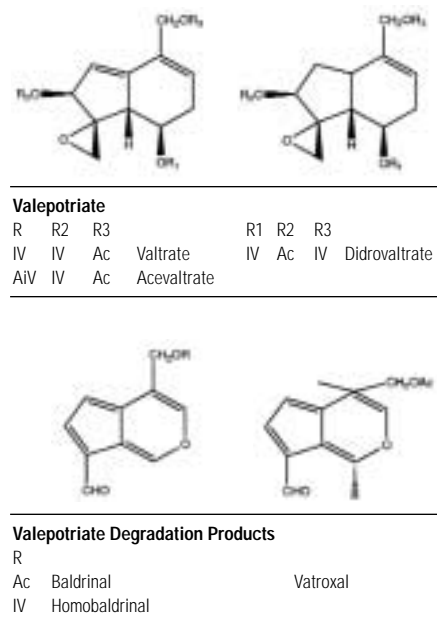
Spot Test

The 1998 edition of the European Pharmacopoeia provides the following spot test for authenticating *Valeriana* spp. This test is specific for valepotriates which occur in several species of valerian and is therefore not specific for *V. officinalis*. Because concern has been raised about the cytotoxicity of valepotriates, this test can be used to insure the absence of valepotriates from powdered valerian products.

Add 5 mL of methylene chloride to 0.2 g of freshly powdered root, let stand for 5 minutes, shake several times, and filter. Rinse the filter cake (solids) with 2 mL of methylene chloride and add the rinse to the filtrate. Collect the filtrate and washings in a test tube and blow dry with nitrogen for the minimum time necessary to remove the solvent. Dissolve the residue in 0.2 mL of methanol. Add 3 mL of a mixture of equal volumes of chilled acetic acid and hydrochloric acid to 0.1 mL of the methanol. Shake well. If valepotriates are present, the solution will turn a blue color within 15 minutes (European Pharmacopoeia 1998).
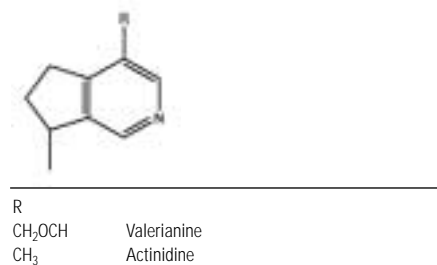

Figure 11 Primary components of valerian essential oil

R1	R2		R	
H	COOH	Valerenic acid	Ac	Bornyl acetate
OH	COOH	Hydroxyvalerenic acid	IV	Bornyl isovalerate
OAc	COOH$_{R1}$	Acetoxyvalerenic acid		
H	CHO	Valerenal		

Figure 12 Valepotriates and their decomposition products

Valepotriate

R	R2	R3			R1	R2	R3	
IV	IV	Ac	Valtrate		IV	Ac	IV	Didrovaltrate
AiV	IV	Ac	Acevaltrate					

Valepotriate Degradation Products

R			
Ac	Baldrinal	Vatroxal	
IV	Homobaldrinal		

Figure 13 Valerian alkaloids

R	
CH$_2$OCH	Valerianine
CH$_3$	Actinidine

Assay for Volatile Oil

There are three primary methods applicable for assaying volatile oil content of valerian root: AOAC International, European Pharmacopoeia, and the United States Pharmacopeia. Each of these is similar; however, the procedures provided by AOAC have been detailed in such a manner as to minimize variables that can lead to differences in volatile oil yields and maximize reproducibility (Ertl 1997). Because the determination of volatile oil is the primary qualitative and quantitative marker for effective valerian products, this method has been adopted (see Ertl *Journal AOAC Int* 80(4): 1-6, 1997).

Thin Layer Chromatography (TLC, HPTLC)

For thin layer chromatography analysis, the method of the European Pharmacopoeia (1998 supplement) and the method proposed by the United States Pharmacopeial Convention (USP) (Pharmacopeial Forum 1998) were compared. The method of the European Pharmacopoeia method was preferred for analysis of valerenic acid, a primary marker compound of *V. officinalis.* Improvements were made to the sample preparation.

Sample Preparation

Shake 0.2 g of freshly powdered valerian in a test tube with 5 mL dichloromethane for 1 minute. Allow the mixture to stand for 5 minutes and then filter. Wash the filter with 2 mL of dichloromethane. Evaporate the combined filtrate and washing to dryness on a water bath. Dissolve the residue in 0.2 mL of dichloromethane and transfer the solution into a small sample vial.

Standard Preparation

Dissolve 1 mg of valerenic acid (available from Indofine Chemical Company, Somerville, NJ; United States Pharmacopeial Convention, Rockville, MD) in 0.5 mL of dichloromethane.

Reagent Preparation

Prepare HCl-acetic acid reagent (1:4) carefully mixing 20 mL of glacial acetic acid with 80 mL of concentrated hydrochloric acid.

Prepare anisaldehyde-sulfuric acid reagent by slowly adding 9 mL of 98% H_2SO_4 to an ice cooled mixture of 85 mL of methanol and 10 mL of glacial acetic acid. To this solution add 0.5 mL of anisaldehyde and mix well. The anisaldehyde-sulfuric acid reagent is colorless and should be stored in a refrigerator. If a color develops, the reagent must be discarded.

Chromatographic Conditions

Stationary Phase: HPTLC plates 10 x 10 cm silica gel 60 with fluorescence indicator (EM Science, Whatman, Machery & Nagel, or equivalent).

Mobile Phase: Hexane:ethyl acetate:glacial acetic acid (65:35:0.5).

Sample Application: 3 µl volumes of both sample solution and standard are applied each as a 10 mm band. Space bands 6 mm apart. Application position should be 8 mm from the lower edge of the plate.

Detection: a) UV 254 nm.

b) Spray plate with the HCl-acetic acid reagent, dry in stream of cold air, heat to 110 ˚C for 5 minutes. Inspect plate in visible light and under UV 366 nm.

c) Spray the plate with the HCl-acetic acid reagent, dry in stream of cold air, place on plate heater (or in oven) at 120 ˚C for 2 minutes (or until color of standard has developed).

R_f Values: Valerenic acid = 0.48. Following application of the HCl-acetic acid reagent, this band appears as a very faint violet color in visible light and as a weak fluorescent band under UV 366 nm. Following subsequent application of the anisaldehyde-sulfuric acid reagent, valerenic acid appears as a strong dark blue band.
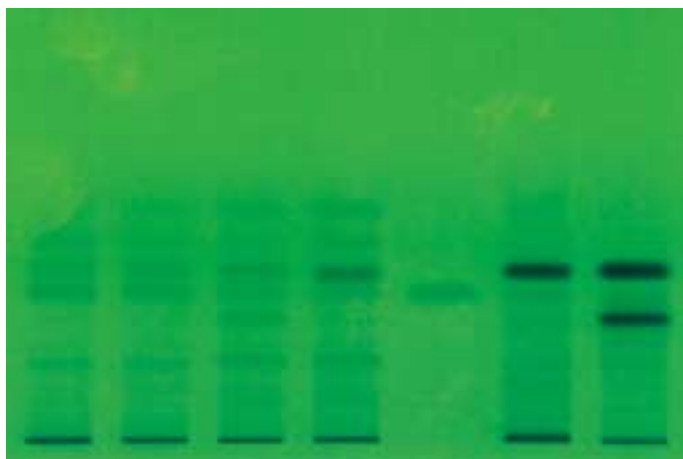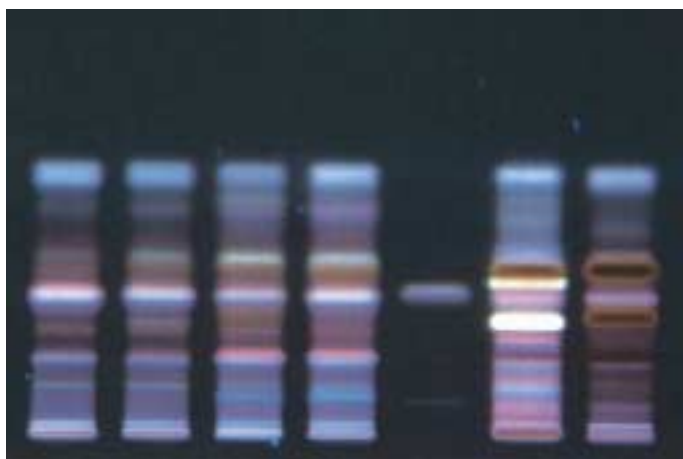
Figure 14 HPTLC plate viewed under 254 nm UV

Lane 1: *V. officinalis.*
Lane 2: *V. officinalis* (organically cultivated).
Lane 3: *V. officinalis* (commercial material from Holland).
Lane 4: *V. radix* (official standard from Swiss pharmacopoeia).
Lane 5: Valerenic acid.
Lane 6: *V. sitchensis.*
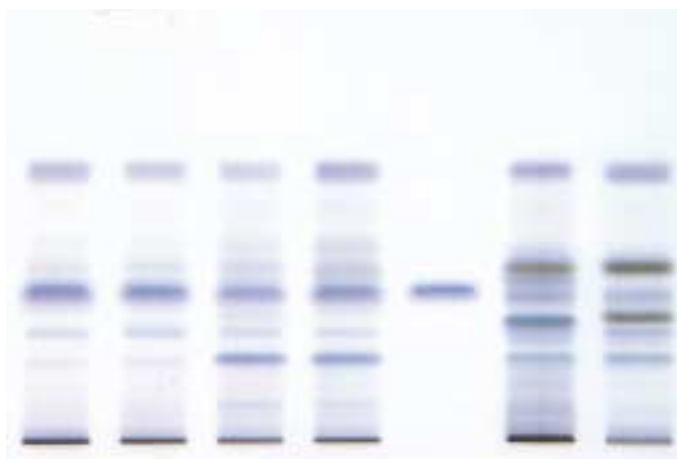**Lane 7:** *V. wallichi* (Indian valerian).
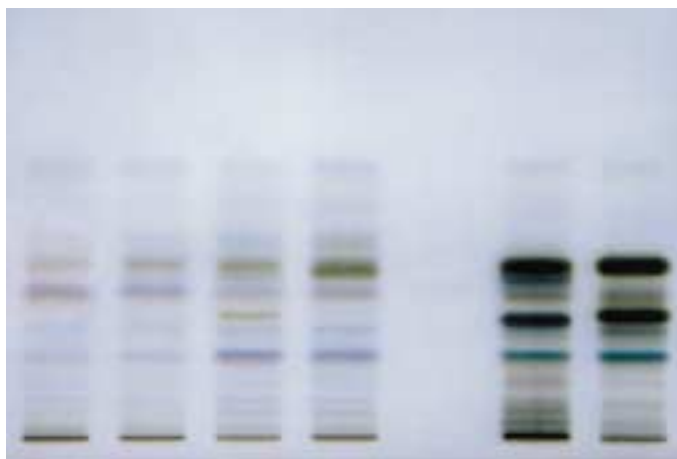
Figure 15 HPTLC plate viewed after application of the HCl-acetic acid reagent in visible light

Lane 1: *V. officinalis.*
Lane 2: *V. officinalis* (organically cultivated).
Lane 3: *V. officinalis* (commercial material from Holland).
Lane 4: *V. radix* (official standard from Swiss pharmacopoeia).
Lane 5: Valerenic acid.
Lane 6: *V. sitchensis.*
Lane 7: *V. wallichi* (Indian valerian).

Figure 16 HPTLC plate viewed after application of the HCl-acetic acid reagent viewed under 366 nm UV

Lane 1: *V. officinalis.*
Lane 2: *V. officinalis* (organically cultivated).
Lane 3: *V. officinalis* (commercial material from Holland).
Lane 4: *V. radix* (official standard from Swiss pharmacopoeia).
Lane 5: Valerenic acid.
Lane 6: *V. sitchensis.*
Lane 7: *V. wallichi* (Indian valerian).

Figure 17 HPTLC plate viewed after exposure to both the HCl-acetic reagent and the anisaldehyde reagent

Lane 1: *V. officinalis.*
Lane 2: *V. officinalis* (organically cultivated).
Lane 3: *V. officinalis* (commercial material from Holland).
Lane 4: *V. radix* (official standard from Swiss pharmacopoeia).
Lane 5: Valerenic acid.
Lane 6: *V. sitchensis.*
Lane 7: *V. wallichi* (Indian valerian).

In Figure 14, valerenic acid is seen as a strong single band at R_f 0.48. In the *V. officinalis* samples, three bands of decreasing intensity are seen above this band. A sharp band is seen at R_f 0.25.

In Figure 15, valerenic acid is seen as a very faint violet band at R_f 0.48. In the *V. officinalis* samples, the band at R_f 0.25 is olive green with a light violet band directly above. Another light blue band appears at R_f 0.4. An olive green and two gray bands are present at an approximate R_f of 0.56, 0.62, and 0.85, respectively.

In Figure 16, valerenic acid is seen as a weak fluorescent band at R_f 0.48. At the same R_f, a blue and a pink band with two broad red bands directly above are seen in the *V. officinalis* samples. There is also a blue band at R_f 0.85 and a blue fluorescence band at R_f 0.25

In Figure 17, valerenic acid is seen as a strong dark blue band. Depending on the purity of the standard, two more bands may appear at a lower R_f. The *V. officinalis* samples test show prominent dark blue bands of valerenic acid at R_f 0.48 and one or two dark blue bands at R_f 0.85. Two or three violet bands are seen between R_f 0.5 and R_f 0.8. Two blue bands are seen below the valerenic acid band.

High Performance Liquid Chromatography (HPLC) for Valerenic Acid

For quantitative analysis of valerenic acid, a modification of the method of Hänsel and Schulz was adopted (Hänsel and Schulz 1982). This same method formed the basis for the method proposed by the Pharmacopeial Convention (USP) for inclusion in the National Formulary (Pharmacopeial Forum 1998). It provides good separation of valerenic acid, acetoxyvalerenic acid, and hydroxyvalerenic acid, and the aldehyde valerenal. In Europe, and in some analytical laboratories in the United States, total valerenic acid content is calculated as the sum of these compounds. In the USP proposal, only valerenic acid content is determined. These differences in calculating valerenic acid content cause confusion and incongruities in the marketplace. Calculation of total valerenic acid values (the sum of valerenic acid, acetoxyvalerenic acid, hydroxyvalerenic acid, and valerenal) is more representative of effective valerian products than determination of valerenic acid alone. Additionally, some analytical laboratories calculate total valerenic acids using each reference standard while others calculate total valerenic acids based on the assumption that the extinction coefficients for each compound are the same. The extinction coefficients of each compound are not the same. However, calculating total valerenic acids in this manner provides a more accurate determination of total valerenic acid values than the calculation of valerenic acid alone. For a more accurate determination of total valerenic acids, laboratories are encouraged to determine the extinction coefficients of the three primary compounds. Valerenic acid is available and is relatively inexpensive. Standards for acetoxyvalerenic acid and hydroxy valerenic acid are available and are relatively expensive. Standards for valerenal are not available but it is considered to have the same extinction coefficient as valerenic acid.

Sample Preparation

For analysis of crude valerian root, weigh 2 g of finely powdered root material and transfer to a 100 mL volumetric flask. Dilute to volume with methanol:water (80:20) and sonicate for 30 minutes. Filter a portion through a 0.45 μm filter into an HPLC vial or centrifuge to obtain a clear test solution.

For analysis of powdered extracts, weigh 100 mg of extract into a 10 mL volumetric flask. Dilute to volume with methanol:water (80:20) and sonicate for 15 minutes. Filter a portion through a 0.45 μm filter into an HPLC vial or centrifuge to obtain a clear test solution.

Characterization of various *Valeriana* spp by TLC (see Figures 14-17)

All of the *V. officinalis* samples tested were identical with the exception of the Dutch sample. *V. sitchensis* and *V. wallichi* give significantly different chromatograms. Information about differentiating between the species is provided below. No attempt has been made to correlate the bands with known compounds. However, the information provided may be useful in quality control assessment of various species of *Valeriana*.

a) Under 254 nm UV, the Dutch sample shows an extra band at R_f 0.37. The most intense band of *V. sitchensis* is at R_f 0.53, and the bands at the higher R_f are missing. *V. wallichi* is characterized by two dominating bands at R_f 0.37 and 0.53, and the bands at the higher R_f are also missing.

b) Under visible light, the Dutch sample has an extra olive green band at R_f 0.37 and an intense violet band at R_f 0.25. The band at the same R_f in *V. sitchensis* and *V. wallichi* is blue. The most intense band of *V. sitchensis* is a brown band at R_f 0.53. There are a blue and a brown band at R_f 0.37. No bands appear at R_f 0.55 and 0.8. *V. wallichi* is similar to *V. sitchensis* with the exception that the band at R_f 0.37 is more intense and of brown color. In the Dutch sample, there is an extra reddish-brown band when viewed under 366 nm UV. *V. sitchensis* is characterized by two very strong white bands at R_f 0.38 and 0.5. An additional red band is present at R_f 0.18. *V. wallichi* shows a sharp violet band at R_f 0.48 between two broad brown bands.

c) The Dutch sample shows an extra olive green band at R_f 0.37. *V. sitchensis* and *V. wallichi* show a pattern similar to that of *V. officinalis*; however, the intensity of the bands is significantly different in all three species.

Standard Preparation

Accurately weigh 5 mg of valerenic acid standard (Indofine Chemical Company, Somerville, NJ; United States Pharmacopeial Convention, Rockville, MD) into a 100 mL volumetric flask. Dilute to volume with methanol:water (80:20) and sonicate for 15 minutes.

Stability and Storage of Preparations

The standard and sample are stable when stored in amber vials and are refrigerated.

Chromatographic Conditions

Column:	C-18, 5 μm, 4.6 x 250 mm (Alltech Hypersil).
Mobile Phase:	Methanol:0.5% phosphoric acid (80:20).
Flow Rate:	1.5 mL/minute.
Detection:	225 nm.
Injection Volume:	20 μL.
Run Time:	15 minutes.
Elution Order:	Hydroxyvalerenic acid, acetoxyvalerenic acid, valerenic acid, valerenal.

Calculation

Calculate the percentage of valerenic acid alone or total valerenic acids using the following formula.

$$100V\,(C/W)(r_u/r_s)$$

V is the volume in mL of the sample preparation; C is the concentration in mg per mL of the standard solution; W is the weight in mg of valerian used to prepare the sample solution; r_u and r_s are the peak responses obtained from the sample solution and the standard solution, respectively.
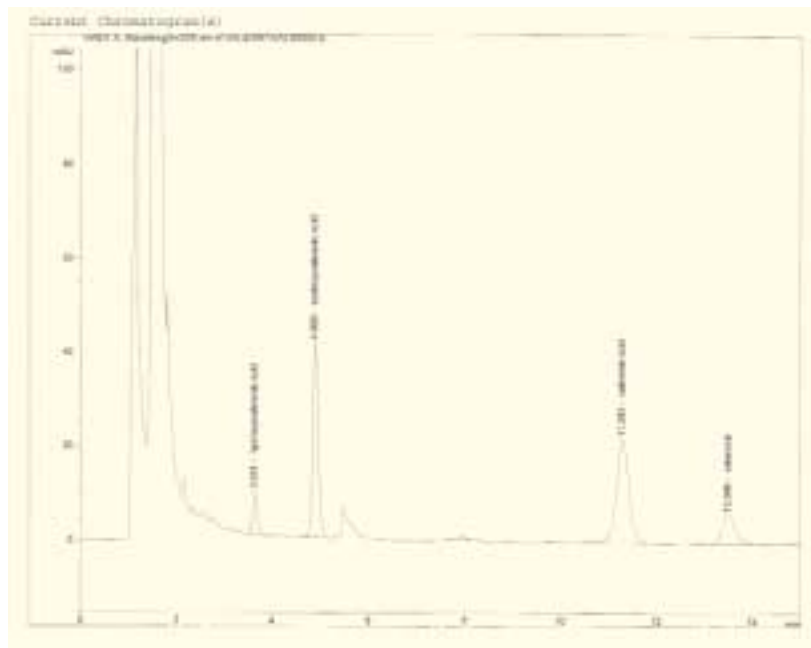
Figure 18 Typical HPLC chromatogram of *Valeriana officinalis*

Chromatogram courtesy of Hauser Laboratories, Boulder, CO

Qualitative Standards

Foreign Organic Matter: Not more than 5% stem bases, not more than 2% other foreign matter (European Pharmacopoeia 1998).

Total Ash: Not more than 12% determined on 1 g herb (European Pharmacopoeia 1998).

Acid Insoluble Ash: Not more than 5% determined on 1 g herb (European Pharmacopoeia 1998).

Loss of Moisture on Drying: Not more than 12% determined on 10.0 g powdered herb (#355) dried at 100 °C to 105 °C for 2 hours (European Pharmacopoeia 1998).

Extractable Matter: Not less than 20%. Mix 2.00 grams of powder (#250) with a mixture of 12 g ethanol (96%) and 8 g of water. Allow to stand for 2 hours, shaking frequently, filter, evaporate filtrate to dryness on a water bath, and dry the residue at 100 °C to 105 °C. The residue should weigh not less than 0.1 g (European Pharmacopoeia 1998).

Microbial Contamination: Negative for *Salmonella* species, *Escherichia coli,* and *Staphylococcus aureus* (Pharmacopeial Forum 1998).

THERAPEUTICS

Pharmacokinetics

The only pharmacokinetic data available for valerian are regarding the valepotriates. The clinical relevance of this is largely inconsequential as valepotriates rapidly degrade in commercial products. Although metabolic by-products of valepotriates are considered to be more active than the valepotriates themselves, these are similarly not present in commercial products.

Valepotriates administered orally to mice are reported to be poorly absorbed, having an efficiency of 0.19% of the administered dose. The greatest quantity of ^{14}C-labeled valepotriates were found in the stomach lining and in the intestines, and unchanged valepotriates were reported in the stomach contents 15 hours after administration. Small amounts of valepotriates and their decomposition products were reported to be found in the blood, liver, kidneys, heart, lungs, and brain (Steinegger and Hänsel 1992). Another study with radioactive didrovaltrate administered to mice orally, intravenously, and intraduodenally also reported poor absorption in the unchanged form. However, the researchers found the bulk of the radioactivity in polymeric degradation products and confirmed a fast degradation or metabolic decomposition with in vitro studies using plasma and liver homogenates (Wagner and Jurcic 1980).

Pharmacodynamics

Research into the pharmacological activity of valerian has almost exclusively focused on its sedative and spasmolytic properties. Individual components have displayed activity, but no single constituent has been shown to account for valerian's total action. Early in the 20th century, it was believed that the essential oil was the component responsible for the sedative effect of valerian (Houghton 1988). However, work by Gstirmer and Kind published in 1951 indicated that the essential oil accounted for only one-third of the sedative activity of the extract (Gstirmer and Kind 1951). In 1969, Eickstedt and Rahman reported that valepotriate esters isolated from valerian demonstrated sedative activity in mice (Eickstedt and Rahman 1969). However, Japanese samples of *V. officinalis* containing low amounts of valepotriates showed a greater effect on hexobarbital-induced sleeping time than Chinese and Nepalese samples containing high amounts of valepotriates (Hikino and others 1980). Also, valepotriates are not water soluble and were excluded as the active hypnotic in an aqueous extract which was found to be an effective sleep aid in clinical trials (Leathwood and Chauffard 1985). In addition, an in vivo study measuring cerebral glucose turnover in rats found that although a dichloromethane extract demonstrated depressant activity, this activity could not be accounted for by valepotriates,

valerenic acid, valeranone, or the essential oil of *V. officinalis* L. (Krieglstein and Grusla 1988). In summary, it has been shown that the sedative and spasmolytic effects attributed to valerian are due to the activity of multiple constituents.

Effect on Sleep

Human Clinical Studies

At least four clinical studies have been conducted on the effects on sleep using the same aqueous extract of *V. officinalis* L. This preparation was made with deionized water heated to 60 °C and subsequently freeze-dried and reportedly contained only trace amounts of valepotriates (0.01%).

The first of these studies, by Leathwood and others (1982), was a double-blind clinical trial wherein 128 subjects received one of three samples: either an aqueous extract of valerian, a commercial preparation containing extracts of valerian and hops strobiles (ratio of 2:1), or a placebo of brown sugar. Both valerian preparations contained 400 mg of valerian extract, the dose recommended in the Swiss pharmacopoeia. Subjects, through questionnaires, reported a reduction in sleep latency ($P < 0.05$) and an increase in sleep quality ($P < 0.05$) as compared to placebo. People who considered themselves poor or irregular sleepers obtained the most benefit. The commercial preparation was not as effective as the extract. These preparations had no effect on night awakenings or dream recall. In a subsequent double-blind, placebo-controlled study, 8 volunteers with mild insomnia were given 450 or 900 mg of extract. Sleep onset was determined by reduction in body movement as measured by wrist-worn activity monitors. Sleep onset was accelerated from an average of 15.8 ± 2.2 minutes to 9.0 ± 1.5 minutes ($P < 0.01$). This effect was seen with the 450 mg dose and increasing the dose was without further effect. Valerian extract did not influence total sleep time or normal levels of movement during the night. The authors concluded that valerian was at least as effective as small doses of barbiturates or benzodiazepines (Leathwood and others 1982; Leathwood and Chauffard 1985).

Another research group, using the same 450 mg valerian extract in a double-blind crossover study, reported a subjective decrease in sleep latency of subjects at home. No significant change in a lab environment as measured with activity monitor bracelets, polygraph, and EEG was reported (Balderer and Borbély 1985). These subjects were all healthy and good sleepers. In another study, 10 healthy male volunteers, who were good sleepers, showed no statistically significant effect on EEG from valerian extract (Leathwood and Chauffard 1982/3).

A more recent double-blind, placebo-controlled crossover study investigated the influence of 600 mg of a proprietary valerian preparation (Sedonium-LI 156; ethanol extract) in subjects with psychophysiological insomnia. Sleep latency was improved in comparison with beginning baseline and in comparison with placebo, despite a positive placebo effect (Donath and others 1996).

In another study, 80 elderly patients with behavioral disorders of nervous origin, including difficulty falling asleep, difficulty sleeping through the night, and rapid fatigue due to the impaired sleep were evaluated in a placebo-controlled study. Patients were given either placebo or 6 tablets daily of Valdispert®, a product containing 45 mg dry valerian extract standardized to 0.05 mg valerenic acid and acetoxyvalerenic acid. Objective (NOSIE) and subjective parameters (von Zerssen's well-being scale) were assessed. Significant improvements in the ability to fall asleep and to sleep through the night ($P < 0.001$) and a decreased level of fatigue ($P < 0.02$) were observed after 14 days of treatment. The medication was well tolerated (Kamm-Kohl and others 1984).

In two large uncontrolled multicenter trials, patients experiencing functional sleep disturbances and anxiety reported subjective improvement after treatment with the valerian preparation Baldrian-Dispert® (corresponding to Valdispert®) for 10 days. In the more recent of the two studies, 1689 patients, both children (average age of 10) and adults (average age of 48), took from 3 to 9 tablets per day. Each tablet contained 45 mg of dry valerian extract. Improvement in sleep and ability to concentrate was noted in the first 2 days of treatment with increasing improvements on subsequent days. Fifty percent of those patients whose primary complaint was difficulty in concentration reportedly were symptom free within the 10-day period. Reduction of

other symptoms, including cardiac palpitations, menopausal neurosis, and depression was observed. Side effects of gastrointestinal upset and headache were reported in only 8 patients (Seifert 1988). Similar results were reported in a study of 11,168 patients treated by 982 German practitioners. Symptoms were eliminated in 70% of subjects, improved in another 24%, and only 6% of patients remained unchanged (Voight-Schmidt 1986). One final study compared the effects of two valerian preparations (equivalent to 4 g) and flunitrazepam with placebo. All three medications were superior to placebo. However, less side effects were observed with the valerian preparations (10% of subjects) as compared to the group taking flunitrazepam (50% of subjects) (Gerhard and others 1996).

In summary, the studies above have demonstrated statistically significant decreases in sleep latency and increases in sleep quality for poor sleepers. No change was reported in night awakenings, dream recall, total sleep time, or the normal levels of movement during the night.

Numerous other studies on the effects of valerian on sleep have been conducted with commercial products containing various adjuncts, particularly lemon balm (*Melissa officinalis*) and passion flower (*Passiflora* spp.). The results of these studies have shown these preparations to have a significant positive effect on sleep disorders, but have not been reviewed here.

The effects of valerian extract on stress were evaluated in a double-blind study using healthy volunteers. Forty-eight men and women were divided into four treatment groups receiving either placebo, 100 mg valerian extract, 20 mg propranolol, or a combination of valerian and propranolol (Kohnen and Oswald 1988). Valerian had no effect on stress-induced increases in heart rate caused by performing mathematical calculations verbally, although the propranolol and combination treatment reduced this physiological activation. Valerian treatment induced a slight improvement in a written concentration test, although there was a trend towards impairment of performance with the valerian-propranolol combination. Both valerian and the combination therapy led to less intense subjective feelings of "somatic arousal".

Animal Studies
The essential oil of valerian and the isolated components valerenal, valerenic acid, valeranone, and isoeugenyl-isovalerate were screened for central nervous system effects on mice upon ip administration (Hendriks and others 1985). The essential oil showed sedative and/or muscle relaxant activity with the oxygenated components exhibiting more activity than the hydrocarbon fraction. Valerenal and valerenic acid were more active than valeranone, producing ataxia at 50 mg/kg. Isoeugenyl-isovalerate did not appear to contribute much to the activity of the oil. In a subsequent study on valerenic acid, the authors reported a decrease in rotorod and traction performance in mice given 100 mg/kg ip. Valerenic acid also produced a dose-related increase in pentobarbital-induced sleep with 50 and 100 mg/kg ip (Hendriks and others 1985). As a result of these tests, the authors described the activity of valerenic acid as a general central depressant rather than a neuroleptic or muscle relaxant.

The antispasmodic effects of the isolated essential oil component valeranone and valepotriates (isovaltrate, valtrate, and didrovaltrate) were demonstrated in a series of in vivo and in vitro studies using guinea pig smooth muscle tissue (Hazelhoff and others 1982). The above compounds at 20 mg/kg iv decreased rhythmic contractions and contractile force in ligated guinea pig ileum. In vitro studies using ileum and stomach tissue showed that the effects of valeranone and didrovaltrate (10^{-5} to 10^{-4}M) were not mediated through receptors of the cholinergic or adrenergic nervous system, but rather demonstrated a direct effect on the muscle tissue. The authors considered the activity to be similar to that of papaverine and suggested an effect on calcium levels in the muscle tissue.

Comparison of the activity of valerian extracts in mice all but eliminated the theory that valepotriates are responsible for the sedative activity. Nepalese and Chinese valerian extracts containing 1.7% and 1.4% valepotriates, respectively, showed no sedative activity in mice after oral administration of the equivalent of 10 g crude drug/kg. However, Japanese valerian root Hokkai kesso, containing 0.05% valepotriates, almost doubled hexobarbital-induced sleep ($P < 0.01$) and approximately halved

stress-induced ulcer formation in mice ($P < 0.05$) (Hikino and others 1980). Kessyl glycol acetates were suggested as the constituents of Hokkai kesso responsible for causing the increase in hexobarbital-induced sleep time; however, they showed no activity in reducing stress-induced ulcer formation. None of the valerian preparations showed any analgesic activity in a pressure/pain assay after oral administration of 10 g crude drug-equivalent/kg.

Results with Hokkai kesso on hexobarbital-induced sleep in mice were repeated by another group who further profiled the psychotropic activity of this extract (Sakamoto and others 1992). Ambulation and rearing was depressed in a dose-related manner after oral administration of 3 to 11 g/kg extract. Immobility induced by a forced swimming test in rats was inhibited with 4 g/kg, and reserpine-induced hypothermia in mice was reversed with 11 g/kg extract. These results led the authors to suggest that valerian may act as an antidepressant.

An ethanolic extract of valerian given to male mice (dose equivalent to 400 mg root/kg ip body weight) did not produce overt sedation or tranquilization, as was observed in mice treated with benzodiazepine and diazepam (a group of sedative-hypnotics) at 2 mg/kg. However, at the same dose the extract prolonged thiopental induced anesthesia and was anticonvulsant against picrotoxin, but not pentetrazol or harman (ED_{50} of 24 mg root equivalent/kg body weight). The authors concluded that valerian does not exert the same type of anti-anxiety effect as diazepam, although they did suggest an interaction with the $GABA_A$-benzodiazepine receptor complex (Hiller and Zetler 1996).

In Vitro Studies

Attempts have been made using in vitro assay techniques to delineate the mechanism of action for the sedative effects of valerian. Several researchers have linked the effects of valerian extracts and/or its components with an effect on the inhibitory neurotransmitter GABA (Mennini and others 1993; Santos and others 1994a, 1994b). GABA mediates sedation in the central nervous system. Benzodiazepines exert their actions via this system. Valerenic acid and acetylvalerenic acid have been reported to inhibit GABA transaminase, thereby prolonging the inhibitory effect of GABA (Riedel and others 1982). However, the effect was small and required mM concentrations.

An aqueous extract of valerian, containing 55 mg valerenic acids/100 g extract, was recently shown to displace radiolabeled GABA from its binding sites on synaptosomes isolated from rat brains (Santos and others 1994a). Analysis of the content of the extract for amino acids revealed that the extract itself contained GABA in sufficient quantity (4.6 mM) to account for the displacement activity (Santos and others 1994b). However, the presence of GABA in the extract is unlikely to account for the activity of valerian in vivo because GABA does not cross the intact blood-brain barrier. Analysis also showed that the extract contained high amounts of glutamine (13 mM) which is able to cross the blood-brain barrier. The usual concentration of glutamine in the brain extracellular fluid is in the range of 0.2 to 0.5 mM. Glutamine has been shown in vitro to stimulate GABA synthesis in synaptosomes and brain slices, and the authors are investigating whether valerian extracts have any effect on rat brain amino acid levels in vivo.

An interaction with the GABA receptor is also suggested for the pineal hormone melatonin which exerts hypnotic and/or sedative effects. A recent study found the valerian extract LI 156 was able to displace radiolabeled melatonin from its binding sites in the human cerebellum. The effect was dose-dependent with an IC_{50} of 0.5 mg/L. The constituents responsible for this effect were not identified, but valerenic acid was ruled out. In contrast to the reports cited above, this study found no interaction between the extract and $GABA_A$ receptors (Fauteck and others 1996).

In another study, valerian extracts showed no binding to benzodiazepine receptors isolated from rat brains (Balduini and Cattabeni 1989). They did show an approximately 30% to 70% displacement of radiolabeled cyclohexyladenosine from adenosine receptors with high concentrations (0.01 to 1 mg/mL) of the hydroalcoholic extract.

A number of studies have investigated the pharmacological activity of specific alkaloids. The alkaloid actinidine, representing approximately 0.015% of the total alkaloids of valerian, has been reported to be a highly active inhibitor of cholinesterase (Torssell and Wahlberg 1967). Pyrryl-α-methylketone exhibits both sedating and anesthetic activity. Isovaleramide is an effective central nervous system depressant at dosages as low as 30 mg/kg ip in mice (Balandrin and others 1996). More recently, the alkaloids l-hydroxypinoresinol, pinoresinol, and pinoresinol-β-D-glucoside, as well as several valerian extracts, were assayed for their affinity to 5-HT$_{1A}$, GABA$_A$-, benzodiazepine-, and μ-opiate receptors (Bodesheim and Hölzl 1997). Of the alkaloids studied, l-hydroxypinoresinol displayed a significant affinity for 5-HT$_{1A}$ receptors (IC$_{50}$ of 2.3 μM/l) and insignificant binding at benzodiazepam receptors. Further studies are needed to determine if these in vitro findings are of clinical relevance.

Other Effects

A preparation of crude alkaloids showed antibacterial activity against gram positive bacteria. Isolated alkaloids, valerine and chatinine, also showed activity, but to a lesser extent (Drobot'ko and others 1958). Otherwise, the alkaloids are considered to be of minor importance (Franck and others 1970; Johnson and Waller 1971; Torssell and Wahlberg 1967). Hypotensive effects have also been reported, but little substantiation for this effect is provided in the literature (Rosecrans and others 1961).

Valepotriates have been reported to promote dilation of the coronary artery and to be of potential benefit for reducing arryhthmias (Petkov 1979). As mentioned previously, the presence of these compounds in commercial products is unlikely.

Actions

Sedative, nervine, antispasmodic, relaxant (Balderer and Borbély 1985; Bradley 1992; European Scientific Cooperative of Phytotherapy (ESCOP) 1990; Hazelhoff and others 1982; Hendriks and others 1985; Kohnen and Oswald 1988; Leathwood and Chauffard 1985).

Indications

Based on a review of the primary pharmacologic literature, valerian alone or in combination with other sedative or antispasmodic herbs is specific for the symptomatic relief of insomnia, restlessness, and spasms due to nervous tension. As with the use of all sedatives, the underlying cause of the condition should be appropriately addressed.

In the traditional herbal literature, King offers insights into the proper use of valerian by stating that it is most effectual when used in patients with impaired cerebral circulation associated with mental depression (King 1866). Traditionally, it has been used for patients who are pale, weak, and asthenic. Clinically it is used for a wide variety of conditions associated with the nervous system, including nervous complaints due to menopause and hot flashes, nervous asthma, the management of infantile convulsions, epileptic seizures or mild tremors, menstrual cramps, as a general sleep aid and for disturbed sleep patterns (use 30 minutes prior to bed), nervous headaches, symptomatic management of attention deficit hyperactivity disorder (ADHD), anxiety, gastric spasms, and colic (Bradley 1992; ESCOP 1990; Felter and Lloyd 1898; Hellemont 1986; Stillé and others 1896; Valnet 1992; Weiss 1988).

Substantiated Structure and Function Claim

According to a review of the literature, valerian preparations equivalent in dosage and composition to those found to be effective in clinical human studies, promote relaxation through an enhancement of GABA neurotransmission (Mennini and others 1993; Riedel and others 1982; Santos and others 1994a, 1994b).

Dosages

Powder	2-3 g or as needed up to 3 times daily (ESCOP 1993).
Cold Infusion	1 cup or as needed up to 3 times daily (ESCOP 1993; Osol and others 1947).
Hot Infusion	1 cup or as needed up to 3 times daily (ESCOP 1993).
Tincture (1:5)	1-3 mL (20-60 drops) (Blumenthal and others 1998) as needed up to 3 times daily (ESCOP 1993).
Fluid Extract (1:1)	0.3-1 mL (10-20 drops) 1 or more times daily (up to 3 times) (ESCOP 1993).
Essential Oil	0.05-0.25 mL (2-6 drops) up to 2 times daily (Felter and Lloyd 1898).
External	100 g per bath (Blumenthal and others 1998; Weiss 1988).

SAFETY PROFILE

Classification of the American Herbal Products Association

Class 1: Herbs which can be safely consumed when used appropriately (McGuffin and others 1997).

Side Effects

In sensitive individuals, valerian can cause heart palpitations and nervousness. Occasional headache and gastrointestinal distress were reported in one clinical study (Seifert 1988). According to the older herbal literature, excessive doses or large continuous doses may cause nausea, diarrhea, headache, agitation, heart palpitations, and dull the senses and response times (Culbreth 1917; Felter and Lloyd 1898).

Because benzodiazepines taken to aid in sleep can impair alertness the morning after administration, a study was conducted to see whether this would also be the case with valerian preparations. In a placebo-controlled study, healthy volunteers were treated with tablets containing valerian and hops, a syrup containing only valerian, or flunitrazepam (1 mg). An objectively measurable impairment of performance on the morning after medication occurred only in the flunitrazepam group. On the contrary, this study showed improved subjective self-assessment (more alert, more active, subjective feeling of well-being) with the valerian and hops tablets and valerian syrup (Gerhard and others 1996).

Recently, a group of physicians from Duke University Medical Center presented a case history suggesting that serious cardiac complications (high output cardiac failure) and delirium experienced by a patient may have been attributable to valerian withdrawal in a manner similar to benzodiazepine withdrawal (Garges and others 1998). Because valerian is considered to exert a benzodiazepine-like action through enhancement of GABA neurotransmission and because a reversal of symptoms was observed with administration of benzodiazepine, the reporting physicians considered there to be a strong correlation between the adverse event and valerian withdrawal. The patient was using 530 mg to 2 g of valerian per dose 5 times daily for many years to help him sleep and relax and had discontinued use upon admission. He had a history of coronary artery disease, hypertension, and congestive heart failure and was admitted for an open biopsy of a lung nodule. Upon admission, he had been using several medications including isosorbide dinitrate, digoxin, furosemide, benazepril,

aspirin, lovastatin, ibuprofen, potassium, zinc, and vitamins. Additional interventions were applied in the course of the biopsy. The acute crisis occurred after administration of naloxone and subsequently stabilized over the course of 3 days. After being discharged the patient continued using valerian and was stable at his 2-month and 5-month assessments.

Consumption of valerian products have been implicated in at least five cases of liver toxicity (see Toxicology).

Contraindications

None cited in the literature (Blumenthal and others 1998; Bradley 1992).

Interactions

Valerian and some valerian preparations have been shown to potentiate the effects of barbiturates (Bounthanh and others 1980; Hendriks and others 1985: Rosecrans and others 1961). At 2 mg/kg po an aqueous alkaline extract (5 to 6:1) increased thiopental-induced sleeping time in mice by a factor of 1.6 ($P \leq 0.01$), and at 200 mg/kg po a 7.6-fold increase was observed. As a comparison, a 4.7-fold increase was observed with concomitant use of chlorpromazine (4.0 mg/kg po) (Leuschner and others 1993). In older literature, it was reported that atropine decreases the hypotensive activity of valerian by 50% (Rosecrans and others 1961). It has also been reported that valerian has been used in conjunction with bromides and other sedatives. Specific data regarding the interaction are lacking (Evans 1989). Also reported in older literature is the ability of valepotriates (20 mg/kg iv) to reduce vasopressin and barium-induced arrhythmia in rabbits (Petkov 1979).

Pregnancy, Mutagenicity, and Reproductive Toxicity

There is a significant amount of literature regarding the mutagenic potential of valepotriates. As previously stated, these compounds degrade rapidly and are typically not found in commercial preparations. These data are as follows.

Valepotriates, such as valtrate and didrovaltrate, contain an epoxide group and thus possess alkylating properties. Part of the in vitro cytotoxicity of valepotriates may be due to their ability to interact with thiol-containing enzymes (Bos and others 1998b). Two groups of valepotriates are distinguished: those of the diene type (valtrate, isovaltrate, and acevaltrate) and those of the monoene type (didrovaltrate and isovaleroxyhydroxydidrovaltrate). The cytotoxic potential of valerenic acid and its derivatives, as well as valepotriates and their derivatives, was investigated against a human small cell lung cancer cell line (GLC_4) and a human colorectal cancer cell line (COLO 320) using the microculture tetrazolium (MTT) assay (Bos and others 1998b). Those of the diene type displayed the highest cytotoxicity with IC_{50} values slightly higher than those of the cytotoxic agent cisplatin (GLC_4: 1µM; COLO 320: 3 µM) which was used as a comparison. Those of the monoene type were found to be 2- to 3-fold less toxic, and the decomposition products of valepotriates, baldrinal and homobaldrinal, were found to be 10- to 30-fold less toxic than their parent compounds (see Table 2).

Valerenic acid and its derivatives (acetoxyvalerenic acid, hydroxyvalerenic acid, and methyl valerenate) displayed a low toxicity with IC_{50} values between 100 and 200 µM. The cytotoxic potential of other compounds of the essential oil (valeranone, kessoglycl, monoacetate, kessoglycl diacetate, cryptofauronol, patchouli alcohol, and maaliol) were comparable to that of valerenic acid (see Table 1) (Bos and others 1998b).

Table 1 Cytotoxicity of constituents of *Valeriana officinalis*
(IC_{50} values [μM] ± standard error [95% confidence interval]; n = 3)

Constituent	GLC$_4$	COLO 320
Valepotriates		
Valtrate	1.4 ± 0.1	3.0 ± 0.3
Isovaltrate	2.5 ± 0.1	5.4 ± 0.5
Didrovaltrate	8.9 ± 0.4	15.2 ± 0.8
Acevaltrate	1.3 ± 0.1	3.6 ± 0.2
Isovaleroxyhydroxydidrovaltrate	2.4 ± 0.2	7.2 ± 0.2
Baldrinals		
Baldrinal	53 ± 2	111 ± 5
Homobaldrinal	31 ± 2	57 ± 10
Isovaltral	0.4 ± 0.1	1.2 ± 0.1
Valerenic Acids		
Valerenic acid	127 ± 9	124 ± 8
Acetoxyvalerenic acid	111 ± 8	124 ± 7
Hydroxyvalerenic acid	123 ± 4	165 ± 3
Methyl valerenate	115 ± 2	183 ± 14

Source: Bos and others (1998b). Reprinted with permission of *Phytomedicine*.

These same researchers conducted similar investigations to determine the cytotoxic potential of 70% ethanol extracts (1:5) (see Table 2). These extracts contained significantly lower concentrations of the compounds investigated than the crude material. Significant degradation of the valepotriates occurs during extraction by percolation, and almost complete deterioration of the valepotriates occurs within 2 months of the extract being stored (Bos and others 1998b).

Table 2 Cytotoxicity of *Valeriana officinalis* tinctures (1:5; 70% ethanol) (IC_{50} values ± standard error [95% confidence interval]; n = 3; in terms of the dilution causing 50% effect in the MTT assay)

	Fresh	Stored
GLC$_4$	1123 ± 57	311 ± 24
COLO 320	531 ± 17	145 ± 8

Source: Bos and others (1998b). Reprinted with permission of *Phytomedicine*.

Another group of researchers found that a mixture of isolated valepotriates (80% dihydrovaltrate, 15% valtrate, and 5% acevaltrate) administered orally at 6, 12, and 24 mg/kg ip for 30 days to female rats before and during pregnancy produced no significant toxic effects. An internal examination of fetuses indicated an increase in retarded ossification, though no changes were detected in postnatal development of the offspring (Tufik and others 1994).

A number of other studies have reported on the cytotoxic and mutagenic potential of valepotriates in in vitro cell systems and on the inhibition of DNA and protein synthesis in in vitro cultured mammalian cells (Bounthanh and others 1981; Hänsel 1990, 1992; Hude and others 1985, 1986; Keochanthala-Bounthanh and others 1990, 1993).

Despite these findings, valepotriates are considered to be of little toxicological concern because they are absent from most commercial products. These compounds are unstable and deteriorate rapidly in the intestines and are poorly absorbed (ESCOP 1990; Hendriks and others 1985). No significant negative effects have been

reported in toxicologic research with animals, and none have been reported in human clinical studies.

Lactation

Specific data are lacking. Based on a review of the available literature, no negative effects are to be expected.

Carcinogenicity

See Pregnancy, Mutagenicity, and Reproductive Toxicity.

Influence on Driving

The effect of a proprietary valerian and lemon balm preparation (Euvegal®) on the psychomotor and mental performance required for operation of machinery or driving of vehicles was tested in a placebo-controlled, double-blind study with 54 participants. A dose of 2 tablets twice daily of a 640 mg blend of valerian root extract and lemon balm leaf extract did not impair reaction time, concentration, or attentiveness as assessed by a battery of psychometric tests. The preparation also did not increase impairment due to alcohol with a blood level of 0.5% (Albrecht and others 1995).

Other researchers reported a slight, but statistically significant impairment of vigilance and retardation in processing of complex information in subjects consuming a higher dose of valerian (equivalent to 4 g containing a minimum of 1.2 mg of sesquiterpenes) (Gerhard and others 1996).

As with other sedatives, care should be taken when using valerian in the daytime while driving, if operating heavy machinery, or if engaged in activities requiring mental alertness.

Precautions

May cause drowsiness. Beacause valerian is considered to work in a manner similar to benzodiazepines, abrupt discontinuation after long-term use may result in withdrawal symptoms (Garges and others 1998).

Overdose

In an attempted suicide, 20 g of crude valerian powder was consumed. Thirty minutes after ingestion, the subject complained of fatigue, spasmodic abdominal pain, chest tightness, tremor of the hands and feet, and lightheadedness. The blood pressure appeared to be slightly low, but otherwise the physical examination was normal except for a bilateral widening of the pupils. Liver enzymes were subsequently found to be normal. The patient was treated with 2 doses of activated charcoal (approximately 400 mg each). All symptoms resolved within 24 hours of admittance (Willey and others 1995).

One other report of supposed valerian overdose has been published as a letter to the editor (Chan 1998). Central nervous system depression and anticholinergic poisoning were reported in patients consuming a product containing valerian (75 mg), hyoscine hydrobromide (0.25 mg), and cyproheptadine hydrochloride (2 mg). Average dosages consumed were approximately 33 times higher than the recommended dose.

According to the clinical literature of Eclectic physician Finley Ellingwood, large doses of valerian can "stimulate the brain causing headache, giddiness, perverted vision, restlessness, agitation, nausea" and large doses of oil can cause "increase of urine with slow pulse and drowsiness ending in deep sleep. It lessens sensibility, motility and reflex excitability, and if the dose be large enough, causes central paralysis" (Ellingwood and Lloyd 1900).

Toxicology

Acute toxicity of valerian is rare. Consumption of approximately 20 g (approximately 10 times the recommended therapeutic dosage) resulted in marked side effects, but failed to produce any significant toxicity (see Overdose) (Willey and others 1995). No reports of chronic toxicity have been reported when valerian is used at recommended therapeutic doses.

The LD_{50} for some valerian preparations and specific compounds has been established (see Table 3). In an early study, an LD_{50} for an ethanol extract of undefined strength was reported to be 3.3 g/kg ip in rats. At daily doses of 400-600 mg/kg ip for 45 days, no significant changes in weight, blood, or urine were observed when compared to controls (Rosecrans and others 1961). With oral doses of an alcohol extract equivalent to 300 and 600 mg/kg, no differences in growth, arterial pressure, weight of key organs, hematological nor biochemical parameters were observed (Fehri and others 1991).

In an early toxicologic study of the essential oil, a LD_{50} of 15g/kg in rats was reported. The oil was found to be the least toxic of 27 essential oils studied, including oils of peppermint and anise (Skramlik 1959). In studies with pure valerenic acid, 50 mg/kg reduced spontaneous motility, 100 mg/kg caused ataxia, 150-200 mg/kg caused muscle spasms, and 400 mg/kg caused heavy convulsions and death within 24 hours (Hendriks and others 1985).

There have been a number of reports associating consumption of valerian products with hepatotoxicity. MacGregor and others reported on the hepatotoxicity of valerian preparations which also reportedly contained skullcap *Scutellaria lateriflora* (MacGregor and others 1989). However, the botanical germander *Teucrium chamaedrys* L., a known hepatotoxic agent, commonly adulterates the skullcap market and may have been the causative agent. Subsequently, four other cases of hepatotoxicity which may have been related to long-term use of valerian have been reported. These products did not contain skullcap, therefore adulteration with germander is unlikely. The effect may have been idiosyncratic because a range of doses were used and consumption of products with greater amounts of valerian have not been implicated (Shaw and others 1997). It is not clear whether these different findings may be related to the type of extract used or different formulations.

Table 3 **Known LD_{50} values for valerian**

Constituent	LD_{50} mg/kg
Essential oil	15 g/kg rats (Skramlik 1959)
Ethanol extract	3.3 g/kg ip (Rosecrans and others 1961)
Valeranone	> 3 g/kg orally administered acute in rats and mice (Rücker and others 1978)
Valerenic acid	Approximately 300 mg/kg ip in mice (Hendriks and others 1985)

INTERNATIONAL STATUS

United States Regulated as a dietary supplement. Generally recognized as safe (GRAS) as a flavoring agent.

Australia Listed in the Australian Register of Therapeutic Goods.

Austria Included in the pharmacopoeia of Austria (Österreichisches Arzneibuch 1990).

Belgium Approved for the following indications: Traditionally used for reducing excitability in adults and children in cases of sleep disorders, although its activity has not been proven in accordance with the current evaluation criteria for medicines (Bradley 1992).

Canada Approved as a traditional herbal sleep aid. A Drug Identification Number (DIN) is required when claims are present. Regulated as a food supplement without claims.

Council of Europe Approved as a flavoring agent (Bradley 1992).

ESCOP Cited as a sedative, antispasmodic, and relaxant (ESCOP 1990).

European Pharmacopoeia Required to contain not less than 0.5% (*V*/w) volatile oil for the whole root and not less than 0.3% (*V*/w) volatile oil for the cut material (European Pharmacopoeia 1998).

France Included in the pharmacopoeia of France. Required to contain not less than 0.5% essential oil (Pharmacopée Française 1987). Approved for the following indications: Traditional medicine for the symptomatic treatment of nervous disorders in adults and children, particularly in case of minor sleep disorders (Bradley 1992).

Germany The crude herb, tincture, and dried extract are included in the pharmacopoeia of Germany. The crude herb is required to contain not less than 0.5% essential oil. Commission E: Approved for sleep disorders caused by nervous conditions (Blumenthal and others 1998).

Italy Included in the pharmacopoeia of Italy. Required to contain 0.5% essential oil (Pharmacopoea Italica 1991).

Switzerland Included in the pharmacopoeia of Switzerland. Required to contain not less than 0.5% essential oil. Tincture: 0.06% essential oil (Pharmacopoea Helvetica 8 1997). Approved by the Swiss registration authority for medicines as a sedative when used singly and in combinations. Indications include: Bei spannungszuständen, innerer Unruhe, Reizbarkeit, Nervosiät, Ein-und Durchschlafstörungen (stressful states, internal anxiety, irritability, nervousness, trouble sleeping through the night). Sold in pharmacies and drogueries.

United Kingdom Included in the British Pharmacopoeia. Required to contain not less than 0.5% (*V*/w) volatile oil for the whole root and not less than 0.3% volatile oil for the cut material. Approved as a sedative. General Sales List, Schedule 1, Table A(R1a) (Bradley 1992; British Pharmacopoeia 1998).

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