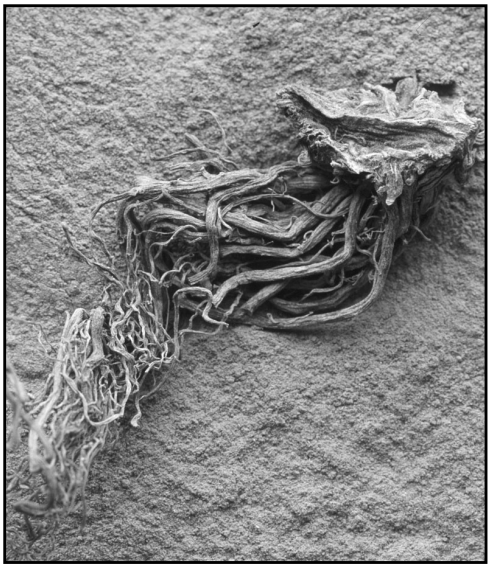
Valerian

Valeriana officinalis L. (syn. V. *exaltata* J.C. Mikan)

[Fam. *Valerianaceae*]

Overview

Valerian has a long history of use in western Europe as a sedative and sleep aid, with medicinal uses dating to Hippocrates' time (ca. 460-377 B.C.E.). In the U.S., valerian root is widely used in sleep aids and sedatives in alcoholic tincture, aqueous infusions, and crude root powdered and dried extracts in capsules and tablets. Valerian is often combined with other herbs traditionally known to promote sleep (e.g., hops, passionflower, lemon balm, lavender, and chamomile). Three such combination products have been clinically studied and are described in the proprietary products section of this book. Valerian ranked 8th in total sales in mainstream retail outlets in the U.S. in 2000, with sales totaling approximately $17 million.



Primary Uses

- Anxiety
- Insomnia
- Sleep disorders
- Restlessness based on nervous disorders

Other Potential Uses

- Increased mood related to enhanced sleep
- Fibromyalgia (in baths)

Pharmacological Actions

Improvement of mild-to-moderate sleeping disorders without adverse effects on REM sleep, and without significant hangover effects.

Dosage and Administration

No time limit has been set for the use of valerian by many authoritative sources. However, long term clinical trials (>30days) have not been conducted.

Internal

INFUSIONS: 2–3 g of fresh or dried root per cup, once to several times daily.

TINCTURE: 1/2–1 tsp. (1–3 ml), once to several times daily.

EXTRACTS: Amount equivalent to 2–3 g of crude herb, once to several times daily

TEA OR DRY EXTRACT (sleep aid): Single dose 1/2 to 1 hour before bedtime, with earlier dose in evening if necessary. Adult: Proportion dose according to body weight, as tea infusion or dry extract. Children 3–12 years old: With medical supervision only.

External

BATH: 100 g for 1 full bath; equivalent preparations.

Contraindications

The World Health Organization (WHO) contraindicates the use of valerian for children under 12 years without medical supervision. However, German authorities note clinical use of valerian in pediatrics is permissible at age 3 and up, as long as valepotriate and baldrinal-free preparations are used.

PREGNANCY AND LACTATION: WHO contraindicates the use of valerian during pregnancy because safety during pregnancy has not been established clinically. WHO also contraindicates valerian during lactation due to the lack of research in this area.

Adverse Effects

Unlike benzodiazepines, valerian appears to cause no residual morning sleepiness; however, it may slightly impair judgment and driving ability for 2–3 hours after intake. Chronic use of high doses of valerian (530 mg to 2 gm per dose, 5 times per day) over many years raises the possibility of withdrawal symptoms if the herb is abruptly discontinued. Rare adverse effects of valerian have included headache and stomach upset.

Drug Interactions

Although many authors have speculated on potential interactions between valerian, alcohol, barbiturates, and benzodiazepines in humans, such interactions have not been documented. Experimental animal data shows valerian potentiation of benzodiazepines.

Clinical Review

In 29 clinical studies on valerian (5,201 participants), all studies demonstrated positive effects for indications including anxiety, sleep disorders, and mood. The majority of clinical trials have consistently demonstrated that valerian is significantly more effective than placebo in improving sleep in persons with sleep

disturbances. Modern human studies have investigated its use in combination with hops, as an alternative to benzodiazepine to treat nonchronic and nonpsychiatric sleep disorders; its use in combination with hops as a sedative to treat disturbed sleep; its effects in combination with hops (*Humulus lupulus*) on driving safety; its use in combination with St. John's wort (*Hypericum perforatum*) as an alternative to diazepam to treat symptoms of anxiety; and its use in combination with camphor, night-blooming cereus (*Selenicereus grandiflorus*), and hawthorn (*Crataegus* spp.) to treat functional cardiovascular disorders, hypotension, or meteorosensitivity. Two double-blind, placebo-controlled (DB, PC) studies concluded that valerian in combination with lemon balm (*Melissa officinalis*) improved sleep quality for insomniacs, and a third concluded it did not impair driving or operating heavy machinery. One randomized (R), DB, PC cross-over study found a valerian, hops, and lemon balm combination effective for individuals experiencing sleep difficulties. One R, DB, controlled study concluded that valerian did not adversely influence alertness, reaction time, or concentration. The approved modern therapeutic applications for valerian appear to be supported by its history of use in well established systems of traditional and conventional medicine, many supporting *in vitro* and *in vivo* pharmacological experiments in animals, extensive phytochemical investigations, and human clinical studies—all of which tend to show CNS depressant activities.

Valerian

Valeriana *officinalis* L. (syn. V. *exaltata* J.C. Mikan)
[Fam. *Valerianaceae*]

Overview

Valerian has a long history of use in western Europe as a sedative and sleep aid, with medicinal uses dating back to Hippocrates' time (ca. 460-377 B.C.E.). In the U.S., valerian root is widely used in sleep aids and sedatives in various forms including teas, tablets, and capsules. Often, valerian is combined with other herbs traditionally known to promote sleep including hops, passionflower, lemon balm, chamomile, and lavender.

Uses

Anxiety; insomnia; sleep disorders; restlessness linked to nervous disorders; enhanced mood based on improved sleep.

Dosage

No duration limit has been set for the use of valerian.

INFUSION (tea): 2–3 g of fresh or dried root per cup, once to several times daily.

TINCTURE: 1/2–1 tsp. (1–3 ml), once to several times daily.

EXTRACTS: Amount equivalent to 2–3 g of crude herb, once to several times daily.

TEA OR DRY EXTRACT (sleep aid): Single dose 1/2 to 1 hour before bedtime, with earlier dose in evening if necessary. Adults: Proportion dose according to body weight, as tea infusion or dry extract; Children 3–12 years old: With professional supervision only.

Contraindications

Consult with a healthcare provider before using in children under 12 years. German pediatric authorities claim that valerian may be used in children age 3 and up, provided the preparations are free of the active compounds valepotriates and baldrinal.

PREGNANCY AND LACTATION: Valerian should not be taken during pregnancy because its safety during pregnancy has not been established clinically. Valerian is contraindicated during breast-feeding because of the lack of research in this area. However, experimental animal data suggest safety of valerian extracts; no adverse effects on fertility or fetotoxicity have been observed.

Adverse Effects

Valerian is considered generally safe. Unlike benzodiazepines, valerian appears to cause little or no residual morning sleepiness. However, it may slightly impair judgment and driving ability for 2–3 hours after intake. Adverse effects may include headache and stomach upset, but these effects are rare.

Drug Interactions

Valerian may potentially interact with alcohol, barbiturates, and benzodiazepines, but these interactions have not been clinically proven in humans.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

Valerian

Valeriana officinalis L. (syn. V. *exaltata* J.C. Mikan)

[Fam. *Valerianaceae*]

Overview

Valerian has a long history of use in Western Europe as a sedative and sleep aid, with medicinal use dating to Hippocrates (ca. 460–377 B.C.E.) (Blumenthal *et al.*, 2000). Valerian is used in countless preparations worldwide. In the U.S., for example, valerian root is known extensively as a dietary supplement in the form of alcoholic tinctures, aqueous infusions (teas), and as a crude-root, powdered and dried extract in capsules and tablets. Often, valerian is combined with other herbs traditionally known to promote sedation or sleep, e.g., hops (*Humulus lupulus*), passion flower (*Passiflora incarnata*), and lemon balm (*Melissa officinalis*) (Blumenthal *et al.*, 1998). Three such combination products have been clinically studied and are described in the section of this book dealing with proprietary products. Valerian ranked eighth in total sales in mainstream retail outlets in the U.S. in 2000, with sales totaling approximately $17 million (Blumenthal, 2001).

Valerian root and two of its preparations, valerian root powder and valerian extract, are official in the *United States Pharmacopeia* (USP) 25th edition, and *National Formulary* (NF) 20th edition. Crude valerian root, fluid extract, alcoholic tincture, and ammoniated tincture were formerly official in the USP from 1820 through 1930 (Boyle, 1991; Lloyd, 1929) and the NF (Grieve, 1979; Leung and Foster, 1996). Valerian root is official in the national pharmacopeias of Austria, France, Great Britain, Hungary, Russia, and Switzerland, among others (Blumenthal *et al.*, 2000). In Germany, valerian is official in the *German Pharmacopoeia,* and approved in the Commission E monographs for its sedative and sleep-promoting activity (Blumenthal, *et al.*, 1998).

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Description

Valerian root extract consists of the fresh or carefully dried (below 40°C) subterranean parts of *Valeriana officinalis* L. (syn. *V. exaltata* J.C. Mikan) [Fam. *Valerianaceae*] (Blumenthal *et al.*, 1998), including the rhizome, roots, and stolons. The whole dried root contains no less than 0.5% (*v/m*) volatile oil, and the cut dried root contains no less than 0.3% (*v/m*) volatile oil. The dried root contains no less than 0.17% of sesquiterpenic acids expressed as valerenic acid, calculated with reference to the dried drug (Ph. Eur. 2001). The NF requires dried valerian root to contain no less than 0.5% volatile oil, and not less than 0.05% valerenic acid (USP-NF, 1999). Valerian root dry extract consists of the native extractive yielded from comminuted valerian root, extracted in 70% alcohol, manufactured according to the *German Pharamacopoeia* monograph. The drug-to-extract ratio ranges from 3:1 to 6:1 (*w/v*) (DAB, 1999). The NF requires that the dry extract contain no less than 0.3% of valerenic acid, with a drug-to-extract ratio between 4:1 and 7:1 (USP, 2002).

Primary Uses

Neurology

- Anxiety: The World Health Organization (WHO) lists uses supported by clinical data, including as a mild sedative and sleep-promoting agent; a milder alternative or possible substitute for stronger synthetic sedatives (e.g., benzodiazepines); and for treatment of nervous excitation and sleep disturbances induced by anxiety (WHO, 1999). This indication is supported by numerous clinical trials (Bourin *et al.,* 1997; Sousa *et al.,* 1992; Kohnen and Oswald, 1988; Panijel, 1985; Boeters, 1969).
- Insomnia: The German Commission E approved the use of valerian for sleep disorders, insomnia, and restlessness based on nervous disorders (Blumenthal *et al.*, 1998). The European Scientific Cooperative on Phytotherapy (ESCOP) notes that valerian is used for "tenseness, restlessness, and irritability, with difficulty in falling asleep" (ESCOP, 1997). These approved indications are supported by numerous clinical trials of varying size, design, and duration for various types of valerian preparations (i.e., valerian only, valerian with other sedative herbs, and valepotriate-only preparations) (Dominguez *et al.,* 2000; Dorn, 2000; Donath *et al.,* 2000; Cerny and Schmid, 1999; Rodenbeck *et al.,* 1998; Schmitz and Jackel, 1998; Dressing *et al.,* 1996; Orth-Wagner, 1995; Schultz *et al.,* 1994; Dressing and Reimann, 1992; Lindahl and Lindwall, 1989; Balderer and Borberly, 1985; Leatherwood and Chauffard, 1985; Gessner and Klasser, 1984; Leatherwood *et al.,* 1982).

Other Potential Uses

- Increased mood related to enhanced sleep (Vorbach *et al.,* 1996; Kamm-Kohl *et al.,* 1984)
- Fibromyalgia (as bath) (Ammer and Melnizky, 1999)

Dosage

Internal

Infusions: 2–3 g of fresh or dried root per cup, one to several times daily (Blumenthal *et al.*, 1998).

Tincture: 1/2–1 teaspoon (1–3 ml), one to several times daily (Blumenthal *et al.*, 1998).

Extracts: Amount equivalent to 2–3 g of crude herb, one to several times daily (Blumenthal, *et al.*, 1998).

Tea or dry extract (sleep aid): Single dose 1/2 to 1 hour before bedtime, with an earlier dose in the evening, if necessary (ESCOP, 1997). For adults, the dose should be in proportion to body weight; use as a tea infusion or dry extract. Children from 3–12 years old should use valerian only under medical supervision (ESCOP, 1997).

External

Bath: 100 g for one full bath; equivalent preparations (Blumenthal *et al.*, 1998).

Infusion: 2–3 g, in 150 ml water (Blumenthal, *et al.*, 1998).

Duration of Administration

Many authoritative sources have set no time limit for the use of valerian (Blumenthal *et al.*, 1998; ESCOP, 1997; WHO, 1999; Upton, 1999). Although long-term valerian use in European clinical practice indicates relative safety, clinical trials of longer than 30 days have not been conducted.

Chemistry

Valerian contains over 150 chemical constituents, many of which are physiologically active. The primary active constituents can be divided into four categories: the essential oils and their sesquiterpenes (e.g., valerenic acid), the iridoids (iridoid esters: valepotriates, valtrate, isovaltrate, acevaltrate, dihydrovaltrate, and isovaleroxyhydroxydihydrovaltrate [IVHD] and their degradation products [baldrinal and derivatives]), amino acids (arginine, GABA, glutamine, tyrosine), and alkaloids (Upton, 1999; Bruneton, 1999; Leung and Foster, 1996). The iridoids are chemically unstable and degrade in moisture, heat (above 40°C), or acidity (pH<3) to baldrinal and isopropylbaldrinal (Bruneton, 1999) and, therefore, are not found in most commercial preparations (Blumenthal *et al.,* 1998). Other constituents include caffeic acid, chlorogenic acid, β-sitosterol, methyl 2-pyrrolketone, choline, tannins, gum, alkaloids, and resin (Bradley, 1992; ESCOP, 1997; Newall *et al.*, 1996).

Pharmacological Actions

Human

Coronary artery dilating and anti-arrhythmic effects. Valerian is included in a German heart tonic to maintain neuro-cardiac stability (Mowrey, 1986). In an open, multi-center trial of 2,243 patients with a variety of functional cardiac disorders, an herbal combination (valerian, hawthorn [*Crataegus* spp.], night-blooming cereus [*Selenicereus grandiflorus*], and camphor [*Cinnamomum camphora*]) was associated with improvement (Bussany-Caspari, 1986). No controlled trials have evaluated valerian's effects in patients with specific cardiovascular disorders.

Sedative-hypnotic. Case series and randomized controlled trials have demonstrated valerian extract is effective in treating mild-to-moderate sleeping disorders without adverse effects on REM sleep, and without significant hangover effects (See the table, "Clinical Studies on Valerian," at the end of this monograph).

Animal

Coronary artery dilating and anti-arrhythmic effects. Valepotriates prevented the appearance of acute coronary insufficiency, abolished vasopressin-induced arrhythmia, provoked a short-lived increase in coronary blood flow, and had moderate positive inotropic and negative chronotropic effects (Petkov, 1979). In mice, valeranone, found in small quantities in valerian and in larger amounts in its relative, *Nardostachys jatamansii*, exerted weak hypotensive effects (Morazzoni and Bombardelli, 1995). In cats, intravenous injection of valerian extracts produced a significant increase in coronary blood flow, a transient fall in blood pressure, and a decrease in heart rate (Zhang *et al.*, 1982).

Spasmolytic. In guinea pig ileum, valerenic acid, valtrate, and valeranone exert a spasmolytic action through direct effects on smooth muscle (Hazelhoff *et al.*, 1982; Wagner and Jurcic, 1979).

Sedative-hypnotic. In mice, intraperitoneal injections of valerenic acid, valerenal, and whole herb extracts produced significant sedation, ataxia, and anti-convulsant effects (Hendriks *et al.*, 1981; Veith *et al.*, 1986). Intraperitoneal injections of 100 mg/kg had sedative effects as strong as barbiturates, doses of 400 mg/kg led to death (Hendriks *et al.,* 1985). In comparison with diazepam and chlorpromazine, valerian extract had weak anti-convulsive properties (Leuschner *et al.*, 1993). Valerian root extract (Valdispert®) reduced motility and increased thiopental-induced and pentobarbital-induced sleeping time (Capasso *et al.*, 1996; Hiller, 1996; Leuschner *et al.*, 1993). The aroma of valerian root exerted sedative effects in mice (Buchbauer *et al.*, 1992). In rats, valerian had sedative effects on electroencephalogram (EEG) activity (Fink and Hoelzl, 1984). Valerian extract, but not its individual chemical constituents, significantly decreased glucose metabolism in the brain (Grusla *et al.*, 1986). Valepotriates suppressed symptoms associated with diazepam withdrawal in rats (Andreatini and Leite, 1994). This has led some authors and clinicians to propose that valerian may be useful in treating benzodiazepine withdrawal syndrome in humans (Brinker, 2001; Rasmussen, 1997). Cats given 10 mg/kg of a valerian extract by gastric lavage had a significant decrease in restless, fearful, and aggressive behaviors (vonEickstedt, 1969). Unlike diazepam, valerian did not affect spontaneous ambulation, rearing, or approach-avoidance conflict in mice in a water-lick conflict test. However, valerian and imipramine significantly inhibited immobility induced by a forced swimming test in rats, and significantly reversed reserpine-induced hypothermia in mice, leading researchers to conclude that valerian may be a useful antidepressant (Sakamoto *et al.*, 1992).

In vitro

Valerian extracts containing amino acids and valerenic acid bind weakly with the GABA (A) receptor in rat brain assays (Ferreira *et al.*, 1996; Holzl and Godau, 1989; Mennini *et al.,* 1993). In rat brain cortex, aqueous extract of valerian inhibited the uptake and stimulated the release of GABA, leading to increased concentrations of GABA in synaptic clefts (Santos *et al.*, 1994a; 1994b; 1994c); these effects may be due in part to the presence of GABA in valerian root extracts (Cavadas *et al.*, 1995), or may be due to valerenic acid's ability to inhibit GABA breakdown (Riedel *et al.,* 1982; Wichtl and Bisset, 1994; Hendriks *et al.*, 1981).

Mechanism of Action

Although the sedative effects of valerian have been demonstrated in human clinical studies, scientists have struggled to agree upon the single chemical compound responsible for valerian's activity. Valerian's effects on the central nervous system (CNS) have been attributed variously to valepotriates, their breakdown products (baldrinals), valerenic acid, valerenal, and valeranone, and other constituents in the essential oil (Wichtl and Bisset, 1994; Bradley, 1992; Houghton, 1988; Hendriks, *et al.*, 1981, 1985; Hendriks, 1977; Holzl, 1998; Wagner, 1980). Multiple compounds may work together synergistically to produce a sedative effect (Upton *et al.*, 1999; Houghton 1999; Weiss and Fintelmann, 2000). Animal studies show that valerenic acid may inhibit enzymes that break down GABA, thus increasing GABA levels and producing a CNS-depressing effect (Newall *et al.,* 1996). An *in vitro* study to elucidate the sedative activity of valerian demonstrated that valerian extract LI 156 acted upon the melatonin receptor in a dose-dependent manner. This effect was not associated with valerenic acid (Fauteck *et al.,* 1996).

Contraindications

As a general precaution, the WHO contraindicates the use of valerian during pregnancy and lactation, and for children younger than 12 years without medical supervision (WHO, 1999). ESCOP also mentions these same precautions, but contraindicates valerian in children less than three years old. However, German authorities note that the clinical use of valerian in pediatrics is permissible beginning at age three, as long as valepotriate- and baldrinal-free preparations are used (Schilcher, 1997).

Pregnancy and Lactation: ESCOP and the WHO contraindicate valerian during pregnancy due to fact that its safety during pregnancy has not been established clinically (ESCOP, 1997; WHO, 1999). However, in pregnant rats given valepotriates for 30 days, there was no impact on fertility, no fetotoxicity, and no other adverse effect on mother or offspring (Tufik *et al.*, 1994). Research on potential mutagenicity and carcinogenicity of valerian preparations has shown that official valerian preparations are extremely low in valepotriates and that these compounds are mostly destroyed in the extraction process (Bos *et al.,* 1998; WHO, 1999).

Adverse Effects

Unlike benzodiazepines, valerian appears to cause no residual morning sleepiness; however, it may slightly impair judgment and driving ability for two to three hours after intake (Gerhard *et al.*, 1996). Chronic use of high doses of valerian (530 mg to 2 gm per dose, five times per day) for many years raised the possibility that withdrawal symptoms may occur if the herb is discontinued abruptly as documented in a case report of a 58 year-old man who had been taking valerian with numerous conventional drugs (Garges *et al.*, 1998). An authoritative German pharmaceutical text (Hobbs, 1979), suggests that continued use may cause minor side effects e.g., headaches, excitability, and insomnia, but subsequent review by the German Commission E did not find sufficient basis to include these side effect in its official monograph on valerian originally published in 1985 and revised in 1990. Cytotoxic effects have been reported *in vitro*, but the compounds responsible for these effects (valepotriates) decompose rapidly during storage and following oral administration (Bos *et al.*, 1998; Bounthanh *et al.*, 1981). In a study of 23 patients taking a nonprescription valerian extract preparation (doses from 0.5 to 12.0 grams), no acute or subclinical evidence of liver damage was observed (Chan, 1998; Chan *et al.*, 1995). The adverse effects of valerian include rare cases of headache and upset stomach (Leathwood and Chauffard, 1982; Leathwood *et al.*, 1982; Schulz *et al.*, 2001). However, an intentional overdose as high as 20 grams, 20 times the normal daily dose of powdered root in capsules (40–50 capsules at 470 mg per capsule), was not associated with significant morbidity. The patient was released from the hospital within 24 hours of admission (Willey *et al.*, 1995). In one report of intentional abuse, a young adult drug user attempted to induce a psychoactive effect by injecting an alcoholic solution of valerian; he became ill, but recovered over the next three days (Mullins and Horowitz, 1998).

Drug Interactions

Animal studies suggest that valerian may potentiate the sedative effects of barbiturates (Brinker, 2001; Hendriks *et al.*, 1981; Hiller, 1996; Leuschner *et al.,* 1993; Sakamoto *et al.*, 1992). Although some authors have speculated on potential interactions between valerian, alcohol, barbiturates, and benzodiazepines in humans, no such interactions have been documented (Braeckow *et al.*, 1972; Brinker, 2001; Miller, 1998). One study found no potentiating effects of valerian on alcohol's impact on concentration, attentiveness, reaction time, or driving performance (Albrecht, 1995).

American Herbal Products Association (AHPA) Safety Rating

Class 1: Herbs that can be safely consumed when used appropriately (McGuffin *et al.*, 1997).

Regulatory Status

Austria: Official in *Austrian Pharmacopoeia* (Meyer-Buchtela, 1999; Upton, 1999).

Belgium: Oral use as Traditional Herbal Medicine (THM), accepted for specific indications (Bradley, 1992).

Canada: Dried root in tablet, capsule, powder, extract, tincture, or tea bags labeled as THM indicated as sleep aid or sedative; requires premarket authorization and assignment of a Drug Identification Number (DIN) and conformance with the Valerian Labeling Standard (Health Canada, 1996).

European Union: "Whole," dried, underground parts containing no less than (NLT) 0.5% volatile oil, and "cut," dried, underground parts (NLT 0.3% volatile oil; NLT 0.17% sesquiterpenic acids), official in *European Pharmacopoeia* (Ph. Eur., 2001).

France: Oral use as THM accepted for specified indications (Bradley, 1992). Dried root (NLT 0.5% volatile oil), official in *French Pharmacopoeia* (Upton, 1999).

Germany: Dried root, for preparation of tea infusion, tincture, or extract is an approved nonprescription drug of the German Commission E Monographs (Blumenthal *et al.*, 1998). Tea infusion and hydro-alcoholic tincture forms are approved nonprescription drugs of the *German Standard License* monographs (Braun *et al.*, 1986 and 1996). Extract or volatile oil for balneotherapy (bath therapy) is approved in the German Commission B8 Monographs (Wichtl and Bisset, 1994). Dry native extract, 3–6:1 (*w/w*), is official in *German Pharmacopoeia* (DAB, 1999). The mother tincture (and liquid dilutions) of dried root are official preparations of the *German Homeopathic Pharmacopoeia* (GHP, 1993)

ITALY: Dried root (NLT 0.5% volatile oil) official in *Italian Pharmacopoeia* (Ph. Ital. 1991).

RUSSIAN FEDERATION: Official in *State Pharmacopoeia of the Union of Soviet Socialist Republics* (Bradley, 1992; Newall *et al.*, 1996).

SWEDEN: Classified as Natural Remedy for self-medication requiring advance application for marketing authorization. A valerian monograph is published in the Medical Products Agency (MPA) "Authorised Natural Remedies," which lists four registered monopreparations, and 10 multiple-herb (with passionflower, lemon balm, or hops) preparations (MPA, 1997 and 2001; Tunón, 1999). Two valerian products (Baldrian-Dispert and Neurol) are regulated as *Pharmaceutical Specialties*, or conventional over-the-counter (OTC) drugs (Tunón, 1999).

SWITZERLAND: Herbal medicine with positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; Ruppanner and Schaefer, 2000). There are 62 valerian phytomedicines and 11 homeopathic preparations listed in the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2000). Dried root official in *Swiss Pharmacopoeia* 1997 (Meyer-Buchtela, 1999; Upton, 1999).

U.K.: *General Sale List* (GSL), Schedule 1, Table A (Bradley, 1992). Dried root (NLT 0.5% volatile oil) and powdered dried root (NLT 0.3% volatile oil) official in *British Pharmacopoeia* (Health Canada, 1996; Upton, 1999).

U.S.: Generally Recognized as Safe (GRAS) (US FDA, 1998). Dietary supplement (USC, 1994). Application for OTC approval for use as a nighttime sleep aid is pending (Pinco and Israelsen, 1994). Valerian root (NLT 0.5% volatile oil; NLT 0.05% valerenic acid) and powdered valerian (NLT 0.3% volatile oil; NLT 0.04% valerenic acid) are official in *U.S. National Formulary* (USP, 2002). Powdered valerian extract, 4~7:1 (*w/w*) (NLT 0.3% valerenic acid) added to NF 19 1st Supplement (USP, 2000). The mother tincture 1:10 (*w/v*), 55% alcohol (*v/v*), of fresh or dried root, is an OTC Class C drug official in *Homeopathic Pharmacopoeia of the United States* (HPUS, 1993).

Clinical Review

Twenty-nine studies are outlined in the following table, "Clinical Studies on Valerian," including more than 5,200 participants. All studies found positive effects for indications including anxiety, sleep disorders, and mood. Five studies (480 participants) report on the effectiveness of valerian for anxiety (Bourin *et al.*, 1997; Sousa *et al.*, 1992; Kohnen and Oswald, 1988; Panijel, 1985; Boeters, 1969). The majority of clinical trials have consistently demonstrated that valerian is significantly more effective than a placebo in improving sleep in persons with sleep disturbances (Balderer and Borbely, 1985; Chauffard *et al.*, 1982; Dressing *et al.*, 1996; Donath *et al.,* 2000; Dorn, 2000; Dressing and Riemann, 1992; Gessner and Klasser, 1984; Jansen, 1977; Kamm-Kohl *et al.,* 1984; Leathwood and Chauffard, 1982, 1985; Leathwood *et al.*, 1982; Lindahl and Lindwall, 1989; Orth-Wagner *et al.*, 1995; Rodenbeck *et al.,* 1998; Schellenberg *et al.,* 1994; Schmidt-Voigt, 1986; Schmitz and Jackel, 1998; Schulz *et al.,* 1994; Vorbach *et al.*, 1996). Modern human studies have investigated the use of valerian in combination with hops, as an alternative to benzodiazepine to treat nonchronic and nonpsychiatric sleep disorders (Schmitz and Jackel, 1998); its use in combination with hops as a sedative to treat disturbed sleep (Fussel *et al.,* 2000; Vonderheid-Guth *et al.*, 2000; Lataster *et al.*, 1996; Vorbach *et al.,* 1996; Kammerer, 1993); its effects in combination with hops on driving safety (Gerhard *et al.,* 1996; Kammerer *et al.,* 1996); its use in combination with St. John's wort (*Hypericum perforatum*) as an alternative to diazepam to treat symptoms of anxiety (Panijel, 1985); and its use in combination with camphor, night-blooming cereus (*Selenicereus grandiflorus*), and hawthorn (*Crataegus* spp.) to treat functional cardiovascular disorders, hypotension, or meteorosensitivity (Busanny-Caspari, 1986). Three double-blind, placebo-controlled (DB, PC) studies concluded that valerian in combination with lemon balm (*Melissa officinalis*) improved sleep quality for insomniacs (Dressing *et al.*, 1996; Dressing and Reimann, 1992), and did not impair driving or operating heavy machinery (Albrecht *et al.,* 1995). A randomized (R), DB, PC, crossover study found a combination of valerian, hops, and lemon balm helpful for individuals experiencing sleep difficulties (Lindahl and Lindwall, 1989). A recent R, DB, controlled study concluded that valerian did not adversely influence alertness, reaction time, or concentration (Kuhlmann *et al.,* 1999).

The approved modern therapeutic applications for valerian appear to be supported by its history of use in well-established systems of traditional and conventional medicine, *in vitro* and *in vivo* pharmacological experiments on animals, extensive phytochemical investigations, and human clinical studies, all of which tend to show valerian's central nervous system-depressant activities (Blumenthal *et al.*, 2000).

Branded Products*

Alluna™: GlaxoSmithKline / One Franklin Plaza / Philadelphia, PA 19102 / U.S.A. / Tel: 888-825-5249 / www.gsk.com. Each tablet contains 500 mg valerian extract (4-6:1) with 120 mg hops extract (5-7:1).

Euphytose®: Roche Nicholas SA / 33 rue de l'Industrie / 74240 Gaillard / France / Tel: +33-04-50-87-7070. Six herbs, including *Crataegus*, *Ballota*, *Passiflora*, *Valeriana*, *Cola*, and *Paullinia*.

Euvegal® forte: Dr. Willmar Schwabe Pharmaceuticals / International Division / Willmar Schwabe Str. 4, D-76227 / Karlsruhe / Germany / Tel: +49-721-4005 ext. 294 / www.schwabepharma.com / Email: melville-eaves@schwabe.de. Each tablet contains 160 mg valerian root extract 4.5:1 and 80 mg lemon balm leaf extract 5.5:1.

Harmonicum Much®: Prof. Dr. Much AG. Information on manufacturer and current product status unavailable.

Hova®: Gebro Pharma GmbH / A-6391 Fieberbrunn / Austria / Tel: +43-53-54-5300-0 / Fax: +43-53-54-5300-0 / www.gebro.com / E-mail: pharma@gebro.com. Each tablet contains 60 mg valerian and 30 mg hop flower extract.

Ivel®: Kanoldt Arzneimittel GmbH / c/o Knoll AG / Knollstrasse 50 / 67008 Ludwigshafen / Germany / Tel: +49-06-21-5890 / Fax: +49-06-21-5892-896 / www.knoll.de / Email: info@knoll.de. Each tablet contains 500 mg valerian extract (4-6:1) with 120 mg hops extract (5-7:1).

LI 156: Lichtwer Pharma AG / Wallenroder Strasse 8-14 / 13435 / Berlin / Germany / Tel: +49-30-40-3700 / Fax: +49-30-40-3704-49 / www.lichtwer.de. Each tablet contains 300 mg dry extract of valerian with a drug/extract ratio of 5:1.

Nature's Way® Valerian Root capsules: Nature's Way Products, Inc. / 10 Mountain Spring Parkway / Springville, UT 84663 / U.S.A. / Tel: (801) 489-1500 / www.naturesway.com. Each

capsule contains 530 mg valerian root with a guaranteed natural potency of 0.1% valerenic acids.

Novo-Baldriparan®: Novo-Nordisk A/S / Novo Allé / 2880 Bagsværd / Denmark / Tel: +45-4444-8888 / Fax: +45-4449-0555 / E-mail: webmaster@novonordisk.com. This product is no longer available.

ReDormin®: Zeller AG / Seeblickstrasse 4 / CH-8590 Romanshorn 1 / Switzerland / www.zellerag.ch. Contains valerian extract ZE91019.

Sedariston® Konzentrat: Steiner Arzneimittel / Postfach 450520 / 12175 Berlin / Germany / Tel: +49-03-07-1094-0 / Fax: +49-03-07-1250-12 / www.steinerarznei-berlin.de. Tablets each contain 50 mg of valerian and 100 mg of St. John's wort.

Sedonium®: Lichtwer Pharma AG. Contains valerian extract LI 156.

Songha Night®: Pharmaton Natural Health Products / P.O. Box 368 / Ridgefield, CT 06877 / U.S.A. / Tel: 800-451-6688 / Fax: 203-798-5771 / www.pharmaton.com / Email: askpharmaton@rdg.boehringer-ingelheim.com. Each coated tablet contains 120 mg valerian extract and 80 mg lemon balm extract.

Valdispert®: Solvay Arzneimittel GmbH / Hans-Bockler-Allee 20 / Hannover 30173 / Germany / Tel: +49-511-8-5724e +006 / Fax: +49-511-8-57312e +006 / www.solvay.com. Unable to verify dosage or manufacturing status.

Valdispert® forte: Solvay Arzneimittel GmbH. Each tablet contains 45 mg *Valeriana officinalis* radix dry aqueous alkaline extract (5–6:1), corresponding to 225–270 mg of dried root, standardized to contain 0.05 mg valerenic acid and acetoxyvalerenic acid.

Valerina Natt®: Pharbio Medical International AB / c/o Cederroth International AB / Box 715 / S-19427 Upplands Väsby / Sweden / Tel: +46-85-90-9630-0 / Fax: +46-85-90-9647-1 / Email: info@cederroth.com / www.pharbio.cederroth.com. Contains 100 mg valerian extract (4:1), corresponding to 400 mg dried root; 45 mg hops (*Humulus lupulus*) extract (8.5:1), corresponding to 382 mg dried strobile; 25 mg lemon balm (*Melissa officinalis*) leaf extract (6.5:1), corresponding to 162 mg dried leaf; and 275 mg of excipient materials.

Valmane®: Lyssia GmbH / c/o Solvay Arzneimittel GmbH. Each tablet contains 50 mg of a valepotriate mixture. Unable to verify current availability of product.

Valverde®: Ciba-Geigy AG / Novartis Consumer Health AG / Route de l'Etraz / CH 1260 Nyon 1 / Switzerland / www.consumer-health.novartis.com. This product is no longer available.

Ze91019: Zeller AG / Seeblickstrasse 4 / CH-8590 Romanshorn 1 / Switzerland / www.zellerag.ch. Extract used in Alluna™ Sleep, Ivel®, and ReDormin®.

* American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Valerian (*Valeriana officinalis* L.)

Anxiety

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Sousa, 1992	Anxiety	R, DB, C n=80 adult patients with various anxiety syndromes		270 mg/day or 30 mg clobazam/day	Valdispert® or clobazam 30 mg/day	The valerian preparation was as effective and well-tolerated as clobazam, according to the Hamilton Anxiety Rating Scale and the Leeds anxiety questionnaire.
Kohnen and Oswald, 1988	Anxiety	DB n=48 adults placed in an experimental situation of social stress	24 hours	100 mg valerian or 20 mg propranolol or a combination of the 2	Valerian extract (brand not stated)	The valerian preparation reduced subjective sensations of anxiety, but the study did not demonstrate any difference between groups.
Boeters, 1969	Anxiety	O n=70 hospitalized patients with dysregulation of the autonomic nervous system due to various etiologies	7 days to 3 months	150–300 mg/day valepotriate mixture	Valmane®	Functional cardiac disorders, tachycardia, hypertension, sweating, restless legs, and other dysregulations were influenced positively by Valmane®. The preparation produced mildly sedative effects and was effective in treatment of restlessness and tension. Apart from mild daytime fatigue, no evidence of somatic adverse effects or psychotropic effects was observed.

Combination Preparations

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Bourin *et al*, 1997	Anxiety	R, PC n=182 patients diagnosed with adjustment disorder and anxious mood	4 weeks	2 tablets 3x/day	Euphytose® (six herbs including *Crataegus, Ballota, Passiflora, Valeriana, Cola*, and *Paullinia*)	Significant improvement in Hamilton anxiety scores comparing combination product to placebo (p=0.012).
Panijel, 1985	Anxiety	DB, C n=100 adults suffering from anxiety disorders	2 weeks	1 tablet/day (50 mg of valerian and 100 mg of St. John's wort /day) or 2 mg diazepam 2x/day	Sedariston® Konzentrat (providing 50 mg of valerian and 100 mg of St. John's wort)	The herbal combination was reportedly effective in 78% vs. only 54% of the diazepam group (p<0.01). Side effects were reported by only 4% of those taking the herbs vs. 14% of those taking diazepam.

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Clinical Studies on Valerian (*Valeriana officinalis* L.) (cont.)

Sleep

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Dominguez *et al.*, 2000	Sleep	O, case study n=20 sleep questionnaires	2 weeks	1–3, 470 mg capsules before bed	Nature's Way® valerian root capsules	Global improvement at Week 2 was significantly better than at Week 1 (Wilcoxon ranks test, p=0.005), perhaps reflecting a time-dependent or dose-response relationship. This case study suggests that valerian can be an agent for improving insomnia in a symptomatic population.
Donath *et al.*, 2000	Sleep	R, PC, DB, CO n=16 men and women with previously established psychophysiological insomnia (ICSD-code 1.A.1.) (mean age 49)	Single dose and 14 days vs. placebo with 13 day washout between	Two, 300 mg capsules dry extract of valerian 1 hour before bedtime vs. placebo	Sedonium® and placebo	No effects on sleep structure and subject sleep assessment were observed after a single dose of valerian. Sleep efficiency increased significantly after multi-dose treatment for both valerian and placebo, compared to baseline polysomnography. However, slow-wave sleep (SWS) latency was reduced after multi-dose treatment with valerian compared with placebo (13.5 vs. 21.3 min., p<0.05). Compared to baseline, SWS percentage of time in bed was increased with valerian (8.1% vs. 9.8%, p<0.05). An extremely low number of adverse events were observed during the valerian treatment period compared with the placebo period (3 vs. 18). Because valerian showed positive effects on sleep structure and sleep perception of insomnia patients, the authors suggest valerian can be recommended for treatment of patients with mild psychophysiological insomnia.
Dorn, 2000	Insomnia	R, DB, Cm n=70	4 weeks	Two, 300 mg tablets 30 minutes before bedtime or 5 mg oxazepam tablet	LI 156 300 mg valerian dried extract tablets; oxazepam 5 mg	In both groups, sleep quality improved significantly (p<0.001), but no statistically significant difference could be found between groups (p=0.70). Effect varied between groups and was between 0.02 and 0.25, with a more favorable adverse effect profile of valerian compared to oxazepam. Primary outcome was measured by the factor "sleep quality". Secondary outcomes were other sleep characteristics including well-being and anxiety (HAMA).
Vorbach, 1996	Sleep quality	C n=121 patients with non-organic sleep disturbances for at least 4 weeks	4 weeks	Two, 300 mg tablets/day	Sedonium® (LI 156)	Four standard rating scales were employed. Significant improvement in sleep quality, feeling of refreshment after sleep, and well-being during the day; no significant side effects reported. Results were observed after 2–4 weeks of use, with no acute effects during first days of study.
Schulz *et al.*, 1994	Sleep	DB, PC n=14 elderly poor sleepers	1 week	405 mg 3x/day	Valdispert® forte	Subjects in valerian group had increase in slow-wave sleep and decrease in Stage 1 sleep. There was no effect on self-reported sleep quality, sleep onset time, REM sleep time, or time awake after onset of sleep.
Balderer and Borberly, 1985	Sleep	DB, PC n=18 healthy subjects with a history of sleep disturbances	3 weeks	450 or 900 mg extract 30 minutes before bed	Aqueous valerian extract (brand not stated)	Valerian extract had mild sleep-promoting action without significant residual or "hangover" effect.
Leathwood and Chauffard, 1985	Sleep	R, PC, DB n=8 mild insomnia	1 night	450 mg and 900 mg	Aqueous valerian root extract (brand not stated)	Significantly decreased sleep latency; there was no further improvement with doubling the dose.
Gessner and Klasser, 1984	Sleep	R, DB n=11 adults	2 nights	1 or 2 capsules (60 or 120 mg)	Harmonicum Much® valepotriate preparation	Both dosages showed a decrease in sleep Stage 4 and a slight reduction of REM sleep, and slight increase of sleep Stage awake, 1, 2, and 3. Changes or Beta-intensity of EEG during REM sleep show stronger hypnotic effect for 120 mg dosage than for 60 mg dosage. Maximum effect was observed between 2 and 3 hours after medication.
Kamm-Kohl *et al.*, 1984	Mood and sleep	PC n=80 hospitalized geriatric patients	2 weeks	6 tablets/day (482 mg valerian extract/day)	Valdispert® forte	Significant improvements in mood and behavioral disturbances, as well as sleep.

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Clinical Studies on Valerian (*Valeriana officinalis* L.) (cont.)

Sleep (cont.)

Combination Preparations

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Fussel *et al.*, 2000	Sleep	PS n=30 patients with mild to moderate, non-organic insomnia	2 weeks	2 tablets in the evening (total of 500 mg valerian extract and 120 mg hops extract per day)	Ze91019 Alluna™ (US) Ivel® (Germany) ReDormin® (Switzerland)	Polysomnography data were recorded on baseline and after 2 weeks. Sleep latency was reduced statistically significantly while sleep efficiency increased. An increase in slow wave sleep was recorded. In a self-assessment, patients reported an improvement of feeling refreshed in the morning after 2 weeks. No adverse events were recorded.
Vonderheid-Guth *et al.*, 2000	Sleep	R, SB, CO 2 studies n=12	1, 2, and 4 hours after application in each study, studies spaced 3 months apart	1st dosage: 1 tablet (500 mg valerian and 120 mg hops) vs. placebo; 2nd dosage: 3 tablets (total 1,500 mg valerian and 360 mg hops) vs. placebo	Ze91019 Alluna™ (US) Ivel® (Germany) ReDormin® (Switzerland)	The study concluded that pharmacodynamic responses could be repeated. The quantitative topographical EEG demonstrated a visible effect on the CNS, especially after intake of the high dosage of the valerian-hops combination.
Cerny and Schmid, 1999	Sleep	R, PC, DB, PG, MC n=95 healthy volunteers (58 women, 40 men)	30 days	3 tablets (total 360 mg valerian and 240 mg lemon balm [*Melissa officinalis*] combination) or placebo	Songha Night® coated tablets and placebo	Valerian/lemon balm group had significantly higher quality of sleep (33%) compared to placebo group (9%) (p=0.04).
Rodenbeck *et al.*, 1998	Insomnia	PC n=15	4 weeks	500 mg valerian with 120 mg hops	Ivel® valerian and hops extract vs. placebo	There was a significant decrease in slow-wave sleep and an increase in Stage II sleep among those assigned to the herbal preparation.
Schmitz and Jackel, 1998	Sleep disorders	R, DB, C n= 46 patients with sleep disorders according to the DSM-IV criteria	2 weeks	Two, tablets (total 200 mg valerian extract with 45.5 mg hops extract) vs. 3 mg benzodiazapine	Hova® compared to benzodiazapine	Patients' state of health improved during therapy with both agents and deterioration after cessation was reported for both groups. Withdrawal symptoms were reported only in benzodiazepine groups.
Dressing *et al.*, 1996	Insomnia	DB, PC n=57 adults with insomnia	2 weeks	Two, tablets 160 mg valerian extract with 80 mg lemon balm extract each), 2x/day	Euvegal® forte valerian and lemon balm tablet vs. placebo	Sleep quality improved in valerian/lemon balm combination compared to placebo (p=0.02) and remained in effect one week after medication was discontinued (p=0.12).
Lataster et al., 1996	Sleep	MC, OL n=3,447	4–6 weeks	Dosage not stated	Valerian and hops extract (each tablet contains 500 mg valerian, 60 mg hops)	The efficacy of the combination was evaluated as good to very good by 75% of the physicians. The number of patients who slept through the night rose from 24.4% to 77.4%. The self-efficacy report of feeling rested upon awakening rose from 26.5% to 64.9%.
Orth-Wagner, 1995	Sleep	O n=225 patients with sleep difficulties	2 weeks	Two, tablets 1–3 times daily	Novo-Baldriparan®	89% noted improvements in ability to fall asleep, and 80% reported improvements in ability to sleep through the night; most also reported an improvement in overall well-being.

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Clinical Studies on Valerian (*Valeriana officinalis* L.) (cont.)

Sleep (cont.)

Combination Preparations (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Dressing and Reimann, 1992	Insomnia	DB, PC n=20 adults with insomnia	9 days	1 tablet (160 mg valerian with 80 mg lemon balm) or 0.125 mg Halcion®	Euvegal® forte valerian and lemon balm tablet vs. placebo	Both active treatments were equivalent and significantly better than placebo. The herbs caused less daytime sedation and impairment of mental functions.
Lindahl and Lindwall, 1989	Sleep difficulties	R, DB, PC, CO n=27 insomniacs	2 nights	400 mg/night	Valerina Natt®	Of the 27 patients, 21 rated valerian-containing mixture as significantly more effective ($p<0.001$) than the control preparation for sleep quality; 24 of 27 patients (89%) reported "improved sleep" and 12 of these patients (44%) reported "perfect sleep" after taking valerian-containing preparation. No adverse effects were observed.
Leathwood *et al*, 1982	Sleep	R, DB, PC, CO n=128	9 nights	400 mg	Hova®, or aqueous valerian extract, or placebo	Subjects had statistically significant ($p<0.05$) decrease in subjective sleep latency and significant improvement in sleep quality. Improvement was most notable among people who were poor or irregular sleepers, and smokers. No detectable hangover effect was noted in the morning.

Hazards in Driving and Operating Machinery

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Kuhlmann *et al.*, 1999	Alertness, reaction time, and concentration	R, C, DB n=99 males and females in first segment and 91 in second segment	Single night plus 2 weeks of nighttime administration	600 mg LI 156 or flunitrazepam (1 mg) and placebo	LI 156 vs. flunitrazepam and placebo	Neither single nor repeated nighttime administration of valerian had adverse impact on reaction time, alertness, and concentration the morning after intake. Valerian subjects showed better improvement in psychometric performance than those on placebo, and significantly ($p=0.4481$) better than those on drug.
Mayer and Springer, 1974	Assess potential hazards in driving	R, DB, PC n=24 healthy volunteers	Acute	200 mg, 400 mg, or 150–200 mg	Valmane® (valepotriates with alcohol) and placebo	Demonstrated a dose-dependent increase in concentration abilities in volunteers; when given in combination with alcohol, the preparation did not affect blood alcohol levels, have sedative effects, and/or affect driving performance.

Combination Preparations

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Gerhard *et al.*, 1996	Assess potential hazards in driving or operating machinery	C, Cm n=80 healthy adults	One night (single oral administration with observation on the following morning)	1.5 g dried extract or 4 g fluid extract	2 Valverde® herbal combinations (containing valerian and hops) and a syrup of valerian were compared to flunitrazepam and placebo (brands not stated)	Objectively measurable impairment of performance on morning after medication occurred only in flunitrazepam group. In addition, 50% of the volunteers in flunitrazepam group reported mild side effects, compared with only 10% from other groups. Examination of acute effects of plant remedies 1–2 hours after administration revealed very slight, but statistically significant impairment of vigilance and retardation in the processing of complex information.
Kammerer *et al.*, 1996	Driving safety	R, DB, CO n=18	21 days	2 tablets after dinner (total of 1,000 mg valerian extract and 120 mg hops extract per day), or placebo	Valerian and hops extract (each tablet contains 500 mg valerian, 60 mg hops)	The study concluded that the combination did not produce significant adverse effects and did not impair psychometrically measured fitness and subjective state of health. In addition, no significant interaction with alcohol is to be expected.
Albrecht *et al.*, 1995	Driving ability and combination with alcohol	R, DB, PC n=54	3 weeks	2 tablets 2x/day or placebo	Euvegal® forte (each tablet contains 160 mg valerian root extract and 80 mg lemon balm leaf extract)	Traffic safety was evaluated using psychometric tests. The treatment group showed no difference in driving ability compared to placebo, and treatment did not potentiate the effect of alcohol consumption. The study concluded that Euvegal® does not cause impairment of the operation of machinery or the driving of vehicles.

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