Valerian Root Extract

For the Treatment of Sleeping Disorders,
Tenseness and Irritability

EUROMED

Introduction

EUROMED is a company specialized in making botanical extracts and active principles used as phytomedicines in pharmacy. EUROMED develops and produces these from therapeutically active raw materials.

The botanical raw materials are subject to strict selection and inspection, and products are manufactured according to methods developed by the EUROMED company. They include inspections to guarantee a standard quality from both analyticochemical and therapeutical points of view and take into consideration the state of art in different fields: research and development, analyses, processes and devices, therapeutic applications on a scientific basis.

EUROMED guarantees the quality of its products by a broad phytochemical know-how.

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1 *Valeriana officinalis L.* Extract: General Information

1.1 Description

Extract of valerian (as available from EUROMED) is a standardized hydroalcoholic herbal extract of the root of *Valeriana officinalis L.* (Fam. *Valerianacae*).

All natural

Valeriana officinalis root extract is a safe and effective herbal medicinal product for the treatment of nervous tension and especially difficulties in falling asleep or lack of sleep quality.

Herbal remedy for sleeping disorders and nervous tension

After a few days of treatment, relief from the above-mentioned symptoms is seen in most patients.

Valeriana officinalis has proved to be sleep promoting and sleep quality enhancing. Valerian extract does not interact with other drugs, food or alcohol [2, 9, 13].

No interactions

Unlike other medications with benzodiazepines, no dependency, adaption, "hang-over-effect" the next morning or other serious side-effects have been reported for the extract of *Valeriana officinalis* at the recommended dosages.

No dependency, no "hang-over-effect"

1.2 Indications

Valeriana officinalis root extract is acknowledged and recommended as treatment for difficulties in falling asleep, tenseness, restlessness and irritability [9, 10, 13].

Valeriana officinalis has been approved as safe (GRAS = generally recognized as safe) for food use in the United States [17, 32].

1.3 Extract Specifications

Valerian root extract consists of the subterranean organs of *Valeriana officinalis L.*, including the rhizome, roots and stolons, carefully dried at a temperature below 40°C.

It contains not less than 0.5 % *V/m* of essential oil. The material complies with the European Pharmacopoeia [13, 14].

Valerian root preparations usually contain about 45 mg to 450 mg of *Valeriana officinalis* extract (as available from EUROMED).

1.4 Dosage and Methods of Administration

A daily oral dose of 500 mg up to 3000 mg is common practice, for tenseness, restlessness and irritability up to 3 times daily; as a sleeping-aid 1 single dose $^1/_2$ to 1 hour before bedtime, with an earlier dose during the evening, if necessary [12, 13, 41, 42, 43].

Table 1 gives a survey of popular European *Valeriana officinalis* monopreparations available on the market.

1.5 Contraindications and Interactions

There are no known contraindications to the longterm use of Valeriana officinalis extract [9].

For pediatrics (children from age one) and geriatrics, non-alcoholic valerian preparations are accepted in Europe as suitable [2, 13].

No interactions with drugs usually prescribed have been reported.

1.6 Side-effects

Well tolerated, non-addictive

No adverse effects have been confirmed. Valerian root is very well tolerated and non-addictive

Table 1: European Monopreparations containing *Valeriana officinalis* root extracts

Preparation Name	Method of Extraction	Content of Extract / mg	Total Extract [mg/day] for diurnal sedation	Total Extract [mg/day] for Sleep-Induction
Baldrian-Dispert/ stark am Tag	Ethanolic ethanolic	45 125	45 - 135 several times 250 - 500 several times	135 - 270 1/2 h before sleep
Baldrianetten	no data	200	200 - 600 up to 5 times	200 - 400 1/2 h before sleep
Baldrian Phyton	no data	200	400 - 1800	400 - 1800
Baldrisedon mono	methanolic	190	380 - 570 several times	380 - 570 1/2 h before sleep
Benedorm Baldrian	ethanolic	442	441 - 1324	441- 882 1 h before sleep
Kneipp Baldrian Tabletten (tablets)	no data	500	2000 - 6000	2000 - 3000 1/2 to 2 h before sleep
Regivital Baldrian Perlen	ethanolic	86	257 - 770	257 2 h before sleep
Sedalint Baldrian	no data	220	440 - 660 up to three times	440 - 660 up to three times
Sedonium	ethanolic	300	600 several times	600 before bedtime
Valdispert/	ethanolic	45	45 - 135 several times	135 - 280
Valdispert 125	ethanolic	125	250 - 500 several times	

2 From Plant to Extract

2.1 Valerian Root (*Valerianae radix*) Botanical Data and Nomenclature

Valerian root

The genus *Valeriana* is found throughout the world and consists of more than 230 species. Only *Valeriana wallichii D.C.* (temperate zones of the Himalaya), *Valeriana edulis Nutt.ssp. procera F.G. Meyer* (Mexico) and especially *Valeriana officinalis L.* with a broad documented clinical efficacy are of importance to phytotherapy.

Valeriana officinalis L. is a perennial herbaceous plant widely distributed mostly in Europe but also in some parts of South America and Asia. It is nowadays cultivated on a large scale for medicinal use in Europe. The plant thrives on the damp surfaces of ditches and ponds, marshlands and at the edges of forrests in temperate zones up to 2400 m.

Valeriana officinalis is distinguished by its short, sometimes stoloniferous rhizomes and grooved stalk, growing to a maximum height of approximately 6 feet.

The rhizomes and roots, with and without stolons, are the basic material used for phytopharmaceutical products. Harvesting period is autumn or spring. The roots are carefully washed with water to remove soil and dried at a temperature below 40°C immediately after harvesting to prevent degradation of the active principles.

Characteristic odor

The smell of fresh roots is at first pleasant with a sweet musky note but soon turning into the typical, for most people rather appaling "valerian" odor.

The name valerian or *Valeriana* first appeared in literature between the 9th and 10th century, its true origin is unknown. Most authors claim that Valeriana derives from the Latin words "valere" (to be in health) or "valeo" (to be strong), propably in reference to the plants powerful healing properties or strong odor. Others suspect that the plant was named after the Roman province Valeria at the river Danube or was given in honour of the Roman emperor PUBLIUS AURELIUS LICINUS VALERIANUS. Other ancient names for valerian are "phu" (or "fu") and "nard" [7, 17, 26, 32, 49].

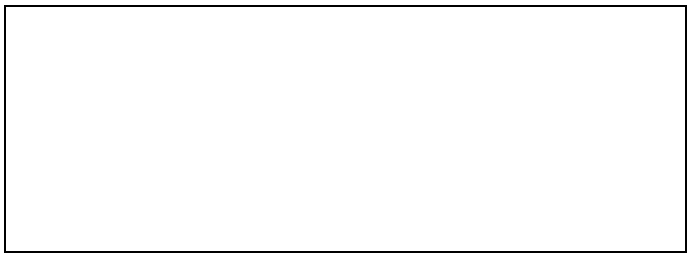


Figure 1: Valerian root

2.2 Historic Use

Ancient medicinal plant

The history of *Valeriana* goes back more than 2000 years (Hippocrates 460-370 B.C.).

The drug has been used not only in European medicine but also in Traditional Chinese Medicine (TCM) and Indian Ayurvedic for centuries. Galen (131-201 A.D.) first prescribed the drug as a treatment for insomnia.

The use of valerian as a sedative or nervine in modern medicine was initiated by JOHN HILL, a British physician, in the 18th century and soon *Valeriana officinalis* developed into a very popular drug prescribed to cure various kinds of symptoms related to nervous conditions like insomnia, restlessness, gastrointestinal disorders, hysteria, anxiety and many more.

Valerian was listed as official medication both in England and the United States until the late 1940‘s (London Pharmacopoeia 1618-1948, United States Pharmacopoeia 1820-1936, National Formulary 1888-1946).

Today it continues to be an official medicinal plant in the pharmacopoeias of many European countries. Valerian is acknowledged and recommended as a mild diurnal sedative in cases of irritability and restlessness and it is known as a safe and efficient sleep-inducing drug due to its antispasmodic effects on smooth muscles and depressant proprieties in the central nervous system [8, 17, 33, 34, 32, 60].

2.3 Chemistry of *Valeriana officinalis L.* Root

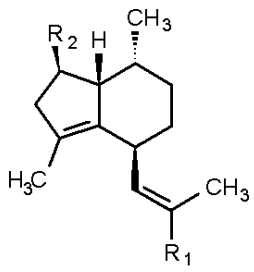
Valeriana officinalis root consists of several groups of substances. They are identified and quantified according to modern scientific analytical methods [23, 27].

Table 2: Contents of *Valeriana officinalis L.* Root

Compounds identified in Valerian root
• Volatile oil 0.3 to 0.8 %, depending on condition of soil and time of harvest [26], 0.1 to 2 % from cultivated plants [49]. So far the following constituents have been isolated: various derivatives of kessane, monoterpenes and sesquiterpenes (Figure 2) [63, 64].
• Iridoids also known as valepotriates and their degradation products baldrinal, homobaldrinal and valtroxal [26].
• Small amounts of alcaloids as well as amino-acids (GABA, thyrosine, glutamine), flavonoids, triterpenes, various minerals and sugars [26].

Sesquiterpenes are considered the main effective substances

Leading substances for identification and standardization are the cyclopentane-sesqui-terpenes valerenic acid acetoxyvalerenic acid, hydroxyvalerenic acid and valerenal (Figure 2), as those components are only found in *Valeriana officinalis L.* [27].



R_1	R_2	
COOH	H	Valerenic acid
COOH	OH	Hydroxyvalerenic acid
COOH	$OCOCH_3$	Acetoxyvalerenic acid
CHO	H	Valerenal

Figure 2: Sesquiterpenes in *Valeriana officinalis*

The active principles of the drug are so far not known, as various tests and trials with isolated constituents did not fully explain the biological activities of *Valeriana officinalis*. Research was mostly concentrated on the sesquiterpenes and valepotriates.

Most authors conclude, that not one single constituent is responsible for the sedative and relaxing properties of *Valeriana officinalis*, but that several components must act synergistically, or that even other unknown substances, so far not isolated, may contribute to the active principle [24, 34, 47, 48, 49].

2.4 Preparation of the Extract and Quality Control

Standard quality assured

The plant material used for *Valeriana officinalis* root extract manufactured by EUROMED originates primarily from cultivations. The growing and processing specifications are established in order to standardize conditions of cultivation, harvest and most importantly drying and storage. Thus the excellent quality of the EUROMED product is guaranteed.

Various substance groups have been isolated in valerian extracts. The best evaluated active components are valerenic acid and valepotriates. As clinical trials showed biological activities of extracts in which valepotriates were absent and the cyclopentane-sesquiterpenes valerenic acid, acetoxyvalerenic acid and valerenal are found only in the species *Valeriana officinalis L.*, EUROMED established the valerenic acids as leading substances for identification and standardisation. The level of those components is measured experimentally in order to optimize the production process and assure a consistent high quality of the *Valeriana officinalis* extract [26].

Inspection of the drug upon its arrival at EUROMED

When the plant material arrives at EUROMED, an exhaustive control of the raw material is carried out according to worldwide established methods, paying special attention to the content of valerenic acids to assure a continuous excellent quality of the final product.

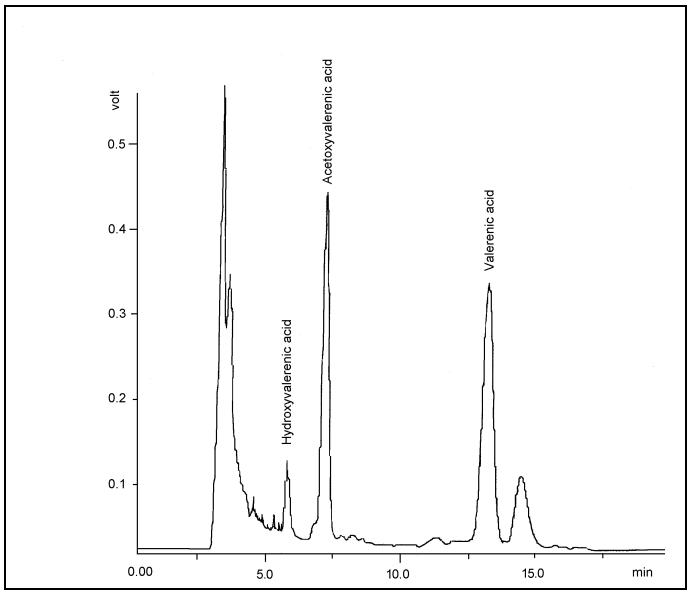


Figure 3: HPL-chromatogram profile of *Valeriana officinalis* root extract

Furthermore, EUROMED evaluates possible contaminations of the drug. In doing so, the company assures that the limits fixed by international norms or literature are not surpassed.

EUROMED applies an extraction process which provides a high yield of valuable constituents and a high-grade extract in a careful way.
According to the original processes EUROMED produces a dry extract from *Valerianae radix*:

- **EXTR. VALERIANAE OFF. E RAD. SICCUM (VALERIAN DRY EXTRACT)**
  Cont. 0.8 % Valerenic Acids.

EUROMED *Valerian root* extract satisfies the highest quality standards. This way it is possible to meet the requirements for an effective and safe medication.

2.5 Standardization

Consistent batch to batch quality

The consistent batch to batch quality of the EUROMED *Valerianae radix* extract is guaranteed by the standardized production process.

The analytical specifications of the EUROMED Valerian root extract are:

Analytical Specifications

* Aspect	Fine powder, brown color, characteristic odor and savor
* Identification	HPLC Fingerprint
* Solubility	Soluble in hydroalcoholic solutions
* Loss on drying	Max. 5.0 %
* Ash	Max. 10.0 %
* Assay	Valerenic acids min. 0.8 % (HPLC Method)
* Microbiology	Acc. Ph. Eur. 3rd ed., 5.1.4., category 3B

Due to EUROMED's standardized production process a consistent quality is guaranteed which meets the highest standards and requirements for effectiveness and safe use of the medication.

3 Sleeping Disorders

Normal sleep is characterized by a defined cycle of different sleep stages (Figure 4), repeated several times during the night with direct correlation to EEG[1]-frequency patterns (alpha-waves: 8 – 13/sec, theta: 4 – 7/sec, delta: 0.5 – 3/sec, beta: 14 – 30/sec) [25], nocturnal body movements, frequencies of breathing and heartbeat as well as body temperature. Sleep onset starts with stage 1, leading gradually over stage 2 to stages 3 and 4 (deep sleep phase), followed by stage 5 or REM[2]-phase. Stage 2, a sufficient amount of stages 3 and 4 during the first sleep cycles and especially stage REM seem to be the most important parameters for the judgement of sleep quality. Significant reduction or absence of REM-phases may even lead to severe psychotropic symptoms. Patients with sleep disorders show a prolonged period of time before onset of sleep stage one and/or various changes in normal sleep patterns [3, 21, 45].

REM stage is important for sleep quality

[1] EEG: Electro-encephalo-gram

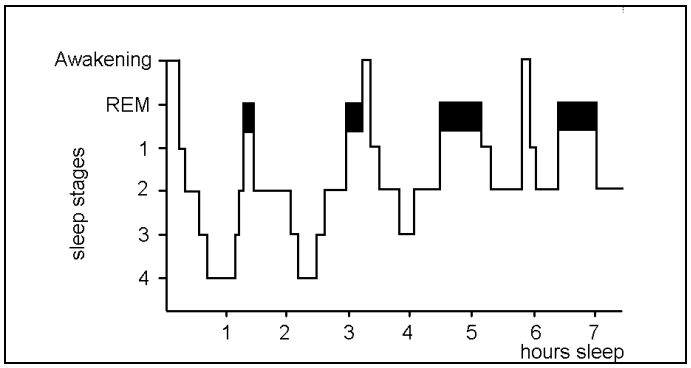


Figure 4: Normal sleep pattern of healthy young adults

About one third of the population worldwide complains of sleeping problems (Table 3). Roughly one third is related to underlying diseases, one third to psychiatric problems and one third to non-organic psychophysiological insomnia. According to definition in literature, symptoms of chronic insomnia are prevalent several times a week for a period of more than a month. The reasons are manifold (Table 4).

Table 3: Sleeping problems

- Difficulty in falling asleep
- Difficulties to sleep through
- Early awakening
- Irritability, restlessness and fatigue during daytime

Table 4: Reasons for sleeping disorders

[2] REM: Papid Eye Movement

- Environmental reasons like shift-working, traffic-noise
- Somatic problems like nervousness, tension, restlessness
- Disorders of circadian rhythm with asynchrony relative to typical environmental patterns
- Psychiatric disorders
- Old age
- Cerebreal and other severe diseases
- Pharmacological interferences like alcohol, caffeine, nicotine, medication

Benzodiazepines and barbiturates are often prescribed medications, but sleep architecture is extremely altered and side-effects are severe (Table 5).

Table 5: Problems in Treatment with Synthetic Sedatives

- Sleep architecture (EEG-patterns, especially sleep-stage 3 and 4 and REM-phase) are influenced in a negative way
- Abuse (suicide attempts)
- Dependency
- Hang-over-effect next morning
- Concentration deficits during daytime
- Danger when driving or operating machines
- Synergistic action with alcohol
- Apathy or disorientation in geriatric patients
- Increase of sleep apnea
- Withdrawal symptoms, when discontinuing therapy

Over the years, the requirement to find a medication that is safe, without adverse effects and not interacting with other drugs or alcohol became mandatory.

As valerian is known for centuries to fulfill these requirements, research concentrated on this drug and its combination-preparations during the last 30 years especially in Germany, France and Switzerland.

According to the results of various tests and trials it can be stated, that extract of *Valeriana officinalis* is a safe and efficient drug to induce sleep, enhance sleep quality and leave the patient rested, refreshed and fully concentrated the next morning. Sleep patterns are normalized, the drug may even be useful to reduce withdrawal symptoms when weaning patients off barbiturates.

Compliance is usually good, patients responses are excellent [1, 3, 4, 8, 33, 32, 36, 37, 45, 47, 50, 54, 59, 61, 66].

4 Pharmacology

The sedative and sleep-inducing effect of Valeriana officinalis is not based on an isolated constituent or mechanism, as it is the case with many herbal remedies [24, 48].

Several constituents are effective

So far a presumably synergistical action of several active components or even **interac**tion of presently not yet isolated components is assumed for the biological activity of the whole extract [24, 34, 47, 48, 49].

4.1 Reduction of local cerebral glucose metabolism in the cortex and limbic system, reduction of motility

By means of desoxy-glucose-technique (SOKOLOFF) possible central nervous system effects of valerian extract on rat brains were evaluated. After intraperitoneal injection of 50 mg/kg bodyweight a marked reduction of local cerebral glucose metabolism especially in the cortex and limbic system could be seen [24].

In another study effects on spontaneous motility, thiopental sleeping-time and pentetrazol-induced toxicity were tested on female mice by administering a commercially available valerian root extract. Pronounced sedative properties were revealed with respect to a reduction in motility and an increase in the thiopental sleeping-time. A direct comparison with diazepam and chlorpromazine showed a moderate sedative activity for the tested extract [44].

4.2 Affinity to GABA-A receptor and release of [^{3}H]-GABA

Hydroalcoholic and aqueous total extracts of valerian root showed affinity to the GABA[3]-A receptor in rat brains. The chemical nature of this activity was not connected with sesquiterpenes or valepotriates. Interaction of unknown constituents could represent the molecular base for the sedative effect observed both in man and experimental animals.

Interaction with GABA receptor is possible

For the hydroalcoholic extracts, a contribution to the sedative effect cannot be excluded due to the interaction of their valepotriate constituents with the allosteric sites of GABA receptors controlling chloride anions influx [48].

An aqueous extract of valerian (100 g of the extract containing 55 mg of valerenic acids) inhibits the uptake and induces the Ca^{2+}-dependent release of [^{3}H]-GABA previously accumulated in synaptosomes isolated from rat brain cortices. This inhibition of uptake and/or stimulation of GABA release from nerve terminals may increase the extracellular concentration of this neurotransmitter in the synaptic cleft at levels sufficiently high to activate GABA receptors [57].

The above mentioned extract contains several amino acids with a relatively high concentration of GABA (about 5 mM) which proved sufficient to induce the release of [^{3}H]-GABA accumulated in synaptosomes by a homoexchange mechanism.

[3] GABA: Gamma-aminobutyric acid

The mechanism of action in vivo is still unclear, as GABA is supposed not to penetrate the blood-brain barrier readily. However there is evidence, that GABA effects are not restricted to synaptic transmissions alone but that it is also present and may even be a neurotransmitter in a variety of cell types inside and outside the nervous system.

Also high concentrations of glutamine (about 14 mM) were found, which could explain sedative effects of valerian extracts *in vivo*, as glutamine can cross the blood-brain barrier and possibly is taken up by nerve terminals and subsequently metabolized to GABA in GABA-eric neurons. Moreover addition of exogenous glutamine stimulates GABA syntheses in synaptosomes and brain slices [58].

4.3 Relaxation of smooth muscles

Isovaltrate, valtrate and the essential oil compound valeranone caused a suppression of rhythmic contractions in a closed part of the guinea-pig ileum *in vivo*. The same compounds and dihydrovaltrate relaxed potassium stimulated contractures and inhibited $BaCl_2$ contractions in guinea-pig ileum preparations in vitro. It can be concluded, that valerian root compounds relax stimulated smooth muscle cells probably by acting as muscolotropic agents [30].

5 Toxicology

Very low toxicity

A low order of toxicity was reported for an ethanolic extract of valerian root. The LD_{50} by intraperitoneal injection into mice was found to be 3.3 g/kg body weight. When this extract was administered intraperitoneally to rats daily for 45 days in doses ranging from 400 – 600 mg/kg bodyweight no significant changes in weight, blood or urine were observed in comparison with control animals [13].

An alcoholic extract of valerian root was administered to rats at dosages of 300 mg/kg and 600 mg/kg body weight per day for 30 days. Compared to control animals, no significant differences were found in growth, arterial pressure, weight of key organs or hematological and biochemical parameters [15].

In acute oral toxicity tests the LD_{50} of valeranone was greater than 3 g/kg body weight in both rats and mice [56].

6 Clinical Pharmacology

Valerian normalizes sleep-architecture

A normalization of sleep-architecture, reduction of sleep-latency and wake periods and improvement of sleep quality is seen in EEG-studies and polysomnography after application of valerian root extracts.

Geriatric patients, most of whom had been taking benzodiazepines, were substituted with a combination-preparation of hop flowers and valerian. The herbal remedy normalized sleep architecture [16].

24 female subjects received either 10 mg diazepam or placebo or a valerian extract preparation (1200 mg dry extract). The resting EEG showed a marked increase in relative power in the delta, theta and slow alpha frequency ranges 120 min after ingestion of valerian extract. In contrast to diazepam, there was no increase in the power of the beta frequency range. The subjectively experienced tiredness increased markedly both after valerian and diazepam 120 min after ingestion [61].

Sleep induction time is reduced

The influence of a proprietary preparation containing 405 mg of an aqueous-alcoholic dry extract of valerian was investigated on female subjects. Valerian reduced sleep induction time and improved sleep quality. These subjective findings were confirmed by EEG: long-wave sleep (sleep-stadium 3 and 4) was increased and sleep-stadium 1 was decreased. No influence was observed on the REM sleep as well as on the frequency of waking during night time [62].

Improvement in the EEG

After single administration of 1200 mg valerian extract a significant increase in the power in the delta and theta frequency bands was seen in an EEG study with 16 healthy volunteers, giving an indication of a specific sedative effect. After repeated administration (600 mg daily) over a course of 14 days, the quantified EEG showed a rise in the theta, alpha-1 and beta-1 frequency ranges. These EEG changes provide objective evidence of a psychosedative effect of valerian [11].

Effects of 60 and 120 mg of a valerian preparation were investigated by computer analysis of sleep stages and psychometric methods. After application of 120 mg valerian, the frequency of REM-phases declined during the first half of the night, whereas during the second part a surplus appeared. Changes in the beta-intensity of the EEG during REM-sleep showed a stronger hypnotic effect for the 120 mg dosage. Maximum effect was observed between 2 and 3 hours post medication [21]

15 patients with psychophysical insomnia were investigated by polysomnography for 4 weeks, taking a combination preparation containing 500 mg valerian and 120 mg hops on 28 consecutive nights, in a double-blind, placebo-controlled, randomized, parallel group design. Verum medication significantly decreased slow-wave-sleep percentages, but increased sleep stage 2. These effects correspond to effects caused by benzodiazepine receptor antagonists and seem to be a feature of the GABA-ergic effects of valerian preparations [55].

A normalization of sleep architecture was seen in patients with chronic sleep disorders after taking a commercially available combination preparation of 500 mg valerian and 120 mg hop for two weeks (Figure 5) [18].

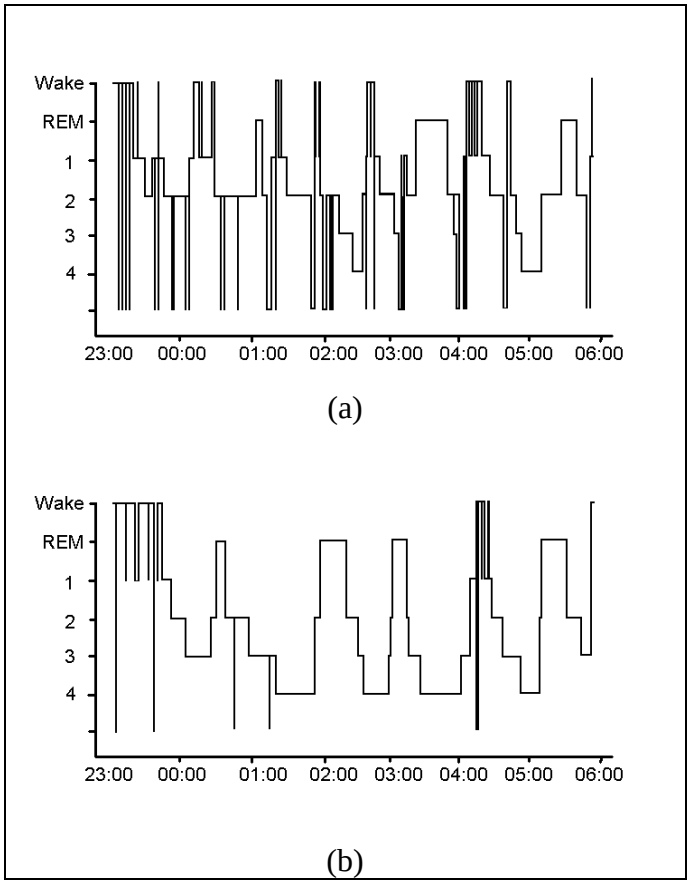


Figure 5: Restructured hypnogramm after therapy with 500 mg valerian and 120 mg hop (b) in comparison to hypnogramm before therapy (a) [18]

7 Proof of Clinical Efficacy

7.1 Clinical Trials with Placebos

Decrease in sleep latency

Increase in sleep quality

In the 1980s, LEATHWOOD, CHAUFFARD et al. published a number of studies on the effect of valerian extract on sleep patterns. Sleep quality was subjectively measured by the patient and to some extent confirmed by EEG. A significant decrease in subjectively evaluated sleep latency and also a significant increase in sleep quality was reported especially among geriatric patients and subjects who considered themselves poor and irregular sleepers (Figure 6). Dream recall and nocturnal movement were apparently not affected, no drowsiness was reported the next morning. The authors concluded, that valerian is at least as effective as small doses of barbiturates or benzodiazepines [41, 42, 43].

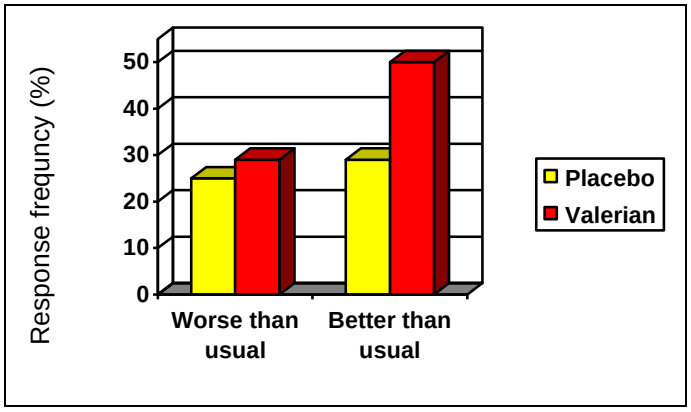


Figure 6: Percentage of habitually poor or irregular sleepers reporting a mean rating over 3 nights of better or worse sleep than usual following placebo or valerian treatment [41, 42, 43].

The sleep-inducing effect of valerian extract was studied in two groups of healthy volunteers, one (n = 10) sleeping at home, the other (n = 8) in the sleep laboratory. Evaluation was conducted on the basis of self-rating scales, questionnaires and night-time motor activity. In the home sleeping group, doses of 450 mg and 900 mg of the valerian extract had a significant, dose-dependent, sleep-promoting effect. Perceived sleep latency and wake time after sleep onset were reduced. Night-time motor activity was enhanced in the middle third of the night and reduced in the last third. Objective and subjective findings in the laboratory group corresponded to those observed under home conditions [6].

78 elderly patients received 270 mg valerian extract in coated tablets or a placebo. The study showed significant improvements in sleep latency time and sleep quality in the valerian treated group according to psychometric scales and subjective ratings [35].

Improvement in CGI

A placebo-controlled double-blind study was carried out on 121 patients suffering from non-organic insomnia according to ICD-10 (F 51.0) over the course of 28 days [66]. 600 mg of an ethanol-water valerian root extract were taken one hour before retiring to bed. In the valerian treated group (n = 61) the Clinical Global Impression (CGI) improved significantly after 2 weeks ($p < 0.05$) and was highly significant after 4 weeks ($p < 0.001$). The change in state was given as “very much improved“ or “improved“ in 55.9 % of the cases, whereas these statements were made for placebo only in 25.9 % of the cases.

Very good efficacy

The self-rating scale according to VON ZERSSEN was used to obtain an objective and quantifiable evaluation of the changes in well-being. After 4 weeks, the insomnia in the valerian treated group was considerably improved in comparison to the placebo treated group ($p = 0.002$). Another self-assessment scale used was GÖRTELMEYER´S sleep questionnaire. A significant difference between placebo and valerian treated group was found for the factor "sleep quality" in favour for the valerian extract ($p = 0.035$). In the valerian treated group the mean of the factor "refreshment after sleep" was close to the one given for healthy persons. The efficacy of the extract was rated as very good to good in 66 % of the cases by patients and in 61 % by physicians [66].

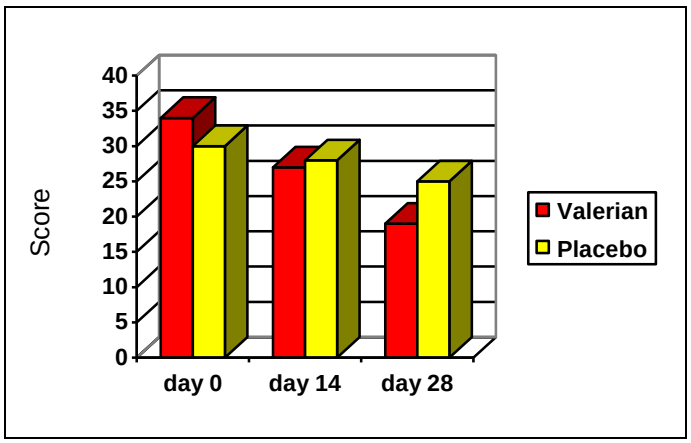


Figure 7: Decrease in the self-rating scale according to VON ZERSSEN during a treatment period of 28 days with placebo or valerian. In the valerian treated group the sore nearly improved to normal values

In a double-blind cross-over study the long term effect of a valerian preparation was tested with 21 volunteers for 9 days. The subjects repeatedly had to fill in the sleep questionnaires SF-A and SF-B according to GÖRTELMEYER as well as the questionnaires VIS-A and VIS-M according to OTT, OSWALD, FICHTE and SASTRE. The statistical analysis showed significant improvement of quality in sleep, recuperation value and sleeping disposition as well as a significant decrease of frequency of waking-up, sleep latency, period of sleep disturbances and bad dreams. Side effects were not reported [22].

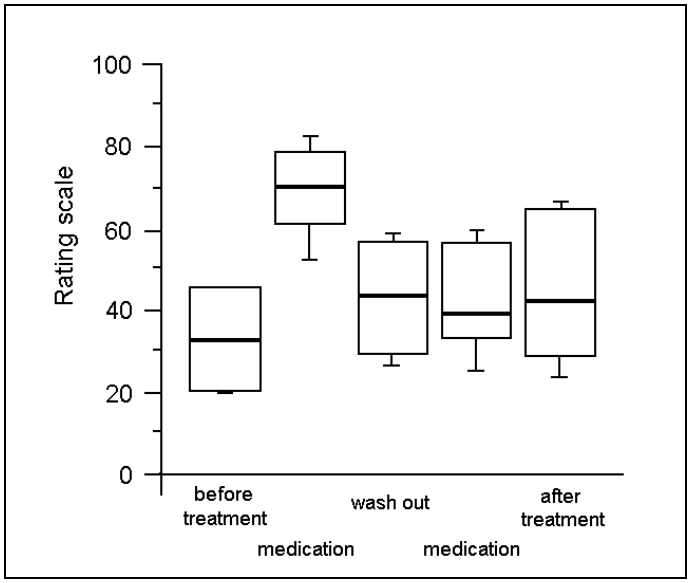


Figure 8:Improvement of sleep quality according to VIS-M during the treatment (median ± SEM): 0 = very bad night, 100 = very good night [22].

7.2 Clinical Trials with Combination Preparations versus Placebo

Combination with hop is common

In a double-blind, placebo-controlled study 4 coated tablets of a compound preparation (60 mg dried valerian extract and 100 mg extract of *humuli lupuli*) were given to 12 subjects complaining of sleep disorders during the second or third of three consecutive nights disturbed by heavy traffic noise (altogether 6 nights in the sleeping laboratory). On the other nights, 4 tablets containing placebo were administered. EEG, EOG[4] and EMG[5] data showed that prior drug administration reduced the noise induced disturbance of sleep stage patterns: slow-wave sleep (stage 3 and 4) and stage REM increased, sleep stage 1 and stage awake decreased [50].

A total of 575 patients (suffering from nervous sleep disorders) from 158 general practitioners were treated with a commercially available combination preparation containing valerian and hops or a placebo for seven days each. The biometric results in 491 patients were evaluated. The verum-medication was rated as more effective as the placebo by both, physicians and patients. 71 % responded to the medication and 89.2 % regarded tolerability of the drug as good or excellent [39].

[4] EOG: Electro-oculogram
[5] EMG: Electro-myogram

Another study was carried out on a valerian preparation combined with hops and balm leaves. Subjects were 27 volunteers with self-reported sleep difficulties. A significant improvement in subjective sleep quality was seen with 44 % reporting perfect sleep and 89 % reporting improved sleep with verum-medication. No side effects were seen [46].

7.3 Drug Monitoring Studies

Study on more than 11,000 patients showed efficacy

In an open multicentric study 11,168 patients were treated for ten days with a commercially available extract of valerian root. 72 % of the patients with difficulties in falling asleep rated the therapy as successful, as well as 76 % of the patients with discontinuous sleep and 72 % with restlessness and tension [60].

60 patients treated with a non-alcoholic syrup containing valerian root extract showed proof of efficacy in 80 %. Sleep latency and awakenings during the night were reduced by 50 % [53].

A multicentric drug monitoring trial performed with 3,447 patients taking a valerian- hops preparation showed the following results: The number of patients who slept through without awakenings increased 5-fold, the number of patients feeling rested the next morning doubled. Tolerance was judged “very good“ or “good“ in 79.5 % of the cases [29, 40].

7.4 Anti-Stress Activities

48 volunteers were placed under experimental "social stress" conditions. In this double-blind study valerian root extract at a low dosage (100 mg) showed no apparent sedative effect but reduced subjective feelings of somatic arousal [38].

225 patients suffering from difficulties in falling asleep, sleeping through the night and/or states of nervous unrest were evaluated in an open, multicenter study. After a 2-week medication of a combination preparation (95 mg valerian root, 15 mg hop grains, 85 mg balm leaves) 82 % reported a significant improvement concerning the state of nervous unrest. External stressors were experienced as being less distressing, intercurrent somatic symptoms like headaches, dizziness, cardiovascular or gastrointestinal discomfort were also reported to be improved [52].

7.5 Therapeutic Safety

Very well tolerated

In general, valerian is very well tolerated. Side effects are rare in clinical trials as well as drug monitoring studies. No adverse effects have been confirmed [5, 9, 12, 13, 19, 20, 28, 31, 36, 51, 65, 66, 67].

Isolated valepotriates may cause gastric complaints as well as allergic reactions, yet, due to their unstable epoxide structure, they are absent from the extract as available from EUROMED [12].

Valepotriates are absent

8 Summary

Valerian has been used for more than 1000 years and is one of the most popular sleep aids at least in Europe. Over the past 30 years, more than 200 studies on the active ingredients and their pharmaco-biological effects have been published in scientific literature. Experimental data indicate a rational scientific basis for mild sedative qualities. Efficacy and safety of valerian root extract (as available from EUROMED) have been proved by a large number of trials. The European market is characterized by combination products, not monopreparations - therefore most of the clinical and pharmacological tests were conducted with valerian root extract in combination with e.g. hops. Commercially available products usually contain alcoholic extracts. Clinical trials also showed, that valerian, unlike chemical sleep medication, does not cause changes in natural sleep patterns, it normalizes sleep-architecture. The drug is very well tolerated and non-addictive. No toxic effects have been observed even after high dosage or overdose. After repeated administration no cummulative effects have been reported [32, 67].

Over 1000 years tradition

Efficacy is proven

Combination products are common

Very good tolerability, no toxic effects

No interactions

There is no interaction with food, drugs or alcohol [2, 9, 13]. Valerian root extract was mostly tested in daily doses of 400 mg (range 45 - 1200 mg) on several hundred subjects.

No side effects

Valerian improves sleep quality and reduces latency in falling asleep and can be considered a viable alternative to synthetic sedatives, moreover as there are no side-effects like hang-over or concentration problems etc. valerian extract even is used as supporting medication to ease withdrawal from benzodiazepines [54].

Mild sedative

Valerian is also a mild diurnal sedative, it is not habit-forming and a proven safe natural ingredient.

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