Agrobiodiversity for Improving Nutrition, Health and Life Quality

Review Article

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Phytochemistry, Neuropharmacology and Emerging Therapeutic Potential of *Valeriana officinalis* L.

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Article Details:
Received: 2025-06-10
Accepted: 2025-07-11
Available online: 2025-11-30

DOI: https://doi.org/10.15414/ainhlq.2025.0018

Valeriana officinalis L. (common valerian) is a well-established medicinal plant traditionally employed for its sedative, anxiolytic, and sleep-promoting properties. Recent advances in phytochemical, preclinical, and clinical research have significantly expanded our understanding of its pharmacological profile. This review provides an integrated synthesis of current evidence concerning the phytochemistry, mechanisms of action, clinical efficacy, safety, and emerging therapeutic applications of *V. officinalis* and related species. The plant's therapeutic effects are primarily mediated by the modulation of gamma-aminobutyric acid (GABA)-ergic, serotonergic, and adenosinergic neurotransmission, complemented by antioxidant, anti-inflammatory, spasmolytic, and neuroprotective activities. Clinical studies consistently support its efficacy in improving sleep onset and quality, as well as in reducing anxiety symptoms, with minimal adverse effects and no evidence of tolerance, dependence, or cognitive impairment. Beyond its well-established neuropsychiatric applications, preclinical data indicate additional cardiovascular, metabolic, cytotoxic, and neuroprotective properties. These include modulation of signal transducer and activator of transcription 3 (STAT3)/platelet-derived growth factor receptor alpha (PDGFRA) signalling in cancer models, neuroprotection against oxidative stress in neurodegenerative disorders, and hypotensive, vasorelaxant, and antiarrhythmic activities. Despite these promising findings, further research is required to address challenges related to extract standardisation, pharmacokinetic characterization, and clinical translation. Overall, *V. officinalis* represents a versatile phytotherapeutic agent exhibiting multifaceted pharmacological actions and substantial potential for integrative and evidence-based clinical applications.

Keywords: valerian; GABAergic modulation; sleep disorders; antioxidant activity; neuroprotection; herbal medicine

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Introduction

Over the past few decades, phytotherapy has gained growing recognition as an alternative or complementary approach to conventional medicine. The increasing use of natural products to prevent and treat of diverse health conditions reflects the public's growing interest in safe, effective, holistic therapeutic options (Yuan et al., 2016). Among medicinal plants, *Valeriana officinalis* L., commonly known as common valerian, is widely recognised for its sedative, anxiolytic, and sleep-promoting properties (Houghton, 1999; Mytych and Aebisher, 2022).

Valerian has a long history of use in traditional European and folk medicine for alleviating insomnia, nervous tension, digestive disturbances, and mild anxiety. It represents the primary species employed in European phytotherapy. Its long-standing traditional use, supported by contemporary pharmacological validation, highlights its importance in both traditional and clinical medicine. Its therapeutic applications date back to ancient Greece and Rome, and it has remained a cornerstone of European herbal pharmacopoeias for centuries (Shinjyo et al., 2020).

Despite its long-standing use, the mechanisms underlying the pharmacological effects of valerian have only recently been elucidated through systematic phytochemical, preclinical, and clinical research (Nandhini et al., 2018; Chandra Shekhar et al., 2024). The variability in extract composition, active constituents, and preparation methods necessitates a comprehensive review to consolidate current knowledge and guide evidence-based clinical applications.

Given the recent global rise in stress-related lifestyle disorders, including depression, and the subsequent increase in benzodiazepine dependence, the demand for natural therapeutic alternatives has grown substantially (Amiri et al., 2024). Consequently, valerian root appears to be one of the best-selling herbal raw materials in both Europe and the United States. Its sedative, anxiolytic, and sleep-promoting properties have positioned it as a valuable herbal remedy in the management of mild to moderate nervous disorders and sleep disturbances, providing a natural alternative to synthetic anxiolytics (Patočka and Jakl, 2010; Bączek et al., 2022). However, despite its long history of use and growing global popularity, variations in the phytochemical composition and pharmacological activity of *V. officinalis* preparations remain an area of active scientific investigation (Nakurte et al., 2021).

Accordingly, to address these knowledge gaps, the present review aims to provide an in-depth overview of *V. officinalis*, encompassing its phytochemistry, mechanisms of action, clinical efficacy, and safety profile. By integrating experimental, preclinical, and clinical findings, the review will shed light on the potential therapeutic applications and limitations of valerian, while also highlighting areas for future investigation.

Botanical Characteristics, Distribution, and Taxonomy

Valeriana officinalis (Caprifoliaceae, formerly Valerianaceae) is a perennial herb widely recognised for its medicinal properties. The genus *Valeriana* comprises more than 250 species distributed across temperate and subtropical regions of Europe, Asia, and the Americas (Backlund and Moritz, 1998). Among these, *V. officinalis* is the most extensively studied species due to its well-documented pharmacological effects, particularly on the central nervous system (Nandhini et al., 2018; Mytych and Aebisher, 2022). Its long-standing traditional use, coupled with modern pharmacological validation, highlights its importance in both traditional and clinical medicine.

Morphologically, common valerian is a rhizomatous, rosette-forming, clonal perennial herb. It develops erect, hollow, and mostly solitary stems that may reach up to 1.5–2.0 m in height. The leaves are pinnate, and the inflorescences are compound cymes bearing numerous small, pale pink to white, strongly fragrant flowers (Kostrakiewicz-Gierałt, 2018) (Figure 1).

The pharmacologically active components are concentrated in the rhizomes and roots, which contain valepotriates, essential oils, flavonoids, and other bioactive compounds (Schulz et al., 1998; Nandhini et al., 2018). Harvesting typically occurs in autumn, when the concentrations of valepotriates and volatile oils are at their maximum, ensuring maximal therapeutic potential. Following collection, the roots are dried and processed into decoctions, tinctures, or standardised extracts to preserve the stability of the active constituents (Bos et al., 1998; Letchamo et al., 2004).

Wild-growing *V. officinalis* is native to the temperate regions of Europe and Asia and has become naturalized in North America. Populations of *V. officinalis* are distributed along riverbanks, in wet meadows and low peat bogs, as well as on sunny forest margins, typically those dominated by alder, within scrub communities, and along roadsides. Currently, *V. officinalis* is among the medicinal plant species experiencing a progressive

Figure 1 Valerian (*Valeriana officinalis* L.)
A – general view of the inflorescence (Kyiv, Holosiivskyi District, Zhukiv Island, Ukraine); B – typical habitats (Vinnytsia Region, Zhmerynka District, vicinity of Tokarivka village, Riv River, Ukraine)
Photo by Oleksandr Shynder

decline of natural populations, primarily due to extensive wild harvesting and habitat degradation. Nevertheless, the species is currently not considered to be endangered (Boczkowska et al., 2020). The species is recognized as highly polymorphic with respect to genome size, developmental traits, and chemical composition (Bączek et al., 2022). Numerous subspecies, forms, and hybrids have been identified within the species, encompassing four ploidy levels: diploid, tetraploid, hexaploid, and octoploid. This pronounced polymorphism underlies the recognition of *V. officinalis* as an aggregate taxon (Bressler et al., 2017; Kirschner and Zeisek, 2017).

Historically, valerian roots were harvested from wild populations. However, owing to increasing demand for this raw material and the high-quality requirements of the herbal industry, *V. officinalis* has now been cultivated commercially in northern parts of Europe and North America (Bączek et al., 2022). Poland is one of the largest producers of this raw material in Europe (Raj et al., 2024). Cultivation requires well-drained, fertile soil and moderate exposure to sunlight. The implementation of standardised cultivation practices enables the consistent production of high-quality raw material, which is essential for achieving reproducible therapeutic outcomes and for conducting reliable pharmacological studies (Mytych and Aebisher, 2022).

The primary herbal drug derived from *V. officinalis* is its dried rhizome and roots. These are used to prepare various formulations, including aqueous and hydroalcoholic extracts, tinctures, capsules, and tablets. These preparations have historically been used for their sedative, anxiolytic, and mild spasmolytic properties, forming the basis of traditional and contemporary phytotherapeutic applications (Shinjyo et al., 2020). Recent pharmacological studies have confirmed these effects, demonstrating the clinical relevance of *V. officinalis* in the management of insomnia, anxiety, and mild neurofunctional disorders (Bent et al., 2006; Nandhini et al., 2018; Valente et al., 2024).

Thus, *V. officinalis* represents a well-characterised medicinal herb whose therapeutic efficacy is underpinned by both traditional ethnopharmacological knowledge and modern scientific research. Its cultivation, harvesting, and post-harvest processing techniques are critical for ensuring high concentrations of bioactive compounds and maximising its therapeutic potential. Ongoing studies continue to elucidate its mechanisms of action, thereby reinforcing its position within integrative medicine and highlighting its relevance for future clinical applications (Li et al., 2022).

Major Classes of Bioactive Compounds

In addition to its distinctive morphological and pharmacognostic features, *V. officinalis* contains a complex array of phytochemicals that collectively underpin its pharmacological activity. The plant's therapeutic properties are attributed to the synergistic action of several classes of bioactive compounds that modulate the nervous system, smooth muscle tone, and oxidative stress pathways (Murphy et al., 2010; Orhan, 2021; Li et al., 2022). The principal groups of these constituents are summarised below:

1. Valepotriates

Valepotriates, including valtrate, isovaltrate, and didrovaltrate, are characteristic iridoid esters present in valerian roots. Although chemically unstable and prone to degradation during extraction and storage, these compounds are believed to contribute significantly to the plant's sedative and anxiolytic effects through modulation of GABAergic neurotransmission and smooth muscle relaxation (Chen et al., 2015; Mytych and Aebisher, 2022; Kokitko and Odyntsova, 2024; Lu et al., 2025). During extraction or isolation, valepotriates may degrade into compounds known as 'baldrinals', nine of which have been identified in *Valeriana* (Çelik and Kırmızıbekmez, 2025). These degradation products retain biological activity and should therefore be considered in pharmacological evaluations of *Valeriana* extracts.

2. Sesquiterpenes and monoterpenes

The essential oil of valerian primarily contains sesquiterpenes (e.g., valerenic acid, acetoxyvalerenic acid, and valerenol) and monoterpenes, which significantly contribute to its pharmacological profile (Ming et al., 1997; Houghton, 1999). In particular, valerenic acid acts as a positive allosteric modulator of GABA_A receptors, providing a mechanistic basis for the herb's sedative and anxiolytic effects (Yuan et al., 2004; Khom et al., 2007; Wu et al., 2023). These terpenoids also exhibit mild anti-inflammatory and neuroprotective activities (Rodríguez-Cruz et al., 2019; Jayaraj et al., 2020).

3. Flavonoids

Valerian roots contain several flavonoids, including linarin, hesperidin, and 6-methylapigenin, which contribute to its antioxidant and mild sedative properties (Marder et al., 2003). These polyphenolic compounds scavenge reactive oxygen species (ROS), enhance endogenous antioxidant defences, and may modulate neurotransmitter systems, thereby complementing the activity of volatile oils and valepotriates (Marder et al., 2003; Wilmsen et al., 2005; Nurzyńska-Wierdak, 2014).

4. Phenolic acids

Compounds such as caffeic, chlorogenic, and ferulic acids exhibit potent antioxidant and cytoprotective properties, mitigating oxidative stress in neuronal and peripheral tissues (Li, 2022; Średnicka-Tober et al., 2022). Phenolic acids also participate in anti-inflammatory pathways and indirectly contribute to valerian's neuroprotective potential (Malva et al., 2004; Das et al., 2021).

5. Alkaloids and other minor constituents

Although present in lower concentrations, certain alkaloids and amino acid derivatives have been identified and are capable of modulating GABAergic and serotonergic neurotransmission (Wu et al., 2023; Senn et al., 2025). These minor constituents likely exert complementary effects, enhancing the overall sedative and anxiolytic action of the plant (Tang et al., 2008; Murphy et al., 2010; Becker et al., 2014; Chen et al., 2015).

The bioactive compound classes found in *V. officinalis*, along with their pharmacological roles, are presented in Figure 2.

The therapeutic profile of *V. officinalis* results from the combined action of these multiple groups of bioactive compounds (Nurzyńska-Wierdak, 2014; Mytych and Aebisher, 2022; Wu et al., 2023). The sedative, anxiolytic, spasmolytic, and antioxidant effects observed in preclinical and clinical studies are due to the synergistic interplay between valepotriates, sesquiterpenes, flavonoids, and phenolic acids. Understanding the chemical composition and standardising extracts based on these active constituents is crucial to ensuring reproducible pharmacological outcomes (Nurzyńska-Wierdak, 2014; Mytych and Aebisher, 2022).

In the study by Raj et al. (2023), a relationship was established between ploidy level and the content of biologically active compounds in *V. officinalis*. Specifically, it was found that a higher ploidy level is associated with higher content of valerenic acids. Wild diploid populations exhibit lower levels of valerenic acids compared to cultivated tetraploid forms. At the same time, wild populations tend to contain higher amounts of essential oils. These findings underscore the complex interplay between genetic factors and cultivation practices in determining the phytochemical profiles of *V. officinalis*.

Figure 2 Bioactive compound classes in *Valeriana officinalis* and their pharmacological roles

Mechanisms of Pharmacological Action

The pharmacological activity of *V. officinalis* is primarily attributed to its complex mixture of bioactive compounds, which act synergistically on multiple neurochemical and molecular pathways. Among these, modulation of the gamma-aminobutyric acid (GABA) system is considered the most prominent mechanism (Yuan et al., 2004; Sánchez et al., 2021). Both valerian extracts and isolated compounds, such as valerenic acid and valerenol, have been demonstrated to interact with GABA_A receptors, thereby enhancing GABAergic neurotransmission (Fernández et al., 2004; Benke et al., 2009). This action is mediated through positive allosteric modulation rather than direct agonism, resulting in potentiation of inhibitory synaptic signalling in within the central nervous system. Furthermore, it has been reported that valerian preparations inhibit GABA transaminase, which is the enzyme responsible for GABA catabolism. This increases synaptic GABA concentrations and prolongs inhibitory neurotransmission (Plushner, 2000; Dietz et al., 2005).

In addition to GABAergic modulation, interactions with adenosine and serotonin receptors constitute another

important mechanism underlying the sedative and anxiolytic effects of *V. officinalis* (Sahin et al., 2024; Senn et al., 2025). Experimental studies suggest that valerian extracts can bind to A(1A) adenosine receptors, leading to neuronal hyperpolarisation and reduced excitability, which collectively promote sedative and sleep-inducing effects (Müller et al., 2002; Yuan et al., 2004). Meanwhile, the modulation of serotonin receptors, such as 5-HT_(1A) and 5-HT_(5A), has been associated with the regulation of mood, anxiety, and circadian rhythms (Dietz et al., 2005; Murphy et al., 2010). These receptor-mediated effects may explain valerian's efficacy in improving sleep onset and quality, as well as alleviating anxiety levels reported by patients in clinical trials (Bent et al., 2006; Fernández-San-Martín et al., 2010; Tammadon et al., 2021).

Furthermore, valerian constituents have also been shown to modulate ion channel function, contributing further to their neurophysiological effects. Electrophysiological studies have revealed that valerenic acid can modulate chloride channels associated with GABA_A receptors, stabilising neuronal membrane potentials and promoting inhibitory transmission (Khom et al., 2007). Interactions with voltage-gated calcium channels have additionally been proposed, potentially leading to reduced neuronal excitability and decreased neurotransmitter release (Calderon-Rivera et al., 2022). This multifaceted modulation of ion channels likely amplifies the overall neurodepressant and anxiolytic actions of *V. officinalis*.

Beyond its role in neurotransmission, *V. officinalis* exhibits pronounced antioxidant and anti-inflammatory properties, which may further contribute to its therapeutic efficacy (Sudati et al., 2009; Lu et al., 2025). Several phytochemicals, particularly phenolic acids and flavonoids, effectively scavenge ROS and enhance endogenous antioxidant defences (Li et al., 2022). Experimental evidence demonstrates that valerian extracts reduce markers of oxidative stress and suppress the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF-α) and interleukin 6 (IL-6) in both neural and peripheral tissues (Zare et al., 2018; Marawne et al., 2022; Kandilarov et al., 2023). Collectively, these effects contribute to neuroprotection, particularly under conditions of oxidative stress, inflammation or sleep deprivation (Malva et al., 2004).

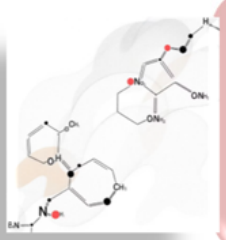
The mechanisms of action of *V. officinalis* are presented in Figure 3.

Finally, the synergistic interactions among multiple phytochemical constituents are considered fundamental to the overall pharmacological activity of *V. officinalis*. Isolated compounds typically exhibit weaker pharmacological effects compared to whole extracts, suggesting that valepotriates, volatile oils, flavonoids, and other secondary metabolites act synergistically to produce the characteristic sedative, anxiolytic, and sleep-promoting properties of the plant (Mytych and Aebisher, 2022). This pharmacodynamic synergy likely reflects the simultaneous modulation of several molecular targets and signalling pathways. A more detailed understanding of these interactive mechanisms could help optimise valerian formulations, improve standardization of herbal preparations, and guide their clinical use in the management of anxiety, insomnia, and related neurofunctional disorders.

Sedative, Anxiolytic, and Antidepressant Effects of *Valeriana* spp.

The sedative and anxiolytic properties of *V. officinalis* are among its most extensively documented therapeutic effects and constitute the foundation of both its traditional and modern applications in phytotherapy. Valerian is widely used to promote relaxation, alleviate anxiety, and improve sleep quality (Hattesohl et al., 2008; Orhan, 2021). It offers a natural alternative to synthetic sedatives, such as benzodiazepines, which are frequently associated with adverse effects, including cognitive impairment and dependency (Caldwell, 2015; Gammoh et al., 2016). These pharmacological effects are primarily attributed to the synergistic action of multiple bioactive constituents, particularly valerenic acid, valerenol, valepotriates, and flavonoids, which target multiple neurochemical pathways implicated in the regulation of mood, arousal, and sleep-wake balance (Ortiz et al., 1999; Marder et al., 2003).

Experimental studies have demonstrated that valerian extracts enhance inhibitory neurotransmission through modulation of the GABAergic system, a central mediator of anxiolytic and sedative processes. Valerenic acid acts as a positive allosteric modulator of GABA_A receptors, augmenting their responsiveness to endogenous GABA and promoting neuronal hyperpolarisation. This mechanism parallels that of benzodiazepines, but valerian's action is milder and involves distinct receptor binding sites, which may underlie its favourable safety and tolerability profile (Benke et al., 2009). Furthermore, certain

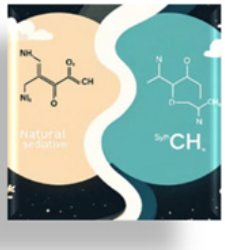


GABAergic modulation

- *Key compounds*: Valerenic acid, valerenol
- *Mechanisms*:
- Positive allosteric modulation of GABA_A receptors → ↑ inhibitory neurotransmission;
- Inhibition of GABA transaminase → ↑ synaptic GABA levels
- *Effects*: Sedation, anxiolysis, sleep promotion

Adenosine receptor interaction

- *Target*: A(1A) adenosine receptors
- *Mechanism*:
- Neuronal hyperpolarisation → ↓ excitability
- *Effects*: Sedation, sleep induction



Serotonin receptor modulation

- *Targets*: 5-HT(1A), 5-HT(5A) receptors
- *Mechanism*:
- Regulation of mood, anxiety, circadian rhythm
- *Effects*: Anxiolysis, mood stabilization, improved sleep onset

Ion channel regulation

- *Targets:*
- Chloride channels (GABA_A-associated) → membrane stabilization
- Voltage-gated calcium channels → ↓ neurotransmitter release
- *Effects:* Neuroinhibition, calming, reduced excitability

Antioxidant and anti-inflammatory activity

- *Key compounds*: Phenolic acids, flavonoids
- *Mechanisms*:
- ROS scavenging;
- ↓ TNF-α, IL-6 production
- *Effects*: Neuroprotection, cytoprotection, stress resilience

Synergistic interactions

- *Observation*: Whole extracts > isolated compounds
- *Mechanism*:
- Multi-target modulation via valepotriates, volatile oils, flavonoids
- *Effects*: Enhanced sedative, anxiolytic, and sleep-promoting efficacy

Figure 3 Mechanisms of action of *Valeriana officinalis*

valerian constituents inhibit GABA transaminase, thereby increasing extracellular GABA levels and further contributing to anxiolytic and calming effects (Khom et al., 2007).

Further evidence supporting the sedative and anxiolytic properties of *V. officinalis* arises from *in vivo* studies in animal models. The administration of valerian extracts has been shown to reduce locomotor activity, prolong barbiturate-induced sleep, and decrease anxiety-like behaviours in the elevated plus maze and open-field tests (Hattesohl et al., 2008; Murphy et al., 2010; Sahin et al., 2024). These preclinical findings are corroborated by clinical evidence: several randomised controlled trials have reported significant improvements in sleep quality, reduced nervousness, and enhanced relaxation following short- and medium-term use of valerian preparations. Notably, these therapeutic effects were achieved without the adverse reactions, next-day sedation, or withdrawal symptoms commonly associated with conventional anxiolytic and hypnotic drugs (Bent et al., 2006; Fernandez-San-Martin et al., 2010; Chandra Shekhar et al., 2024). Some studies also suggest beneficial effects in patients with generalised anxiety disorder and stress-related conditions, although the evidence remains inconsistent, and further well-designed, large-scale clinical trials are required to establish definitive efficacy (Shinjyo et al., 2020; Tammadon et al., 2021).

The anxiolytic activity of valerian may involve not only the GABAergic system but also the serotonergic and adenosinergic neurotransmission, both of which modulate mood, anxiety, and circadian rhythms. Binding to adenosine A1 receptors leads to neuronal inhibition, while modulation of serotonin 5-HT1A receptors is associated with mood regulation and anxiolysis (Murphy et al., 2010; Wang et al., 2022). Alongside GABAergic effects, this multimodal mechanism contributes to valerian‘s overall sedative and calming properties (Hattesohl et al., 2008).

Importantly, different species and extracts of *Valeriana* exhibit distinct pharmacological profiles, enriching our understanding of the genus‘s therapeutic potential (Çelik and Kırmızıbekmez, 2025). For example, aqueous and ethanol extracts from *Valeriana* spp. have demonstrated sedative and sleep-inducing properties without causing significant drowsiness (Bisset et al., 2004). In animal experiments, intraperitoneal administration of aqueous extracts of *V. jatamansi* (2.78 $g \cdot kg^{-1}$) or oral administration (55.6 $g \cdot kg^{-1}$) significantly inhibited locomotor activity in mice (Cao and Hong, 1994). Some studies have revealed that the essential oil and iridoid fractions are primarily responsible for this sedative action (Wagner et al., 1980; Hendriks et al., 1981).

Similarly, aqueous extracts of *V. officinalis* have been shown to inhibit cortical excitation, reduce reflex excitability, and induce smooth muscle relaxation (Nam et al., 2013). Essential oil fractions were identified as the active components mediating suppression of autonomic activity and potentiation of the central depressant effects of sodium pentobarbital and chloral hydrate (Xu et al., 1997). These sedative and hypnotic effects have been mechanistically associated with increased expression of interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α), indicating a role for neuroimmune modulation (Zhang et al., 2010). Additional compounds, such as valerianone, flavonoids, and valeric acid, appear to act synergistically on GABA receptors, enhancing GABA release and inhibiting its reuptake to regulate central nervous system (CNS) activity (Ortiz et al., 1999; Marder et al., 2003).

Beyond sedation and anxiolysis, extracts from *Valeriana* spp. also exhibit significant antidepressant properties, mediated through a combination of neurochemical and neuroplastic mechanisms. Aqueous extracts of *V. officinalis* have been shown to alleviate depressive-like behaviours in animal models by increasing serotonin (5-HT) levels, promoting the proliferation of hippocampal neurons, and enhancing phosphorylation of cyclic AMP response element-binding protein (CREB) (Tang et al., 2008; Zhou et al., 2010). These findings indicate that valerian may influence both monoaminergic neurotransmission and the intracellular signalling cascades central to synaptic plasticity and the pathophysiology of depression.

Consistent with these observations, Neamati et al. (2014) demonstrated that the hydroalcoholic extract of *V. officinalis* significantly reduced depression-like behaviours in ovalbumin-sensitised rats. Animals treated with 100 or 200 $mg \cdot kg^{-1}$ of the extract exhibited reduced immobility in the forced swim test and increased exploratory activity in the open field test, particularly in the central zone. These behavioural changes suggest an antidepressant-like effect potentially mediated by attenuation of neuroinflammation and enhancement of neurogenesis, supporting the neuroprotective potential of *V. officinalis* through modulation of neuroimmune pathways (Neamati et al., 2014).

Further evidence for these effects was provided by Qin et al. (2009), who demonstrated that administration of *V. officinalis* to rats subjected to chronic mild stress reversed depression-like symptoms, as indicated by restored body weight and sucrose intake. Treatment with valerian was found to significantly reduce serum cortisol levels and decrease the number of caspase-3-positive hippocampal neurons, indicating both endocrine and neuroprotective effects. Given the established role of hippocampal neurodegeneration and hypothalamic-pituitary-adrenal (HPA) axis dysregulation in the development of depressive disorders, these findings provide mechanistic support for the adjunctive use of *V. officinalis* in managing depression (Qin et al., 2009). Collectively, this body of evidence suggests that *V. officinalis* possesses clinically relevant antidepressant potential.

In addition to its antidepressant effects, *Valeriana* spp. display robust anxiolytic activity, as evidenced by various behavioural models, including the elevated plus maze, light/dark preference tests, and zebrafish assays. Murphy et al. (2010) demonstrated that valerian root extract exerts potent anxiolytic effects in rats comparable to those of diazepam in the elevated plus maze test. The active compound, valerenic acid, was found to interact with the GABA_A receptor system, indicating a mechanism of action similar to that of benzodiazepines. Rats treated with valerian extract or valerenic acid spent significantly more time on the open arms of the maze, reflecting reduced anxiety-like behaviour. Importantly, unlike benzodiazepines, valerian does not produce significant sedation or cognitive impairment at anxiolytic doses, thereby underscoring its favourable safety profile and therapeutic promise.

Consistent results were obtained by Del Valle-Mojica and Ortiz (2012), who reported significant anxiolytic effects of *V. officinalis* extracts and valerenic acid in zebrafish. Treated animals spent more time in the white compartment of the dark/light preference test, an effect attenuated by antagonists of metabotropic glutamate receptors I and II. The anxiolytic response was attenuated by antagonists of metabotropic glutamate receptors I and II, indicating that these receptors mediate the behavioural effects of valerian. This highlights a novel mechanism of action involving glutamatergic signalling, which may function in parallel with or independently of GABAergic pathways. Collectively, these findings underscore the therapeutic potential of *V. officinalis* through its modulatory effects on both GABAergic and glutamatergic neurotransmission.

Complementary results were obtained by Pinder et al. (2024), who showed that valerenic acid (12 mg·kg^{-1}) significantly reduced anxiety-like behaviour in young adult female mice, with efficacy comparable to that of diazepam. The anxiolytic action of VA was confirmed in the elevated plus maze test, without alterations in locomotor or depression-like behaviour in the open field and tail suspension tests. These results indicate that valerenic acid exerts a selective anxiolytic action independent of sedative or antidepressant effects, reinforcing its potential as a safe and effective therapeutic candidate for anxiety disorders.

The pharmacological effects of *Valeriana* spp. are presented in Figure 4.

In summary, *V. officinalis* and related species exhibited well-documented sedative, anxiolytic, and antidepressant properties, mediated through complex interactions with various neurochemical systems, such as the GABAergic, serotonergic, adenosinergic, and glutamatergic pathways. The synergistic actions of valerenic acid, valepotriates, flavonoids, and essential oil constituents enhance inhibitory neurotransmission, modulate mood-related signalling, and provide neuroprotection. Evidence from both experimental and clinical studies consistently demonstrates that valerian improves sleep quality, reduces anxiety, and alleviates depressive symptoms, without producing the cognitive impairment or dependency commonly associated with synthetic sedatives. The multimodal pharmacological profile and favourable safety margin of *V. officinalis* highlight its therapeutic potential as a natural alternative or adjunct in the management of anxiety, insomnia, and mood disorders.

Sleep-Promoting Effects

The sleep-promoting properties of *V. officinalis* have been extensively explored in both experimental and clinical contexts. These investigations consistently demonstrate its efficacy as a mild, non-addictive hypnotic agent (Bent et al., 2006; Chandra Shekhar et al., 2024). In contrast to many conventional sedative-hypnotics, valerian facilitates sleep initiation and maintenance without significantly disrupting sleep architecture or causing notable next-day cognitive impairment. Owing to its favorable tolerability and safety profile, *V. officinalis* is considered a valuable phytotherapeutic option for individuals with mild to moderate insomnia, sleep-onset difficulties, or reduced sleep quality (Shinjyo et al., 2020; Tammadon et al., 2021).

GABAergic modulation (core mechanism)

- **Active compounds**: Valerenic acid, valerenol, valepotriates
- **Mechanisms**:
  - Positive allosteric modulation of GABA_A receptors → enhanced inhibitory signaling;
  - Inhibition of GABA transaminase → increased synaptic GABA levels
- **Effects**: Sedation, anxiolysis, sleep promotion
- **Evidence**: *In vitro* studies, behavioral assays (elevated plus maze, locomotor tests), clinical trials

Serotonergic and adenosinergic pathways

- **Targets**: 5-HT(1A), 5-HT(5A), A1 adenosine receptors
- **Mechanisms**:
  - Mood regulation, circadian rhythm stabilization, neuronal inhibition
- **Effects**: Anxiolysis, emotional balance
- **Evidence**: Animal models, light/dark preference tests, clinical trials

Glutamatergic modulation (emerging mechanism)

- **Targets**: Metabotropic glutamate receptors I & II
- **Mechanisms**:
- Regulation of excitatory neurotransmission independent of GABA
- **Effects**: Anxiolysis without sedation
- **Evidence**: Zebrafish assays, receptor antagonist studies

Neuroimmune and endocrine effects

- ***Compounds:*** Flavonoids, valerianone, valeric acid
- ***Mechanisms:***
  - ↓ TNF-α, IL-1β → anti-inflammatory action
  - ↓ cortisol, ↓ caspase-3 → neuroprotection, HPA axis regulation
- ***Effects:*** Antidepressant, cytoprotective
- ***Evidence:*** Chronic stress models, forced swim test, hippocampal markers

Neuroplasticity and monoaminergic support

- ***Mechanisms:***
  - ↑ 5-HT levels, ↑ hippocampal neurogenesis
  - ↑ CREB phosphorylation → enhanced synaptic plasticity
- ***Effects:*** Antidepressant, regenerative
- ***Evidence:*** Behavioral models, molecular assays

Species-specific and extract-dependent profiles

- ***Species:*** *V. officinalis*, *V. jatamansi*
- ***Extracts:*** Aqueous, ethanolic, essential oils
- ***Mechanisms:***
  - Cortical inhibition, smooth muscle relaxation
  - Potentiation of barbiturate effects
- ***Effects:*** Sedation, sleep enhancement without residual drowsiness
- ***Evidence:*** Pharmacological studies, animal experiments

Figure 4 Pharmacological effects of *Valeriana* spp.

Electroencephalographic (EEG) studies provide valuable insight into the neurophysiological mechanisms underlying the hypnotic effects of *V. officinalis*. The administration of valerian extracts has been associated with characteristic alterations in brainwave patterns during the pre-sleep transition and throughout sleep itself. Specifically, increases in delta (0.5–4 Hz) and theta (4–8 Hz) power have been reported, reflecting deeper non-REM sleep stages and enhanced relaxation. In addition, several studies have also observed reductions in alpha activity during the transition to sleep, consistent with decreased cortical arousal and facilitated sleep onset (Shinomiya et al., 2005; Tokunaga et al., 2007). The study of Choi et al. (2018) showed that a Valerian/Cascade mixture significantly improved sleep quality in rodents by increasing non-rapid eye movement (NREM) sleep and reducing sleep latency. EEG analysis revealed a 53% increase in NREM duration and a marked enhancement of delta wave activity, indicative of deeper sleep. The mixture also counteracted caffeine-induced sleep disturbances and exhibited strong binding affinity (91%) for GABA-benzodiazepine receptors. Valerenic acid and xanthohumol were identified as key contributors to this GABAergic sleep-promoting effect (Choi et al., 2018). Importantly, unlike many synthetic hypnotics, valerian does not significantly suppress rapid eye movement (REM) sleep or alter REM cycles in most experimental and clinical studies (Bent et al., 2006; Shinjyo et al., 2020).

In clinical trials, valerian has been shown to reduce sleep latency (i.e., the time taken to fall asleep) by an average of 5–15 minutes, depending on the extraction method, dosage, and duration of administration. This effect often becomes more pronounced with repeated nightly use, suggesting cumulative neurochemical adaptation over time (Bent et al., 2006; Shinjyo et al., 2020). Several randomised controlled trials (RCTs) have reported improvements in subjective measures of sleep onset and continuity, with participants commonly describing faster sleep initiation and fewer nocturnal awakenings. Objective polysomnographic assessments in some trials indicate modest increases in total sleep time and slow-wave sleep (SWS), both of which are essential for physical restoration and cognitive recovery (Donath et al., 2000; Stevinson and Ernst, 2000).

Beyond facilitating sleep onset, valerian intake is frequently associated with deeper and more restorative sleep, reduced nocturnal restlessness, and greater alertness upon waking. Unlike benzodiazepines and non-benzodiazepine hypnotics, valerian generally does not cause major changes to sleep stages or impair next-day psychomotor performance, rendering it a potentially safer option for long-term use (Guadagna et al., 2020; Chandra Shekhar et al., 2024).

Several clinical studies have demonstrated improvements in overall sleep quality following the administration of valerian at daily doses ranging from 160 to 600 mg (Leathwood et al., 1982; Lindahl and Lindwall, 1989; Herrera-Arellano et al., 2001; Poyares et al., 2002; Ziegler et al., 2002; Müller and Klement, 2006; Taavoni et al., 2011, 2013). However, other studies have failed to identify significant effects on sleep quality when assessed using the Pittsburgh Sleep Quality Index (PSQI) or subjective assessments (Oxman et al., 2007; Cuellar and Ratcliffe, 2009; Barton et al., 2011). Furthermore, valerian has been reported to reduce wake time after sleep onset (Leathwood et al., 1982; Poyares et al., 2002), shorten sleep latency (Donath et al., 2000; Waldschütz and Klein, 2008), extend sleep duration (Donath et al., 2000; Waldschütz and Klein, 2008), and improve insomnia severity scores (Wheatley, 2001). Nevertheless, Jacobs et al. (2005) found no significant changes in the Insomnia Severity Index (ISI) compared with placebo. Similarly, in a small trial, Diaper and Hindmarch (2004) observed no alterations in polysomnographic parameters or psychometric outcomes following a single-dose administration of 300 mg or 600 mg of valerian. Consistent with these findings, Coxeter et al. (2003) reported no significant differences in total sleep time or the number of nocturnal awakenings in a cohort of 24 participants.

In addition to clinical outcomes, several trials have investigated the underlying mechanisms responsible for the sleep-promoting effects of valerian. Notably, Mineo et al. (2017) demonstrated that a single oral dose of *V. officinalis* extract significantly reduced intracortical facilitation, a neurophysiological alteration commonly associated with decreased anxiety. The effects of combination therapies have also been investigated, particularly formulations combining valerian with hops (*Humulus lupulus* L.), indicating that the interaction between these botanicals could result in greater reductions in sleep latency and improvements in sleep efficiency compared with valerian monotherapy. The rationale for this combined approach lies in the complementary pharmacodynamics of both plants: Valerian primarily enhances GABAergic neurotransmission, while hops is believed to exert mild sedative effects through

adenosinergic and melatoninergic modulation, mechanisms that support circadian rhythm regulation and facilitate sleep onset.

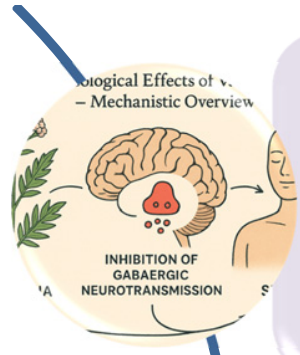
A pilot study by Füssel et al. (2000) examined the impact of a fixed valerian-hops extract combination (Ze 91019) on sleep architecture in individuals with mild to moderate non-organic insomnia. Following two weeks of evening treatment, polysomnographic data revealed reduced sleep latency and wake time after sleep onset, together with increases in sleep efficiency and slow-wave sleep. Patients also reported improved morning refreshment, and no adverse events were observed. These findings support the potential of valerian-hop combinations to improve both objective and subjective indices of sleep quality, underscoring the relevance of synergistic herbal formulations in clinical sleep management. However, confirmation in larger, rigorously controlled trials remains warranted.

Based on these observations, Morin et al. (2005) conducted a randomised, placebo-controlled trial comparing the efficacy of a valerian-hops combination with diphenhydramine in adults with mild insomnia. Both treatments yielded modest improvements in subjective sleep parameters. The valerian-hops formulation produced a small reduction in sleep latency and significantly improved physical quality of life after 28 days, although polysomnographic parameters remained largely unchanged. Diphenhydramine, by contrast, increased sleep efficiency and total sleep time during the initial 14 days. Importantly, both treatments were well tolerated with no evidence of serious adverse events or rebound insomnia, suggesting that the valerian-hops combination may represent a safe adjunctive therapy for mild insomnia (Morin et al., 2005).

Further support comes from the randomised, placebo-controlled feasibility trial by Schicktanz et al. (2025), in which Ze 91019 significantly increased sleep duration in individuals experiencing occasional insomnia with a mean daily gain of 21.7 minutes and an increase of 48.7 minutes on the shortest night. Despite these improvements in sleep metrics, next-day cognitive performance or psychological parameters remained unaffected, suggesting that the valerian-hops combination promotes restorative sleep without impairing daytime functioning. Notably, the study design, which integrated wearable sleep tracking technology and online assessments, proved highly feasible and achieved strong participant adherence. Ze 91019 was well tolerated throughout the study, further reinforcing its potential as a safe and effective phytotherapeutic intervention for mild sleep disturbances (Schicktanz et al., 2025).

The sleep-promoting effects of *V. officinalis* are presented in Figure 5.

In summary, valerian appears to exert sleep-promoting effects primarily through enhancing relaxation, facilitating the transition into deeper non-rapid eye movement (non-REM) sleep stages as measured by EEG, reducing sleep latency, and improving both subjective and objective indices of sleep quality. Its favourable safety profile, characterised by minimal alteration of REM sleep and absence of next-day psychomotor or cognitive impairment, renders it a viable phytotherapeutic alternative to conventional hypnotics. However, further rigorously designed, placebo-controlled trials employing well-characterised and standardised extracts are warranted to elucidate optimal dose-response relationships, clarify mechanisms of action, and strengthen the evidence base for clinical recommendations.



Neurophysiological mechanisms

GABAergic modulation:

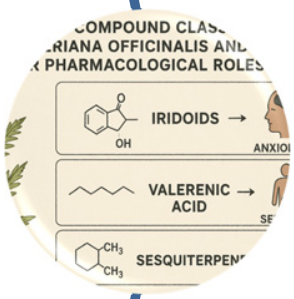
Valerenic acid and valerenol bind to GABA_A–benzodiazepine receptors; Enhance inhibitory signaling without direct agonism

EEG changes:

- ↑ Delta (0.5–4 Hz) and theta (4–8 Hz) waves → deeper NREM sleep
- ↓ Alpha activity → reduced cortical arousal

Additional targets:

- ↓ Intracortical facilitation; Potential adenosinergic and melatoninergic synergy (with hops)



Clinical effects

Sleep latency:

- ↓ by 5–15 minutes on average;
- Enhanced with repeated nightly use

Sleep architecture:

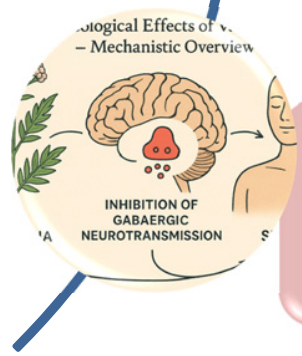
- ↑ NREM and slow-wave sleep (SWS);
- Minimal impact on REM cycles

Subjective improvements:

Faster sleep initiation; Fewer awakenings; Deeper, more restful sleep; Feeling refreshed upon waking

Safety profile:

No next-day sedation or cognitive impairment; Suitable for long-term use



Dosage and efficacy range

Effective doses: 160–600 mg/day

Variable outcomes:

- Positive results in multiple RCTs;
- Mixed findings in PSQI and ISI-based studies;
- Some trials show no significant changes in sleep metrics

Comparative trials

Versus diphenhydramine:

Comparable subjective improvements; Better tolerability, no rebound insomnia

Feasibility studies:

Wearable sleep tracking confirms ↑ sleep duration

High adherence and safety

Combination therapies

Valerian + hops (Ze 91019):

↑ Sleep efficiency, ↓ latency, ↑ SWS

No adverse effects or rebound insomnia, Enhanced physical quality of life

Maintains daytime cognitive function

Mechanistic synergy:

Valerian → GABAergic enhancement

Hops → adenosine/melatonin modulation

Figure 5 Sleep-promoting effects of *Valeriana officinalis*

Neuroprotective and Cognitive Effects of *Valeriana officinalis* and Related Species

There is increasing evidence that *V. officinalis* and related species possess significant neuroprotective properties that may contribute to the preservation of cognitive function and protection against neurodegenerative processes (de Oliveria et al., 2009; Patočka and Jakl, 2010; Piccirillo et al., 2025) (Table 1). Preclinical studies have demonstrated valerian extracts can alleviate oxidative stress and neuronal damage caused by reactive oxygen species (ROS) (Malva et al., 2004; Marcucci et al., 2023). The phenolic compounds, flavonoids, and valepotriates found in valerian are thought to neutralise free radicals, increase the production of endogenous antioxidant enzymes, and prevent lipid peroxidation in neuronal tissues (Średnicka-Tober et al., 2022). These antioxidant effects collectively protect neurons from oxidative damage, a key pathophysiological hallmark of ageing and neurodegenerative disorders such as Alzheimer‘s, Parkinson‘s and Huntington‘s (Olufunmilayo et al., 2023).

In addition to its antioxidant actions, valerian modulates multiple neurotransmitter systems that further contribute to its neuroprotective potential. It enhances inhibitory GABAergic signalling and

Table 1 Neuroprotective and cognitive-enhancing effects of *Valeriana officinalis* and related species

Research area/ mechanism	Experimental model/study type	Extracts	Observed effects	References
Antioxidant and free radical scavenging activity	*in vitro*; neuronal tissue; animal models	ethanolic or methanolic extracts containing phenolics, flavonoids, and valepotriates	reduction of ROS-induced oxidative stress; inhibition of lipid peroxidation; increased activity of endogenous antioxidant enzymes (SOD, CAT, GSH-Px); enhanced total antioxidant capacity (T-AOC)	Malva et al., 2004; Średnicka-Tober et al., 2022; Marcucci et al., 2023
Protection against oxidative neuronal injury	rodent models of neurodegeneration	crude valerian extract	attenuation of neuronal cell death; protection against oxidative damage associated with Alzheimer's, Parkinson's, and Huntington's diseases	de Oliveira et al., 2009; Patočka & Jakl, 2010; Olufunmilayo et al., 2023; Piccirillo et al., 2025
GABAergic modulation and anti-excitotoxic effects	rat hippocampal neurons; models of cerebral ischemia and excitotoxicity	70% ethanolic extract	enhancement of GABAergic transmission; inhibition of glutamate-induced Ca^{2+} influx; reduction of excitotoxic neuronal death	Malva et al., 2004; Yuan et al., 2004; Guerriero et al., 2015
Serotonergic and adenosinergic system modulation	cellular and animal models	whole extract (aqueous or ethanolic)	improvement in synaptic plasticity and stress resilience; promotion of cognitive performance and mood stability	Shinjyo et al., 2020
Cognitive enhancement in Alzheimer's disease models	rats with Alzheimer's disease-like pathology	ethanol extract of *V. officinalis*	improved learning and memory; increased catalase and T-AOC activity; reduced acetylcholinesterase activity and MDA levels	Yoo et al., 2015; Zhang and Zuo, 2018
Protection against Parkinson's disease-related neurotoxicity	*Drosophila melanogaster* exposed to rotenone	aqueous extract	restoration of SOD and catalase activity; prevention of oxidative damage and locomotor deficits	Sudati et al., 2013
Cerebrovascular protection (anti-ischaemic effects)	rat model of middle cerebral artery occlusion	*V. officinalis* tincture	reduction in cerebral infarct volume, neuronal injury, and expression of *C-Fos* and *C-Jun*; neuroprotection in post-ischaemic brain injury	Wang et al., 2004
Cognitive and psychomotor effects in humans	Human clinical and pilot studies	Valerian root extract (oral, variable dose)	Improved attention, memory, and resistance to mental fatigue; enhanced sleep quality; limited sample size in clinical trials	Bent et al., 2006; Samaei et al., 2018; Halson et al., 2020; Sahin et al., 2024

stabilises neuronal excitability, thereby reducing glutamate-induced excitotoxicity (Malva et al., 2004; Yuan et al., 2004). This mechanism is particularly relevant in pathological conditions such as cerebral ischaemia, traumatic brain injury, and chronic stress, where excessive glutamatergic activity promotes neuronal apoptosis (Guerriero et al., 2015). Furthermore, interactions with serotonergic and adenosinergic systems are believed to support synaptic plasticity and stress-response pathways, thereby promoting enhanced cognitive resilience (Shinjyo et al., 2020).

The neuroprotective efficacy of *Valeriana* spp. has also been investigated in disease-specific experimental models. For instance, ethanol extracts of *V. officinalis* have been demonstrated to improve learning, memory performance, and spontaneous activity in rats with an Alzheimer‘s disease model, accompanied by elevated serum catalase activity, increased total antioxidant capacity (T-AOC), and reduced acetylcholinesterase activity (Yoo et al., 2015; Zhang and Zuo, 2018). Concurrently, enhanced superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities, together with decreased malondialdehyde (MDA) levels, indicate reinforcement of the endogenous antioxidant defence system. Collectively, these biochemical changes suggest a dual neuroprotective mechanism involving both antioxidant activity and enhancement of cholinergic neurotransmission.

Consistent with these findings, valerian extracts have demonstrated notable neuroprotective activity across various experimental models. A 70% ethanol extract of *V. officinalis* (10 ng·ml^{-1}·100 µg·ml^{-1}) prevented neuronal cell death induced by Aβ25–35 in rat hippocampal neurons by inhibiting excess Ca^{2+} influx and suppressing ascorbate/iron-mediated lipid peroxidation (Malva et al., 2004). Similarly, aqueous extracts have exhibited protective effects in *Drosophila melanogaster* exposed to rotenone, restoring the expression of key antioxidant enzymes such as SOD and catalase (Sudati et al., 2013). These findings support the potential application of valerian extracts in mitigating Parkinson’s disease (PD)-related neurotoxicity.

While preclinical evidence for valerian’s neuroprotective effects is substantial, clinical data remain limited and fragmented. Preliminary human studies suggest that valerian may enhance cognitive performance, particularly in domains related to attention, memory, and resistance to mental fatigue (Samaei et al., 2018; Halson et al., 2020). However, the available clinical trials are few in number, and they often involve small sample sizes and employ heterogeneous methodologies. Consequently, more rigorously designed, placebo-controlled investigations are needed to confirm these cognitive benefits in populations affected by neurodegenerative diseases or age-related cognitive decline.

Notably, valerian‘s neuroprotective properties may complement its well-known sedative and anxiolytic effects. Restorative sleep plays a critical role in memory consolidation, neurogenesis, and overall brain homeostasis. By simultaneously improving sleep quality and mitigating oxidative and excitotoxic neuronal damage, valerian may contribute to enhanced cognitive performance and promote long-term brain health (Bent et al., 2006; Shinjyo et al., 2020; Sahin et al., 2024). Moreover, experimental data also suggest cerebrovascular benefits: *V. officinalis* tincture reduced cerebral infarct volume, neuronal injury, and the expression of proto-oncogene *C-Fos* and transcription factor *C-Jun* in a rat model of reversible middle cerebral artery occlusion (Wang et al., 2004), suggesting potential applications in post-ischaemic neuroprotection.

In conclusion, *Valeriana* spp. display multifaceted neuroprotective and cognitive-enhancing properties mediated through antioxidant mechanisms, modulation of GABAergic and cholinergic neurotransmission, and interactions with disease-specific molecular pathways. While extensive preclinical data strongly support the therapeutic potential of valerian in models of Alzheimer‘s, Parkinson‘s, and Huntington‘s diseases, and cerebral ischaemia, further well-designed clinical trials are urgently required to confirm its efficacy, establish optimal dosing strategies, and elucidate valerian’s role in the prevention and management of cognitive decline and neurodegeneration.

Anticonvulsant and Antiepileptic Effects of *Valeriana officinalis* and Related Species

Valerian has long been recognised for its sedative and anxiolytic properties (Table 2). More recently, pharmacological research has considerably broadened its therapeutic profile by identifying anticonvulsant and antiepileptic potential, suggesting possible applications in the management of seizure disorders (Eadie, 2004; González-Trujano et al., 2021; Manavi, 2023). These effects are attributed to valerian’s diverse phytochemical composition, which includes valerenic acid, valepotriates, flavonoids, and iridoids, compounds known to interact with molecular targets in the central nervous system involved in neuronal excitability and synaptic transmission (Zhang et al., 2014).

Table 2 Anticonvulsant and antiepileptic properties of *Valeriana officinalis* and related species

Mechanism/research focus	Experimental model/study type	Extracts/ compounds	Observed effects	References
Sedative, anxiolytic, and anticonvulsant potential	general pharmacological and behavioural studies	whole plant extract (aqueous and ethanolic)	reduced seizure frequency and severity; delayed seizure onset; prolonged latency in chemically and electrically induced seizures	Eadie, 2004; González-Trujano et al., 2021; Manavi, 2023
Modulation of GABAergic neurotransmission	PTZ- and MES-induced seizures in rodents	ethanolic and aqueous extracts	increased seizure threshold; reduced convulsion frequency; enhanced brain GABA levels	Wu et al., 2005; Nouri and Abad, 2011
GABA_A receptor modulation by valerenic acid	*in vitro*/*in vivo* rodent studies	valerenic acid	positive allosteric modulation of GABA_A receptors; enhanced inhibitory synaptic transmission; reduced neuronal hyperexcitability	Zhang et al., 2014
Regulation of GABA uptake and release	rat hippocampal neurons/epileptic rat models	aqueous extract; iridoids from *V. officinalis*	inhibition of [^{3}H]GABA uptake; stimulation of GABA release; down-regulation of GABA transporter GAT-1 expression in hippocampus	Santos et al., 1994; Luo et al., 2004; Luo et al., 2005
Activity of *V. jatamansi* extracts	rodent models (picrotoxin- and thiosemicarbazide-induced seizures)	aqueous extract	potentiation of pentobarbital-induced sedation; reduced spontaneous motor activity; delayed seizure onset; increased GABA availability under inhibited synthesis or receptor blockade	Cao and Hong, 1994
Regulation of excitatory–inhibitory amino acid balance	PTZ-induced seizures and amygdala-kindled temporal lobe epilepsy in rats	essential oil and crude extract of *V. officinalis*	increased hippocampal GABA; decreased glutamate; reduced seizure duration and severity; latency prolongation; effect reversed by adenosine A1 receptor antagonist	Wu et al., 2008; Rezvani et al., 2010
Antioxidant mechanism contributing to seizure control	rodent models of epilepsy/oxidative stress assays	ethanolic or aqueous extracts	increased activity of endogenous antioxidants; reduction in oxidative damage; protection against excitotoxic neuronal injury	Sudati et al., 2009; Aguiar et al., 2012; Thusoo et al., 2014

Experimental studies using rodent models of epilepsy have consistently demonstrated that both aqueous and ethanolic extracts of *V. officinalis* can reduce seizure frequency and severity. For instance, administration of these extracts delays seizure onset and prolongs latency in chemically induced convulsions, such as those induced by pentylenetetrazole (PTZ) or maximal electroshock (MES). These anticonvulsant effects are largely mediated through modulation of GABAergic neurotransmission, a principal inhibitory pathway regulating neuronal excitability. Valerenic acid functions as a positive allosteric modulator of GABA_A receptors, enhancing inhibitory signalling and counteracting hyperexcitability. Concurrent studies have confirmed that the aqueous extract of *V. officinalis* increases seizure threshold, prolongs latency, and reduces convulsion frequency in PTZ-induced models, which is consistent with an increase in brain GABA levels (Wu et al., 2005; Nouri and Abad, 2011).

Further mechanistic insights show that aqueous extracts of *V. officinalis* inhibit the uptake and promote the release of [^{3}H]GABA, thereby elevating synaptic GABA concentrations (Santos et al., 1994). Additionally, iridoids found in valerian roots and rhizomes have been shown to down-regulate the expression of the GABA transporter GAT-1 in the hippocampus of epileptic rats, thereby enhancing GABAergic signalling by inhibiting its reuptake (Luo et al., 2004, 2005). Together, these findings highlight valerian's capacity to modulate GABA availability at multiple regulatory levels.

The anticonvulsant properties of other *Valeriana* species, particularly *V. jatamansi*, provide further evidence of GABA-mediated activity. Aqueous extracts of *V. jatamansi* not only potentiate the sedative and hypnotic effects of pentobarbital sodium, but also suppress spontaneous motor activity and delay seizure onset in picrotoxin- and thiosemicarbazide-induced models. As thiosemicarbazide inhibits glutamic acid

decarboxylase, thereby lowering cerebral GABA synthesis, and picrotoxin acts as a GABA receptor antagonist, these data suggest that *V. jatamansi* may exert its effects by increasing GABA availability and counteracting GABAergic inhibition (Cao and Hong, 1994).

Beyond GABAergic modulation, valerian appears to influence the balance of excitatory and inhibitory amino acids in the brain. For example, the essential oil of *V. officinalis* alleviated PTZ-induced convulsions in epileptic rats by increasing hippocampal GABA levels and reducing glutamate concentrations (Wu et al., 2008). Similarly, valerian extracts reduced seizure duration and severity and prolonged latency to forelimb clonus in amygdala-kindled temporal lobe epilepsy models. Interestingly, the anticonvulsant effect was reversed by 8-cyclopenthyl-1,3-dimethylxanthine, a selective adenosine A1 receptor antagonist, suggesting that activation of adenosine pathways may complement GABAergic mechanisms (Rezvani et al., 2010).

Valerian's antioxidant activity represents an additional mechanism relevant to seizure control (Sudati et al., 2009). Oxidative stress contributes to both epileptogenesis and seizure propagation (Aguiar et al., 2012). Experimental data show increased levels of endogenous antioxidants following valerian treatment (Thusoo et al., 2014), suggesting a dual mechanism involving neurotransmitter modulation and redox homeostasis. This antioxidant effect may further protect neuronal structures from excitotoxic damage associated with recurrent seizures.

Despite promising preclinical findings, clinical data on the anticonvulsant efficacy of valerian remain absent. Nonetheless, its favourable safety profile, historical use in traditional medicine, and concomitant sedative-anxiolytic benefits position valerian as a promising candidate for further investigation, particularly as an adjunctive therapy for drug-resistant epilepsy and comorbid sleep and anxiety disorders (Shinjyo et al., 2020). Future research should prioritise the standardisation of extract formulations, the establishment of dose-response relationships, and the implementation of well-designed clinical trials integrating electrophysiological and molecular techniques to clarify the precise pathways underlying valerian's anticonvulsant effects.

Cardiovascular Effects of *Valeriana officinalis* and Related Species

V. officinalis, a medicinal plant traditionally valued for its sedative and anxiolytic properties, has recently attracted increasing scientific interest due to its potential cardiovascular and cerebrovascular effects. These activities are mediated by a variety of phytochemicals, including valerenic acid, valepotriates, flavonoids, and essential oils, which modulate autonomic and vascular regulatory pathways (Li et al., 2022).

Preclinical studies have demonstrated that *V. officinalis* extracts exert hypotensive, bradycardic, and vasorelaxant effects. In animal models, administration of valeric acid has produced a dose-dependent reduction in both systolic and diastolic blood pressure, accompanied by a decrease in heart rate (Onyszkiewicz et al., 2020). These effects are thought to result from a dual mechanism involving central GABAergic modulation, attenuating sympathetic outflow, and direct actions on peripheral vascular smooth muscle tone. Valerenic acid, in particular, acts as a positive allosteric modulator of GABA_A receptors in the central nervous system, thereby reducing cardiovascular reactivity and promoting autonomic balance (Khom et al., 2007; Benke et al., 2009).

Although clinical evidence remains limited, small-scale human studies suggest that valerian may modestly lower blood pressure and alleviate symptoms such as palpitations and anxiety-related tachycardia. Importantly, the plant has demonstrated a favourable safety profile, with minimal adverse cardiovascular effects at therapeutic doses. In the semi-experimental study by Hosseini et al. (2025), twelve healthy volunteers consumed *V. officinalis* tea (VOT) to assess its impact on autonomic regulation and cardiac function. The results revealed a significant, progressive reduction in heart rate and systolic blood pressure over 30 minutes following VOT intake. These changes were interpreted as a shift toward enhanced parasympathetic activity and reduced sympathetic tone, based on heart rate variability indices, suggesting that VOT may beneficially modulate sympathovagal balance in healthy individuals.

Beyond its haemodynamic actions, *V. officinalis* exerts cardioprotective, antiarrhythmic, and cerebroprotective properties, including protection against cerebral ischaemia-reperfusion injury. In an isolated rat model of cardiac ischaemia-reperfusion, aqueous extracts of *V. officinalis* alleviated myocardial spasm and improved the regularity, strength, and smoothness of cardiac contraction and relaxation (Yang et al., 2012). These cardioprotective effects were associated with decreased serum levels of lactate dehydrogenase, creatine kinase, and

Table 3 Cardiovascular and cerebrovascular effects of *Valeriana officinalis* and related species

Effect/outcome	Type of extract/ compound	Experimental model/ subjects	Mechanism of action	References
Hypotensive and bradycardic effects	Valeric acid, ethanolic extract	animal models (rats, cats); human volunteers	central GABA_A-receptor modulation-reducing sympathetic outflow; direct vascular smooth muscle relaxation	Khom et al., 2007; Benke et al., 2009; Onyszkiewicz et al., 2020; Hosseini et al., 2025
Autonomic regulation (parasympathetic dominance)	Valerian tea (VOT)	healthy volunteers	increased parasympathetic activity, reduced sympathetic tone (HRV indices)	Hosseini et al., 2025
Cardioprotective and anti-ischaemic effects	aqueous extract	rat cardiac ischaemia–reperfusion model	decreased Ca^{2+} overload; enhanced antioxidant enzyme activity (SOD, GPx, ATPases); reduced LDH and MDA	Yang et al., 2012
Antioxidant and anti-inflammatory protection	crude extract, essential oil	*in vitro* and *in vivo* animal models	inhibition of xanthine oxidase, suppression of ROS, increased PGI_2/TXA_2 ratio, reduced TNF-α, and improved coronary circulation	Yin et al., 2000
Antiarrhythmic effects	aqueous, n-butanol, essential oil, and ethyl acetate extracts	rats and mice (aconitine-, chloroform-, $BaCl_2$-, $CaCl_2$-induced arrhythmia)	inhibition of Na^+ influx, β-receptor blockade, Ca^{2+} antagonism	Chen and Yu, 1990; Wen et al., 2009
Cerebrovascular protection	essential oil	mice, rabbits	increased brain microcirculation and perfusion; inhibition of vasospasm, platelet aggregation, and inflammation	Luo et al., 2001; Yang et al., 2002; Li et al., 2004
Vasorelaxant effect on vascular smooth muscle	essential oil	rat vascular smooth muscle cells	inhibition of angiotensin II-induced contraction (NO-independent)	Yang et al., 2002
Reduction of cerebral vasospasm post-subarachnoid haemorrhage	aqueous extract	rabbit basilar artery model	free radical scavenging, anti-inflammatory, anti-aggregatory, and immunomodulatory effects	Luo et al., 2001

malondialdehyde, and elevated activities of superoxide dismutase, glutathione peroxidase, and ATPases, alongside a significant reduction in intracellular Ca^{2+} in cardiomyocytes. Collectively, these findings suggest that myocardial protection involves Ca^{2+} regulation and antioxidant mechanisms.

Further studies have shown that this cardioprotective effect may also involve the inhibition of xanthine oxidase activity, suppression of free radical production, an increased prostacyclin 2/thromboxane A_2 ratio, the inhibition of platelet aggregation, enhancement of coronary microcirculation, decreased TNF-α production, and the mitigation of aseptic inflammation in reperfused tissue (Yin et al., 2000). In anaesthetised cats, ethanolic extracts of *V. officinalis* significantly slowed heart rate, lowered blood pressure, and reduced the arterial-venous oxygen partial pressure ratio, confirming their ability to decrease myocardial oxygen consumption and promote coronary vasodilation (Zhang et al., 1982).

Moreover, aqueous and n-butanol extracts of *V. officinalis* significantly delayed the onset of aconitine-induced ventricular extrasystoles and ventricular fibrillation (VF) in rats, reducing the overall incidence of VF. Similarly, essential oil and ethyl acetate extracts reduced chloroform-induced VF in mice. Aconitine induces arrhythmia by stimulating myocardial Na^+ channels and accelerating Na^+ influx, whereas chloroform-induced VF involves adrenal medulla activation, adrenaline release, and β-receptor stimulation. Therefore, the antiarrhythmic effect of valerian appears to be mediated by the inhibition of Na^+ influx and β-receptor blockade (Wen et al., 2009). Furthermore, essential oils from *V. officinalis* shortened the duration and reduced the incidence of $BaCl_2$-induced arrhythmias in rats, antagonised $CaCl_2$-

induced arrhythmias in mice, and lowered mortality, indicating a Ca^{2+}-antagonistic action mechanism (Chen and Yu, 1990).

V. officinalis essential oil has also shown notable cerebrovascular protective properties. In mice, it enhanced brain microcirculation as evidenced by increased uptake of technetium-99m ethyl cysteinate dimer, higher brain radiation counts, and elevated brain-to-blood ratios. Furthermore, it counteracted acute cerebral ischaemia induced by norepinephrine and improved cerebral perfusion, likely through arterial spasm relief, increased cerebral blood flow, inhibition of platelet aggregation, and enhancement of microcirculation (Li et al., 2004). The essential oil has been shown to inhibit the contraction of rat vascular smooth muscle cells induced by angiotensin II, confirming a vasodilatory effect independent of endogenous NO pathways (Yang et al., 2002). Additionally, aqueous extracts increased the peak systolic velocity and diameter of the basilar artery following subarachnoid haemorrhage in rabbits, effectively reducing cerebral vasospasm. This cerebroprotective effect was likely mediated through free radical scavenging, inhibition of inflammation, prevention of platelet and leukocyte aggregation, and modulation of immune responses (Luo et al., 2001).

Collectively, the available evidence indicates that *V. officinalis* exerts multifaceted cardiovascular and cerebrovascular actions, including blood pressure reduction, vasorelaxation, myocardial protection, antiarrhythmic effects, and attenuation of cerebral vasospasm, through an integrated network of GABAergic modulation, antioxidant defence, ion channel regulation, vascular smooth muscle relaxation, and anti-inflammatory mechanisms. Despite these promising preclinical findings, clinical evidence remains scarce. Future studies should prioritise rigorously designed randomised controlled trials targeting mild hypertension, stress-related cardiovascular dysfunction, arrhythmias, and cerebrovascular circulation disorders. Standardisation of extract composition, detailed dose-response assessments, and advanced molecular and electrophysiological assessments will be essential for validating the therapeutic potential of *V. officinalis* in cardiovascular and cerebrovascular medicine.

Cytotoxic and Antitumor Effects

V. officinalis is a medicinal plant traditionally valued for its sedative and anxiolytic properties. In recent years, its pharmacological profile has expanded considerably, with increasing evidence supporting its cytotoxic and antitumour potential, thereby positioning it as a candidate for oncological research. The roots and rhizomes of *V. officinalis* contain a diverse array of bioactive compounds, including iridoids (notably valepotriates and valtrate), sesquiterpenes, lignans, flavonoids, and essential oils (Çelik and Kırmızıbekmez, 2025). Of these compounds, valtrate has emerged as a key molecule with potent cytotoxic effects across various cancer cell lines. *In vitro* studies have demonstrated that valtrate induces apoptosis, arrests the cell cycle at the G2/M phase, and inhibits proliferation and migration in breast (Yang et al., 2017; Tian et al., 2020), pancreatic (Chen et al., 2021), ovarian (Li et al., 2013,) and glioblastoma cells (Liu et al., 2023). These effects are mediated through multiple molecular pathways, including the inhibition of the transcription factor STAT3 and the downregulation of platelet-derived growth factor receptor alpha (PDGFRA), both of which play central roles in tumour progression and therapeutic resistance (Carpenter and Lo, 2014; Xiong et al., 2014; Pandey et al., 2023).

Mechanistic investigations have further clarified the molecular pathways underlying valtrate's antitumour effects. In glioblastoma models, for example, valtrate suppresses PDGFRA expression, thereby reducing tumour invasiveness and proliferation (Liu et al., 2023), while in pancreatic cancer cells, it directly inhibits STAT3, a pivotal regulator of oncogenic signalling and chemoresistance (Chen et al., 2021). Furthermore, although valerian compounds are predominantly associated with central nervous system activity, recent evidence suggests that GABAergic modulation may contribute to tumour suppression via neuroimmune and neuroendocrine interactions (Zhao et al., 2025). These findings highlight the multifaceted pharmacodynamics of *V. officinalis* constituents and their potential to modulate tumour cell viability, apoptosis, and metastatic behaviour through distinct yet interconnected mechanisms.

Beyond *V. officinalis*, other species of the *Valeriana* genus, such as *V. wallichii* and *V. jatamansi*, have also demonstrated notable cytotoxic and antitumour activities, further broadening the oncopharmacological relevance of this botanical group. Studies on the cytotoxic and antitumour activities of *Valeriana* have primarily focused on their iridoid constituents. Valtrate, didrovaltrate, and baldrinal isolated from *V. wallichii* exhibited marked cytotoxicity towards liver cancer cells. Valtrate displayed the strongest activity among them, being twice as toxic as didrovaltrate and eight times as toxic as baldrinal. Didrovaltrate induced a rapid toxic effect, with hepatoma cell death observed

within two hours of exposure to 66 μg·ml^{-1}, and complete lethality after five hours (Bounthanh et al., 1981). Similarly, didrovaltrate significantly inhibited the proliferation of Krebs' II ascites tumour cells at 100 mg·kg^{-1} (von der Hude et al., 1986).

Iridoid compounds isolated from *V. jatamansi*, including didrovaltrate, acetoxyhydrin, volvatrate B, isovaleroxyhydroxy-dihydrovaltrate, 10-acetylpatrinoside, valeranivalvatrate Z1-Z3, valvatrate, and acevatrate, exhibited moderate cytotoxicity against several human cancer cell lines, including the prostate (PC-3M), hepatoma (Bel7402), the lung adenocarcinoma (A549), and colon carcinoma (HCT-8), with IC_{50} values ranging from 1.0 to 8.5 μM (Lin et al., 2015; Xie et al., 2019). Valejatanin A exhibited strong cytotoxicity against the human colon carcinoma (HT29), human leukaemia (K562), and mouse melanoma (B16) cell lines, with IC_{50} values of 22.17, 15.26, and 3.53 μg·ml^{-1}, respectively. Other compounds, such as 8-acetoxypatchouli alcohol and valerol A, displayed moderate activity against the B16 mouse melanoma cell line (IC_{50} = 31.43 and 30.78 μg·ml^{-1}, respectively) (Quan et al., 2019). Furthermore, 8,9-dihydro-7-hydroxy-dolichodial and valeridoid F were cytotoxic to three types of human glioma stem cells, effectively inhibiting their proliferation with IC_{50} values ranging from 30.19 to 47.55 μM (Quan et al., 2020).

Iridoids such as valtrate, didrovaltrate, and baldrinal have been shown to induce apoptosis in MKN-45 gastric cancer cells by increasing the expression of caspase-3 and caspase-9 (Ye et al., 2004, 2007). These compounds were found to upregulate p53 protein expression and downregulate survivin expression, further supporting their pro-apoptotic mechanisms. The valepotriate fraction of *V. wallichii* exhibited pronounced cytotoxic effects on untransformed mouse early haematopoietic progenitor cells (CFU-GM and CFU-EOS) and human peripheral blood T lymphocytes (Tortarolo et al., 1982). *In vivo*, valepotriate inhibited transplanted S180 tumour growth in mice by 58–68% at doses of 100–150 mg·kg^{-1}, prolonged survival in Ehrlich ascites carcinoma-bearing mice by 62–66%, and enhanced immune responses such as erythrocyte rosette formation. Histopathological observations revealed valepotriate-induced flake necrosis in the tumour core, surrounded by lymphocyte and macrophage infiltration, indicating both direct cytotoxic and immunomodulatory effects (Zhang et al., 2010). Additionally, the total flavonoids isolated from *V. jatamansi* significantly reduced the average tumour weight in H22 liver cancer-bearing mice by 25–31%. These effects were associated with the suppression of the JAK/STAT signalling pathway (Yan et al., 2011).

The following table summarises the major bioactive compounds isolated from *Valeriana* species and the corresponding cancer types in which antitumour activity has been reported.

Taken together, these data suggest that *V. officinalis* and other *Valeriana* species have a wide range of anti-tumour activities, primarily mediated by diverse classes of phytochemicals, particularly iridoids. These effects operate via different molecular mechanisms, including induction of apoptosis, cell cycle arrest, inhibition of proliferation and migration, and modulation of oncogenic signalling pathways. Despite these promising preclinical results, translation into clinical applications remains limited. Current limitations include poor bioavailability, insufficient pharmacokinetic characterization, and a lack of standardised extract formulations. Furthermore, comprehensive toxicological profiling is necessary to assess potential off-target effects and ensure safety in therapeutic contexts. Future research should prioritise *in vivo* validation, activity-guided fractionation, and rigorously designed clinical trials to establish efficacy and safety in human populations. Evaluating potential synergistic interactions with conventional chemotherapeutics and targeted therapies may further enhance therapeutic outcomes.

Table 4 Cytotoxicity profiles of compounds isolated from *Valeriana* spp., categorised by cancer type

Cancer type	Active compounds	IC_{50} range/effects
Breast, pancreatic, ovarian, glioblastoma	valtrate	apoptosis, migration inhibition, STAT3/PDGFRA suppression
Liver (hepatoma)	valtrate, didrovaltrate, baldrinal	didrovaltrate: complete cell death in 5h at 66 μg·ml^{-1}
Prostate, lung, colon	iridoids from *V. jatamansi*	IC_{50}: 1.0–8.5 μM
Colon, leukemia, melanoma	Valejatanin A, valerol A	IC_{50}: 3.53–31.43 μg·ml^{-1}
Glioma stem cells	valeridoid F, dolichodial derivatives	IC_{50}: 30.19–47.55 μM
Gastric (MKN-45)	valtrate, didrovaltrate	↑ apoptosis markers

Given their multifaceted pharmacological bioactivity and favourable safety profile in traditional medicine, *Valeriana* species represent promising candidates for further oncopharmacological exploration (Li et al., 2022; Çelik and Kırmızıbekmez, 2025).

Additional *Valeriana* spp. Applications: *in vitro* and *in vivo* Findings

In addition to its well-established sedative and anxiolytic properties, *V. officinalis* and related species exhibit a broad spectrum of pharmacological activities extending beyond the central nervous system. These include anti-inflammatory, antimicrobial, antiviral, antidiabetic, antioxidant, hepatoprotective, metabolic, and neuropharmacological effects. This section summarises the current evidence derived from both *in vitro* and *in vivo* studies (Table 5).

Beyond its classical neuropsychiatric profile, valerian has been investigated for its potential to modulate inflammatory and metabolic pathways. *In vitro*

Table 5 Additional pharmacological applications of *Valeriana officinalis* and related species: *in vitro* and *in vivo* evidence

Pharmacological effect/ application	Active extracts or compounds	Experimental model (*in vitro*/ *in vivo*)	Mechanism of action/main findings	References
Anti-inflammatory activity	ethanolic and aqueous extracts	cell culture models (macrophages, hepatocytes)	inhibition of TNF-α, IL-6; suppression of NF-κB signalling	Kandilarov et al., 2023; Liu et al., 2024; Suciu et al., 2025a,b
Cognitive and neuroprotective effects	standardised valerian extracts	rodents (learning, memory, stress tests)	improved cognition and stress resilience via neurotransmitter modulation, antioxidant, and anti-inflammatory pathways	Nam et al., 2013; Jung et al., 2015
Analgesic and anticonvulsant activity	Valerian extracts	rodent pain and seizure models	enhancement of GABAergic signalling and neuronal inhibition	Malva et al., 2004
Antibacterial activity	total alkaloids, essential oils	bacterial cultures (Gram-positive and Gram-negative)	broad-spectrum inhibition (MIC 62.5–400 μg·mL^{-1}; IC_{50} 36.9–374.7 μg·mL^{-1})	Wang et al., 2010
Antifungal activity	essential oil, alkaloids	*Candida albicans*, *Magnaporthe oryzae*	inhibition of spore germination and fungal growth	Wang et al., 2010
Antibacterial and antifungal (other species)	essential oils and ethanolic extracts (*V. jatamansi*, *V. wallichii*)	*P. aeruginosa*, *S. aureus*, *C. albicans*	alkaloids as key active constituents; effective against multidrug-resistant strains	Agnihotri et al., 2011; Khuda et al., 2012; Babu et al., 2015
Antiviral activity	methanol extracts, valtrate	*V. wallichii*, *V. fauriei* (HCV, HIV-1)	inhibition of HCV replication and suppression of HIV-1 P24 via Rev-transport inhibition	Murakami et al., 2002; Ganta et al., 2017
Antibacterial compounds (new isolates)	iridoids and valeridoids (*V. jatamansi*)	*S. aureus*, *Streptococcus* spp., *Salmonella enteritidis*	protection of A549 cells; inhibition of α-hemolysin cytotoxicity	Quan et al., 2022; Zhu et al., 2024
Antidiabetic/metabolic regulation	ethanolic extracts, rupesin F, valerianoside A, valerenic acid	enzyme inhibition assays; 3T3-L1 adipocytes	α-glucosidase inhibition (IC_{50} 12–17 μg·mL^{-1}); PPARγ agonism; enhanced glucose uptake and adiponectin secretion	Takahashi et al., 2022; Wu et al., 2023; Maurya and Agnihotri, 2024
Antioxidant effects	alepotriates, valerenic acid	HepG2 cells, animal tissues	activation of Nrf2 pathway; increased GST, GCL, GPx, HO-1 expression; elevated GSH	Afzal et al., 2023
Anxiolytic and neuropharmacological actions	valerenic acid	rodent behavioural models	diazepam-like anxiolytic effect without motor impairment	Pinder et al., 2024
Cardioprotective and metabolic modulation	valerenic acid	animal models	enhanced fatty acid oxidation, mitochondrial function, PPARα regulation	Liu et al., 2025

experiments have demonstrated that valerian extracts can inhibit the production of pro-inflammatory cytokines such as TNF-α and IL-6, and modulate NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signalling pathways (Kandilarov et al., 2023; Liu et al., 2024; Suciu et al., 2025a,b), suggesting potential utility in managing systemic inflammatory conditions.

Animal studies have revealed hypoglycaemic effects, demonstrating improvements in blood glucose regulation in diabetic rodents, which are potentially mediated by enhanced antioxidant defences and reduced oxidative stress. Mild hepatoprotective effects have also been observed in hepatotoxicity models, indicating the broader cytoprotective potential of valerian.

Further evidence of cognitive and stress-modulating effects of valerian comes from neurobehavioural studies. The chronic administration of standardised extracts improved learning, memory, and stress resilience in rodents (Nam et al., 2013; Jung et al., 2015), likely through a combination of neurotransmitter modulation, antioxidant activity, and anti-inflammatory mechanisms (Nam et al., 2013). Some studies also indicate mild analgesic and anticonvulsant properties, supporting the multifaceted neuropharmacological potential of valerian (Malva et al., 2004).

In addition to its systemic pharmacological profile, *V. officinalis* exhibits notable antimicrobial activity. Total alkaloids and essential oils demonstrate broad-spectrum antibacterial activity, particularly against Gram-positive bacteria (MIC 62.5–400 μg·mL^{-1}; IC_{50} 36.93–374.72 μg·mL^{-1}). Moderate antifungal activity against *Candida albicans*, and inhibition of *Magnaporthe oryzae* spore germination have also been documented (Wang et al., 2010).

Similar or stronger effects have been observed in other *Valeriana* species. Essential oils of *V. jatamansi* were active against *Pseudomonas aeruginosa*, *Bacillus pumilus*, *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Staphylococcus epidermidis* (Agnihotri et al., 2011). Ethanolic extracts demonstrated activity against multidrug-resistant *S. aureus* and *P. aeruginosa*, with alkaloids identified as the key active constituents (Babu et al., 2015). Extracts from *V. wallichii* inhibited several bacterial and fungal strains (Khuda et al., 2012), while methanol extracts exhibited anti-HCV activity (Ganta et al., 2017). Valtrate from *V. fauriei* acted as a Rev-transport inhibitor, suppressing HIV-1 P24 production without host cell toxicity (Murakami et al., 2002).

Recent phytochemical analyses have attributed some of this antimicrobial activity to specific iridoids and valeridoids. Zhu et al. (2024) isolated 18 compounds from *V. jatamansi*, several of which protected A549 cells against cytotoxicity induced by *Staphylococcus aureus* α-hemolysin. Valeridoids G, H, J, K, Q, 9-epi-valtral C, desacylbaldrinal, and baldrinal exhibited variable antibacterial spectra (Quan et al., 2022). Notably, 9-epi-valtral C displayed broad-spectrum activity against *Streptococcus* spp. and Gram-negative bacteria, while valeridoid Q demonstrated potent anti-*Salmonella enteritidis* activity.

Valeriana species have also shown promising effects on metabolic regulation. Ethanolic extracts and isolated compounds from *V. jatamansi* exhibited potent α-glucosidase inhibitory activity (IC_{50} = 12.16–17.45 μg·mL^{-1}), with rupesin F and valerianoside A displaying particularly high potency (Maurya and Agnihotri, 2024). Valerenic acid acts as a partial peroxisome proliferator-activated receptor gamma (PPARγ) agonist, promoting adipocyte differentiation, adiponectin secretion, and glucose uptake in 3T3-L1 adipocytes (Takahashi et al., 2022). Both extracts and valerenic acid have also been shown to inhibit α-amylase and α-glucosidase *in vitro* (Wu et al., 2023) indicating that *Valeriana* metabolites modulate both insulin-dependent and insulin-independent pathways, supporting their potential role in managing metabolic disorders.

The antioxidant potential of *Valeriana* species is well documented. Valepotriates and valerenic acid from *V. officinalis* activate the Nrf2 pathway, thereby increasing the expression of glutathione S-transferase (GST), glutamate-cysteine ligase (GCL), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1) in HepG2 cells and elevating intracellular glutathione levels (Afzal et al., 2023). Neuropharmacologically, valerenic acid produced anxiolytic effects comparable to diazepam without affecting locomotion (Pinder et al., 2024) and exerted cardioprotective effects via enhanced fatty acid oxidation, mitochondrial function, and the regulation of peroxisome proliferator-activated receptor alpha (PPARα) and glycolytic enzymes (Liu et al., 2025).

Collectively, these data emphasise the remarkable pharmacological diversity of *V. officinalis* and related species. Beyond their classical sedative and anxiolytic properties, extracts and metabolites of *Valeriana* display multi-target activities relevant to inflammation, infection, metabolism, oxidative stress, and neuroprotection. In combination with

the cytotoxic potential discussed previously, these pharmacological properties highlight the therapeutic versatility of *Valeriana* species. Further bioactivity-guided isolation, pharmacokinetic characterisation, and clinical evaluation are warranted to fully exploit their therapeutic potential.

Clinical Applications and Evidence for *V. officinalis* and Related Species

V. officinalis has long been used in clinical practice for its sedative, anxiolytic, and sleep-promoting properties. Its most well-established therapeutic application is the treatment of mild to moderate insomnia, particularly among individuals experiencing difficulty initiating or maintaining sleep (Das et al., 2021). Randomised controlled trials and meta-analyses consistently indicate that valerian extracts can reduce sleep latency, improve subjective sleep quality, and increase overall restfulness, without causing significant next-day sedation or cognitive impairment (Bent et al., 2006; Chandra Shekhar et al., 2024; Yeom and Cho, 2024). Standardised preparations, typically containing 0.3–0.8% valerenic acids, have demonstrated efficacy when administered regularly over 2–6 weeks (Bent et al., 2006; Chandra Shekhar et al., 2024). In addition to alleviating sleep disturbances, valerian has shown promise in alleviating anxiety and stress-related symptoms. Clinical studies suggest that supplementation with valerian extracts can lower anxiety levels, promote relaxation, and reduce physiological stress markers, such as heart rate and cortisol concentrations (Jung et al., 2015; Sahin et al., 2024). While the strongest evidence exists for generalised anxiety and situational stress, preliminary data indicate potential benefits for patients with mild anxiety disorders (Shinjyo et al., 2020). Nevertheless, larger trials are required to confirm these findings.

In addition to its benefits for sleep and anxiety, valerian may offer support in additional clinical contexts. Its spasmolytic activity has been applied in the management of functional gastrointestinal disorders such as irritable bowel syndrome and dysmenorrhoea, where it alleviates discomfort by relaxing smooth muscle tissue (Mirabi et al., 2011; Behboodi Moghadam et al., 2016; Feng et al., 2022). Furthermore, its antioxidant and neuroprotective properties have prompted exploratory investigations into potential applications in neurocognitive disorders and age-related cognitive decline (Malva et al., 2004). However, these applications require further clinical validation. Combination therapies incorporating valerian alongside other phytotherapeutic agents, such as hops (*Humulus lupulus*) (Sun, 2003; Morin et al., 2005; Koetter et al., 2007; Dimpfel and Suter, 2008; Maroo et al., 2013), lemon balm (*Melissa officinalis*) (Müller and Klement, 2006; Gromball et al., 2014; Ross, 2015), and passionflower (*Passiflora incarnata*) (Velasquez et al., 2024), have been evaluated as strategies to enhance sleep quality and reduce anxiety. These synergistic formulations may provide greater benefits in individuals with complex sleep disturbances or heightened anxiety, although standardised clinical evidence remains limited.

Recent randomised controlled trials have further strengthened the clinical evidence for the sleep-modulating properties of valerian. In a double-blind, placebo-controlled crossover study, Ota et al. (2023) reported that *Valeriana fauriei* root extract (2 g·day^{-1} for two weeks) significantly improved both sleep onset and overall sleep quality in 89 individuals suspected of having insomnia, with no adverse effects observed. Similarly, Chandra Shekhar et al. (2024) conducted a parallel-group trial involving 80 adults with reported sleep disturbances. They found that *V. officinalis* extract, when administered over eight weeks, enhanced both subjective and objective sleep parameters, including sleep latency, efficiency, and total sleep time, while also reducing anxiety and daytime fatigue. While both studies demonstrated favourable outcomes and good tolerability, limitations such as small sample sizes and restricted insomnia severity highlight the need for larger, more robust trials incorporating objective sleep assessments.

Overall, the available clinical evidence suggests that *V. officinalis* and related species are safe and well-tolerated phytotherapeutic agents for the treatment of mild insomnia and anxiety. Emerging data also indicate potential applications in the areas of gastrointestinal and neurocognitive health. Standardisation of extracts, optimisation of dosing regimens and inclusion of both subjective and objective outcome measures in future trials are critical steps towards strengthening evidence-based clinical recommendations.

Safety and Tolerability of *Valeriana officinalis*

V. officinalis is generally considered safe for short- and medium-term use in adults, with a low incidence of adverse effects reported in clinical studies (Chandra Shekhar et al., 2024). The most commonly observed side effects are mild and transient, including headaches, gastrointestinal discomfort, dizziness, and vivid dreams. Rarely, allergic reactions or paradoxical stimulation may occur (Leathwood and Chauffard, 1985; Donath et al., 2000; LiverTox, 2020). Although

long-term safety data are limited, available evidence suggests that valerian does not induce tolerance, dependence, or withdrawal symptoms (Tammadon et al., 2021), distinguishing it from conventional benzodiazepine-based sedatives.

Toxicological studies in *in vitro* and animal models indicate a high margin of safety for standardised valerian extracts. Acute and subchronic toxicity studies have shown no significant organ damage, behavioural toxicity or reproductive effects at commonly used doses (Bao et al., 2024). However, variability in commercial preparations underscores the importance of using standardised extracts with a defined valerenic acid content to ensure consistent efficacy and safety.

Any potential drug interactions should be carefully considered. Valerian's modulation of the central nervous system may enhance the effects of sedatives, hypnotics or anxiolytics, including benzodiazepines, barbiturates and certain antihistamines (Sahin et al., 2024). While clinically significant interactions are uncommon, the concurrent use of valerian with alcohol or other CNS depressants should be approached with caution (Chen et al., 2002). There is limited evidence to suggest possible mild interactions with cytochrome P450 enzymes, but these are generally not considered to be clinically relevant at therapeutic doses (Kelber et al., 2014). Nevertheless, patients taking medications with narrow therapeutic indices should consult a healthcare professional before using valerian.

Special populations, such as pregnant or breastfeeding women, children, and individuals with liver or kidney impairment, require particular caution due to limited safety data. Most guidelines recommend avoiding valerian use during pregnancy and lactation, and paediatric use should be approached with care (Kenda et al., 2022). While valerian is generally well tolerated by older adults, monitoring is recommended due to their increased sensitivity to sedative effects and the potential risk of falls.

In conclusion, *V. officinalis* demonstrates a favourable safety profile with minimal risk of adverse effects, dependence, or tolerance. Standardised extracts are recommended to ensure predictable pharmacological activity, and patients should be advised regarding possible interactions with CNS depressants (Shinjyo et al., 2020). Continued post-marketing surveillance and rigorous clinical trials are needed to further clarify long-term safety and inform evidence-based recommendations across diverse patient populations.

Conclusions

Valeriana officinalis is a well-established medicinal herb that has traditionally been used to treat sleep disturbances, anxiety, and stress-related disorders. Modern studies suggest that its effects are due to modulation of the GABAergic, serotonergic and adenosinergic systems, as well as its antioxidant, anti-inflammatory, spasmolytic and neuroprotective properties. Clinical evidence supports the use of standardised valerian extracts for improving sleep quality and reducing anxiety, with minimal adverse effects and no risk of dependence. While preclinical data suggest additional benefits in terms of neuroprotection and cognitive support, further large-scale human trials are needed to confirm these findings and optimise dosage and standardisation. Overall, *V. officinalis* represents a versatile, non-addictive phytotherapeutic agent with promising applications in the treatment of neuropsychiatric and stress-related conditions.

Conflicts of Interest

The authors have no competing interests to declare.

Ethical Statement

This article does not include any studies that would require an ethical statement.

Funding

This study was funded by the statutory activities of the Institute of Biology at the Pomeranian University in Słupsk (Poland). The authors would like to express their sincere gratitude for this support.

Acknowledgements

Not applicable.

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