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Review Article

Exploring *Valeriana* species: Unraveling anticonvulsant potential through phytochemistry and pharmacology

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Abstract

Background and aims: The Valerianaceae comprises about 300 species of annual and perennial plants found worldwide. Several species are utilized for biological purposes, while others are consumed. The various *Valeriana* species have different therapeutic effects, including sleep aid, sedative and anxiolytic, and anticonvulsant effects. The study intends to review the phytochemistry, pharmacological activities, and molecular pathways of these plants to explore their potential as therapeutic options for seizures and epilepsy.

Methods: Until 2023, all relevant information about *Valeriana* species was gathered from PubMed, Scopus, Web of Science, and Embase. Valerianaceae, *Valeriana*, valeric acid, and *Valeriana officinalis*, phytochemical composition, in vivo investigations, epilepsy, neuroprotective, anticonvulsant, GABA, seizure, and preclinical and clinical research were among the search terms utilized for this review.

Results: Based on the results obtained from the studies conducted in this field, significant anticonvulsant effects of various compounds extracted from the *Valeriana* species have been observed in multiple animal models, including pentylenetetrazole (PTZ)- and maximal electroshock (MES)-induced seizures in mice, rats, and zebrafish. It has also been determined that the molecular and pharmacological mechanisms involved in these anti-epileptic effects are increasing the GABA pathway, inhibiting the NMDA receptor and adenosine pathways, and nitric oxide (NO) modulation. Moreover, these compounds synergize with clonazepam, diazepam, phenobarbital, and phenytoin.

Conclusion: It is recommended to prepare proper drug forms and study its anticonvulsant effects in clinical studies.

Keywords: *Valeriana* species, Anticonvulsant, Epilepsy, Phytochemical, Phytomedicine, *Valeriana officinalis*

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Introduction

Several *Valeriana* species have originated a strange aroma reported many centuries ago, documented by Galen and Dioscorides. The medicinal effects of Valerian, on the other hand, have elongated and been comprehended in Ayurvedic and Chinese medicine (1). The medicinal concessions of Valerian are well determined, which have been established by a dozen Pharmacopoeias and comprehensive usage in diverse areas of the world, including Europe and Asia in the modern era (2). The *Valeriana* species includes more than three hundred annual and perennial plants that may be found worldwide, except for Australia and are mostly found at high elevations. Valepotriates are prevalent in the *Valeriana* species and are thought to be implicated because of their sedative properties (3). A summary of historical images and compounds in these plants is shown in Figure 1.

Valerian root has long been used to treat sleep disturbances caused by a body's circadian rhythm shift. The term "Valerian" emanates from the Latin word "valere," which means "to be powerful and healthy." It has been used as an herbal cure since ancient Greek and Roman times. Currently, the plant is mainly used to cure insomnia and is one of Europe's most popular sleeping aids (4). The US Food and Drug Administration (FDA) has certified Valerian as a GRAS (generally recognized as safe) food additive. "The existing data show that valerian could enhance sleep quality without creating negative effects," according to a new comprehensive assessment of research (5).

Epilepsy is a neurological and chronic condition with various origins, including hereditary, structural, and metabolic dysfunctions and unknown causes (6). The World Health Organization estimated in 2012 that 50 million individuals worldwide had epilepsy (6). The failure of existing anti-seizure medications (ASMs) to treat seizures in about 30 percent of epileptic cases makes treatment problematic. It declares that new therapies are essential (7-9). Low patient compliance (10-12), ASMs-induced cognitive difficulties (13), and the development

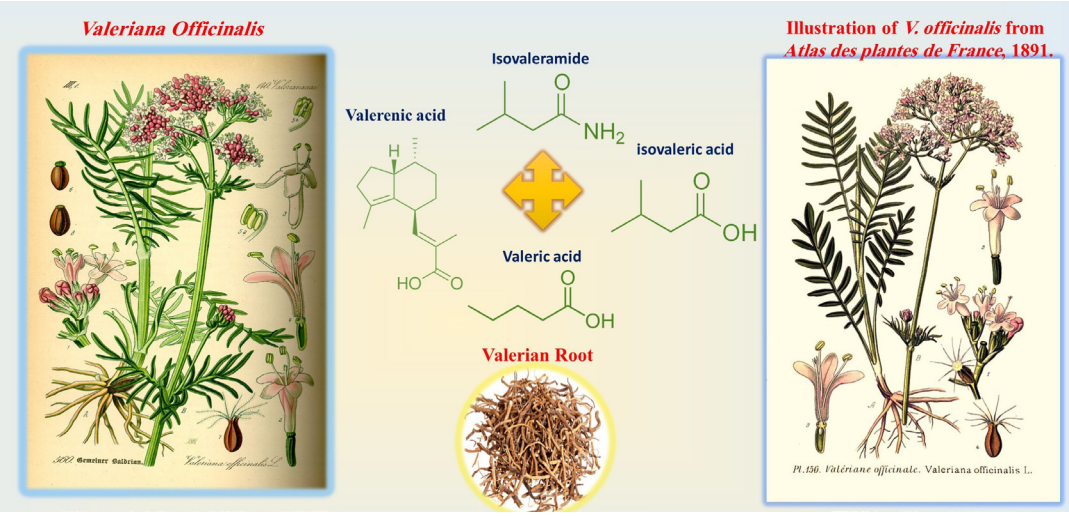

Figure 1. The historical background of therapeutic effects of subfamily Valerianaceae

of medication resistance (14,15) are some of the additional issues linked with contemporary ASMs. Patients frequently mix numerous medicines, including natural items, to improve seizure control (16) or to treat other health disorders (17,18). ASMs' interactions with other medications, such as natural products, are a clinical issue (19-21). Synergistic therapy can minimize medication doses while reducing the risk of side effects (22).

Valerian root extracts have been used to cure a broad spectrum of conditions, including anxiety and sleeplessness (23), as well as for epileptic seizures (24-26). Valerian, alongside ASMs, has been demonstrated to increase patient relaxation (26,27). Nonetheless, only a few studies have looked into the anti-seizure characteristics of valerian extracts (28,29), and additional research is needed to see if they affect the remedial benefits of ASMs.

This study aims to contribute valuable insights into the anti-seizure characteristics of different species of *Valeriana* genus extracts, addressing the current gap in research on this subject. By exploring the interaction between *Valeriana* species and ASMs, the study aims to assess whether *Valeriana* species could complement existing therapies, potentially minimizing medication doses and mitigating side effects associated with contemporary ASMs. Ultimately, the goal is to provide a scientific foundation for considering *Valeriana* species as a potential adjunct therapy in managing epilepsy, offering new perspectives and avenues for further research in neurological disorders.

Materials and Methods

Every aspect of the search and extraction procedure followed PRISMA guidelines for scoping review, which are addressed throughout the study. A query was built to guide a literature search and develop a screening procedure for relevant papers. The literature search was conducted using four major online databases (Scopus, Embase, PubMed, Web of Science) until 31 December 2022, without inception date or language restrictions, using the discipline-specific terms "Valerian" and "*Valeriana officinalis*" and "*Valeriana* extract" and the Medical Subject Headings (MeSH) search phrases "anticonvulsant," "epilepsy," and "seizure."

Figure 2 depicts a flow chart of the screening process, which comprised three steps and was based on the PRISMA 2020 flow diagram: Identification, screening by setting, and application based on Critical Appraisal methods for use in JBI of included research, and lastly, result evaluation (30). Studies involving and describing the effectiveness of *Valeriana officinalis* in different animal studies and clinical trials were considered eligible. Review papers, case studies, protocols, editorials, and comments were omitted from the search.

Phytomedicine Profile

Valeriana is the largest genus of the Caprifoliaceae family. It is native to North America but endemic to Europe and Asia. The herb has yellow-brown rhizomes that grow in moist soil. Stems are hollow and covered with bunches of white blossoms and complex leaves (3,31). Even though *Valeriana officinalis* L. is the "universally" recognized species, different *Valeriana* sp. are used for similar reasons based on the region or nation (2).

Valerian was used as a tranquilizer to remedy epilepsy in Middle Ages Europe (32). The therapeutic qualities of valerian were also utilized to treat sleeplessness, anxiety, and nervous ailments such as nervous stomach distress by the late 16th century. Valerian roots and other therapeutic herbs were brought to North America by English colonists in 1620. Valerian was used as a sedative, a therapy for nerve illnesses, and a treatment choice for insomnia from the 1700s through the mid-1900s. From 1820 until 1936, it was included in The United States Pharmacopoeia as an approved remedy. In west Europe, aqueous extracts of valerian are an authorized over-the-counter medication for treating anxiety and nervousness, disrupted sleep patterns, and panic disorders (33).

Valerian has a prolonged chronology of usefulness as

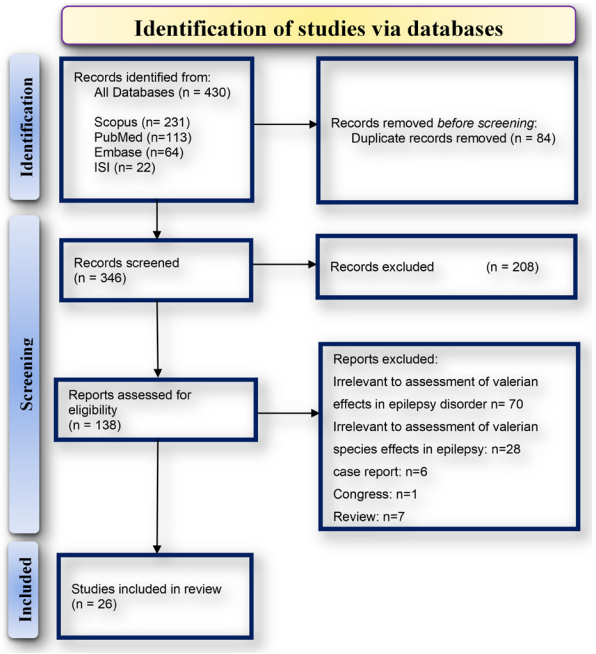

Figure 2. Study protocol for data selection

a favorable hypnotic in Western Europe. It was called *Phu* by Dioscorides, a Greek physician, because of its strong odor. Nonetheless, the Greek physician Galen was the first to mention Valerian's sedative possessions. The presence of valepotriates, borneol derivatives, and isovaleric acid has been ascribed to the *Valeriana* species' antispasmodic, relaxing, and soothing characteristics (34-36). For example, it has been used in Brazil and the United States for its hypnotic, anticonvulsant, and anxiolytic properties (35,37).

In the same way, earlier in vivo experiments in mice and rats have shown it has anxiolytic and antidepressant characteristics but not sedative or myorelaxant effects. Many investigations in the last few decades have confirmed the traditional usage of these plants. The most often used is *V. Officinalis*, which has soothing, anticonvulsant, tranquilizing, and anxiolytic effects. Extracts from the roots of this plant can be used to treat minor neurotic anxiety and sleep disturbances, according to the European Medicine Agency (38).

Phytochemistry

Valeriana species contains approximately 150 chemical components, which have also been illustrated to be active pharmacologically. However, a few chemical ingredients are responsible for the sleep-inducing effects (1,38,39). It is hypothesized that its pharmacological effect results from interactions between many compounds rather than a single molecule or family of chemicals. *Valeriana* species essential oil contains sesquiterpenes (valeric acid), iridoid esters (valepotriates such as isovalerate, valtrate, didrovaltrate, isovaleric acid, isodihydrovaltrate, homovaltrate, acetoxy-valtrathydrin) (40), amino acids (GABA, tyrosine, glutamine), lignans (hydroxy-pinoresinol) Isovaleramide, Isovaleric acid, and alkaloids (actinidine, chatinine, shyanthine, valerianine, and valerine) that among these, valeric acid is a standardized marker for the plant's root extracts. It has been linked to the plant's anxiolytic activity in several in vitro and in vivo investigations (38,39,41,42). Figure 3 shows the structural chemistry of these compounds.

The sedative characteristics were not entirely attributed to a single component or a family of chemicals (41). Furthermore, various valerians with identical actions have distinct compositions (42). These analyses suggest the preliminary agreement that multiple chemicals in *Valeriana* species extracts interact synergistically to induce sedative or anxiolytic effects (41) (Figure 4). For example, 6-methyl apigenin, a flavone compound that is a substrate of the benzodiazepine binding site of the GABAA receptor with anxiolytic properties in mice, has been identified from the rhizomes of the various species of valerians (43). Two glycosylated flavanones, 2S-hesperidin and linarin, with sedative-hypnotic effects have been identified. Also, synergistic interactions were observed when these two glycosides were combined with other components of the same *Valeriana* species extract (44-46).

As mentioned before, Valerian's therapeutic effects are likely due to the synergistic interactions of its many chemical components rather than a single molecule or family of chemicals. This complex composition presents opportunities for further investigation and exploration of the various compounds' specific interactions and synergistic effects. Future research could focus on identifying and elucidating the mechanisms of action of these compounds individually and in combination, shedding light on their contribution to Valerian's overall pharmacological activity.

Based on the information presented, it is evident that *Valeriana* species plants, particularly *Valeriana officinalis*, possess potential anticonvulsant effects. However, more research is needed to elucidate the specific compounds responsible for these effects and their mechanisms of action. Additionally, clinical studies are required to evaluate the efficacy and safety of *Valeriana* species as a therapeutic option for epilepsy management.

Phytopharmacology

GABAergic system

In the CNS, gamma-aminobutyric acid is the core inhibiting pathway (47). It has been well established that GABAA operates several essential roles in modulating seizure threshold as inhibitory activity (48-51). In respect, GABAA receptors are ligand-gated ion channels that carry out Cl- (52). Benzodiazepines are considered positive allosteric GABA receptors that increase the chloride ions current through the membrane of neurons (53).

Valeriana officinalis extracts have been utilized for sedative, hypnotic, tranquilizer, and anticonvulsant activities in traditional medicine, and they may interact

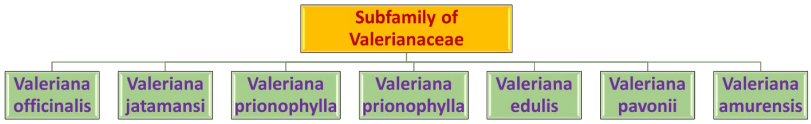

Figure 3. Different types of valerian whose anticonvulsant effects have been reviewed in this study

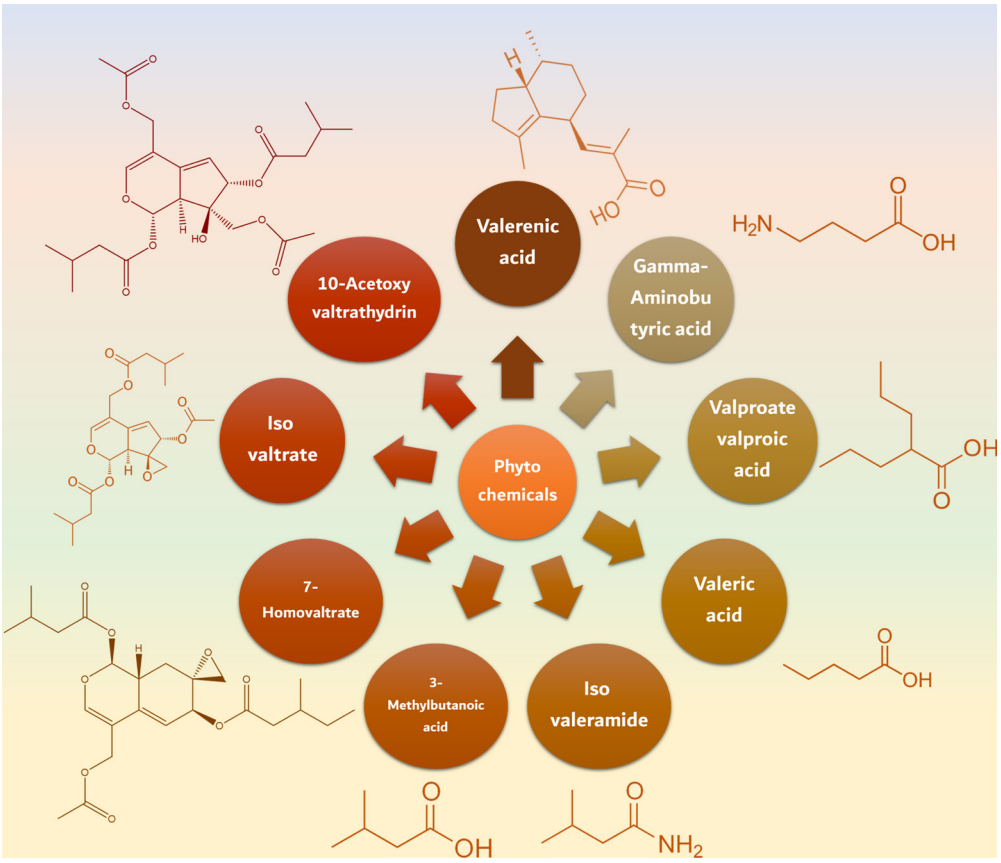

Figure 4. Various compounds extracted from multiple *Valeriana* species

with GABA receptors. Certain compounds from the plant have also been identified to have unique pharmacological effects, such as synergistic interactions between valepotriates, according to research, and valeric acid, unlike its analogs and derivatives, allosteric regulation of GABAA receptors. Valepotriate components have been shown to have soothing and spasmolytic effects in pharmacological studies. In contrast, sesquiterpenes and valeric acid have been found to cause sleepiness (54,55). In vitro, valeric acid is likewise concerned about the growth in BDNF levels. These findings suggest valeric acid could be considered the primary active ingredient in *Valeriana* species as a GABA agonist (29,56,57-59).

Moreover, it has been indicated that, in the mammalian brain, the interaction of GABAA receptors allows for quick inhibitory neurotransmission. Valeric acid modulates GABAA receptors bearing b2- or b3-subunits while having no impact on b1-subunits (60). Indeed, valeric acid is a β2/3-selective GABAA receptor modulator with anxiolytic and antiseizure effects in animals, making it a promising therapeutic candidate. Considering that EC50 > 30 mm results in direct receptor activation, with EC50 values in the 5–20 mm range, valeric acid is a potent modulator of GABAA receptors produced in Xenopus oocytes. In addition to its activation function, compounds extracted from *Valeriana* species may also promote GABA release and reuptake by binding directly to GABAA receptors (61,62). In another study, Valepotriate (5, 10, and 20 mg/kg) increases the expression of GABAA, glutamic acid decarboxylase 65, and Bcl-2 while lowering the expression caspase-3 (63). In the in vitro assay, isovaleramide (300 μM) exhibited a 42% inhibition of the binding of ^{3}H-FNZ to its sites (64,65).

The interactions of *Valeriana* species extracts with GABAA receptors were investigated using [3H] flunitrazepam binding as an indication. Independent of valeric acid standardization, there was significant variation across the extracts, with some moderately increasing [3H] flunitrazepam binding. In fact, at modest concentrations (EC50 4.13 * 10-10 mg/ml), *Valeriana* species extracts increase [3H] flunitrazepam binding. The increased [3H] flunitrazepam binding is replaced by inhibition at higher dosages (IC50 of 0.482 mg/ml). Finally, *Valeriana* species extracts suppress synaptosomal

[3H] GABA uptake, which has a biphasic interaction with guvacine. The findings show that *Valeriana* species extracts affect GABAA receptors (66).

N-methyl D-aspartate receptors

N-methyl D-aspartate receptors (NMDAR) or ionotropic glutamate receptors are one of the vital excitatory receptors on synapses of neurons in the CNS, and neuroplasticity, excitatory neurotransmission, and neurotoxicity in the brain as well (47-49). Glutamate levels in the extracellular fluid rise during seizures in temporal lobe epilepsy, and glutamate can directly activate NMDAR and cause neuroexcitatory damage, according to previous research (50).

In addition to the involvement of GABA neurotransmission in *Valeriana officinalis* effects, blockage of ionotropic and metabotropic glutamate receptors is another possible mechanism of action of valerian. Valeric acid, a marker compound for *Valeriana officinalis*, increased the [(3)H] Glutamate binding. For instance, the binding of [(3)H]Glutamate in aqueous *Valeriana* species extracts increased from 1 10-7 to 10-3 mg/mL (51). Moreover, *Valeriana* species extracts demonstrated a minor inhibitory impact on [3H]MK-801 binding, indicating that NMDA and compounds extracted from *Valeriana* species interactions exist (52). Aqueous and hydroalcoholic extracts showed significant changes in receptor selectivity for ionotropic glutamate receptors. The aqueous extract reduced [(3)H] FW binding to AMPA receptors after, but the hydro alcoholics extract significantly increased its binding to these receptors. (53). The anxiolytic characteristics of this plant might be explained by the selective interaction of valeric acid with metabotropic glutamate receptors.

Adenosine A1 receptor

Through a mixture of adenosine receptor-dependent and -independent mechanisms, adenosine exerts anticonvulsant and proconvulsant effects. Maladaptive changes in adenosine biochemistry, specifically increased expression of the astroglia enzyme adenosine kinase, facilitate epileptogenesis (54,55). Adenosine receptors are a promising therapeutic target for controlling epileptic seizures in this regard. Adenosine is well-suited to establish or restore a continuous balance between excitation and inhibition as a homeostatic bioenergetic network regulator, and its anticonvulsant effectiveness is well-documented (56).

In this regard, the possible involvement of the adenosine A1 receptor in the anticonvulsant effects of compounds extracted from *Valeriana* species has been examined. For instance, using selective A1 receptor antagonist (10 and 20 μM; intracerebroventricular) reduction in the anti-seizure efficacy of aqueous *Valeriana* species' extract has been shown (29). As a result, it has been determined that some compounds extracted from the *Valeriana* species' anticonvulsant activity are likely mediated through adenosine system stimulation.

Nitric Oxide

The neuromodulator nitric oxide (NO), which has both proconvulsive and anticonvulsive effects, is well recognized. Many natural substances interact with this signaling system, a promising therapeutic target crucial in the seizure threshold (57,58). For instance, it has been discovered that the well-known iridoids *Valeriana jatamansi* and its derivatives may block nitric oxide synthase (NOS). The production of NO in many cells is mediated by the enzyme NOS. These substances prevent the generation of NO from LPS-induced murine microglial BV-2 cells, which have anti-inflammatory properties (59). Silymarin is obtained from the fruits, which are pressed to remove most fats and further defatted with petroleum ether. The resulting cake is typically extracted with acetone or ethyl acetate, and the remaining fat is separated after dilution with water. Silybin is then obtained from the silymarin solution by precipitation with ethanol.

As indicated in Table 1, it was also investigated how the nNOS inhibitor 7-nitroindazole (7-NI) and *Valerian officinalis* extract (200 mg/kg, i.p.) affected the pentylenetetrazole (PTZ)-kindled seizure model's electrocardiographic parameters and behaviors. Under normal circumstances, 7-NI and VAL did not impact blood pressure or heart rate. However, they did improve the seizure stage and frequency. The extended corrected QT values and elevated blood pressure seen in PTZ-kindled animals were likewise decreased by 7-NI therapy (60).

Cannabinoid Receptors

In animal models of epilepsy, cannabinoid receptor activators may serve as a preventative measure against seizure susceptibility (61). Roots from *Valeriana edulis* were used to demonstrate its anticonvulsant properties. The root and rhizome of *Valeriana jatamansi* also recovered the lowered expression levels of cannabinoid receptor 1. Post-traumatic stress disorder in animals (62). Additionally, the valepotriate fraction increased the decrease of excitatory activity brought on by *V. edulis* extract compared to that brought on by ethosuximide neural apoptosis inhibition. Cannabinoid receptors were shown to be possibly implicated in the anticonvulsant mechanism of action and GABAA receptor participation (40).

Another fresh perspective is the potential of *Valeriana* species as a source of novel compounds that can modulate multiple neurotransmitter systems. The essay highlights the complexity of Valerian's pharmacological effects, which arise from the interactions between various compounds. This suggests that *Valeriana* species may be a source of novel compounds that can modulate multiple neurotransmitter systems simultaneously, offering a potential advantage over single-target drugs. Future research could explore identifying and isolating new

bioactive compounds from *Valeriana* species and their possible use as multi-target drug candidates for epilepsy. This essay offers a fresh perspective by highlighting the potential of Valerian as a multi-target therapeutic agent and a source of novel compounds that can modulate multiple neurotransmitter systems, as well as the need for further research to fully understand its molecular mechanisms of action. It opens up new avenues for future research in natural products and epilepsy.

Therapeutic Effects

Fabio Colonna reported in Phytobasanos in 1592 that *Valeriana* species root had cured his epilepsy. Following that, claims of valerian's anticonvulsant properties surfaced. In the 18th and 19th centuries, it was broadly accepted as the most effective treatment. In the best conditions, high dosages of compounds extracted from *Valeriana* species can provide epileptic patients with potentially valuable amounts of anticonvulsant agents. Compounds extracted from *Valeriana* species have anticonvulsant properties. Still, their volatile chemical composition and volume, as well as their odor and taste, rendered them implausible for wide use (24).

Isovaleramide (3-methylbutanamide) has been studied for its anticonvulsant properties, and it may be considered in clinical trials for epilepsy in the future (63). Isovaleramide doses as high as 2,400 mg/day have been administered to human volunteers (64) and tolerated without significant side effects. The suggested maximum limit of oral dosage for sedation of *Valeriana* species root is 10 g/d. The lowest therapeutic dose for treating epilepsy in people susceptible to isovaleramide, as well as the percentage of the isovaleramide dose converted to isovaleric acid in vivo, remain unknown (1). For instance, Valproic acid dosages as low as 400 mg/d can treat juvenile myoclonic epilepsy; however, higher doses may be necessary on occasion. If isovalerate had a similar high reaction to epilepsy and all other parameters were equal, compounds extracted from *Valeriana* species doses of 30 to 50 g/d might have had a natural anticonvulsant effect.

The anticonvulsant activity and neurotoxicity of compounds extracted from *Valeriana* species were investigated in rats. The results showed that the *Valeriana* species extract increased the seizure threshold significantly compared to the maximum electroshock seizure model, as offered by a decrease in the extension/flexion ratio. On the other hand, the extract of *Valeriana* species proved ineffective against seizures caused by PTZ. The rotarod test demonstrated negligible neurotoxicity at dosages that improved the seizure threshold (65). Isovaleramide, at the oral dose of 100 mg/kg, was shown a 90% index protection against the MES-indued seizure in mice, comparable to sodium phenytoin (20 mg/kg, 100%).

In adult Danio rerio, valeric acid and *Valeriana* species' extracts (aqueous and ethanolic) significantly prolonged the latency to the start of PTZ-induced seizures in zebrafish. The ethanolic *Valeriana* species extract was more effective than the aqueous extract at preventing seizures. In adult zebrafish, valeric acid and extracts from *Valeriana* species show anticonvulsant effects. *Valeriana* species' extracts significantly improved the anticonvulsant impact of both clonazepam and phenytoin, suggesting that they might be helpful in epilepsy treatment (66).

Furthermore, valepotriate demonstrated considerable anticonvulsant action in MES- and PTZ-induced seizure at doses of 5, 10, and 20 mg/kg, with ED50 values of 7.84 and 7.19 mg/kg, respectively (67). In another study, using PTZ (35 mg/kg)-kindling model of the anticonvulsant efficacy of *V. edulis* crude extract and valepotriate fraction (100 mg/kg, i.p.) was evaluated. EEG recordings from rats' frontal and parietal cortices revealed substantial decreases in seizure latency, frequency, and duration (Table 1). These results were enriched in the company of the valepotriate fraction compared to that generated by ethosuximide (40,60). However, at dosages of 50–150 mg/kg, *Valeriana* prionophylla Standl showed no protective effect against PTZ-induced seizures (68).

One perspective that can be offered is the need for further research to determine the optimal therapeutic doses of *Valeriana* species and its compounds. While high doses of a compound extracted from *Valeriana* species have been shown to provide anticonvulsant effects, the lowest therapeutic dose for treating epilepsy in people susceptible to isovaleramide and the percentage of the isovaleramide dose converted to isovaleric acid in vivo remain unknown. Further research is needed to determine the optimal doses of *Valeriana* species' extracted compounds and their compounds to maximize their therapeutic potential while minimizing side effects.

A new perspective could involve exploring the optimal dosage and administration methods for *Valeriana* species' extracted compounds in specific clinical applications. Further research could focus on conducting clinical trials to evaluate the efficacy and safety of *Valeriana* species for various conditions, including epilepsy, anxiety disorders, and sleep disturbances. This would provide valuable insights into the appropriate use of *Valeriana* species' as a therapeutic agent and help healthcare professionals recommend optimal dosages for specific patient populations.

Synergistic Effects

Combining two or more phytochemicals/foods to prevent chronic inflammation synergistically is one way to close the gap between anti-inflammation studies and research into why it reduces chronic inflammation. We propose five mechanisms: increasing phytochemical bioavailability, increasing antioxidant capacity, and targeting the same and different signaling pathways pharmacodynamic. Continuing this review study, the synergy effect between *V. Officinalis* and ASMs is investigated (22).

Phenytoin

In a PTZ-induced seizures model in zebrafish, the

Table 1. Preclinical studies on the anticonvulsant effects of *Valeriana* species

Plant Species	Extract/ Compound	Animals	Model/ assay	Dose/ Administration	Effects	Ref.
Valeriana officinalis	extract	Wistar rats	PTZ-kindled seizure model	200 mg/kg, i.p.	Ameliorate the seizure; Improve BP and HR in PTZ-kindled rats via NO pathway.	(60)
Valeriana edulis	roots	Male Wister rats (280-320 g)	PTZ-induced convulsive behavior	100 mg/kg, i.p.	valepotriates in *Valeriana edulis* exert anticonvulsant effects via GABA and cannabinoids systems.	(40)
Valeriana officinalis	aqueous extract	Male Sprague-Dawley rats	PTZ-induced kindling	200, 500 and 800 mg/kg, i.p.	anticonvulsant effect for aqueous extract of *Valeriana officinalis* via adenosine A_1 receptor	(29)
Valeriana edulis	roots	Male ICR mice (25–34 g)	PTZ-induced seizures	100, 300 and 1000 mg/kg	Neuropharmacological profile similar to diazepam.	(69)
Valeriana officinalis	Extracts: valeric acid	Zebrafish	PTZ (0.1–20 mg/mL)-induced seizures	37 µg/mL	Valeric acid and valerian extracts have anticonvulsant properties	(66)
Valeriana prionophylla Standl.	Hydroalcoholic Extract	Adult female Swiss mice; male Wistar rats	PTZ-induced seizures	50, 100, 150 mg/kg	Did not show any protective effect against PTZ-induced convulsions.	(68)
Valeriana pavonii	Isovaleramide	mice	maximal electroshock	20 mg/kg, p.o,	Isovaleramide is one of the active anticonvulsant constituents of *Valeriana pavonii*	(70)
Valeriana jatamansi	Valepotriate	mice	PTZ-induced epilepsy	5, 10, and 20 mg/kg	valepotriate had anti-epileptic activity and the mechanisms might be associated with regulation of GABA and inhibition of neuronal apoptosis.	(67)

protective index of phenytoin was significantly increased from 3.63 to 13.18 when rats were pretreated with 12.5, 25, 50, and 75 mg/kg of phenytoin in conjunction with 50 mg/kg of valerian. The synergistic impact of both medications was confirmed in dosage response trials of phenytoin alone and in combination with Nardostachys jatamansi extract on blood levels of phenytoin. Only the extracts of the ethanolic *Valeriana* species exhibited interaction with phenytoin but not with valeric acid. The favorable interaction of ethanolic extracts of*Valeriana* species with phenytoin recommends that sufficient concentrations of the ethanolic extract could improve the effects of sub-therapeutic doses of phenytoin. Neither the aqueous *Valeriana* species extracts nor valeric acid interacts with phenytoin directly (66).

Clonazepam

A probable interaction of valerian extracts with clonazepam was studied in the same study. Ethanolic valerian extracts greatly enhance clonazepam's antiepileptic properties. Valerian formulations and valeric acid functioned synergistically with a low dose of clonazepam to delay the latency of convulsions significantly and increase survival. The mentioned findings point to new therapeutic options for epileptic patients. Valeric acid and valerian extracts worked along with clonazepam to extend the period between the beginning of a seizure and the start of the latency phase (66).

Phenobarbital

In mice, *Valeriana jatamansii* water extract combined with pentobarbital sodium increases sedative and hypnotic effects, reduces spontaneous activity, and opposes thiosemicarbazide-induced convulsions. Although it does not impact the convulsions caused by picrotoxin, it can extend the latent period of picrotoxin-induced convulsions in mice. After IP injection of water extract, mice's writhings can decrease (71).

Furthermore, the volatile oil of *Valeriana amurensis* significantly suppressed the autonomic activity of mice. The synergic activity of pentobarbital sodium with volatile oil dramatically boosted the rate of mice falling asleep and extending their sleeping period. Furthermore, treating volatile oil decreased the frequency of writhing responses in mice generated by acetic acid. It antagonized the convulsion caused by thiosemicarbazide in mice (72).

Diazepam

In various in vitro, in vivo, and clinical studies, the synergistic effect between diazepam and compounds extracted from valerian has been investigated and identified (43,44,73-75). However, it is worth mentioning that no study has been conducted on the synergistic effects between diazepam and the extracted compounds from the *Valeriana* species. Therefore, according to the mechanisms mentioned in the anticonvulsant effects of valerian compounds, it seems logical that the effective compounds found in these plant species can act as bio-enhancers and synergistically with diazepam in epilepsy.

The findings of this review suggest that *Valeriana* species have the potential to be developed as a natural alternative or adjunct therapy for epilepsy. Identifying specific compounds and their mechanisms of action could lead to the development of novel anticonvulsant drugs. Furthermore, exploring the synergistic effects of Valerianaceae compounds with conventional antiseizure medications may offer new treatment strategies for drug-resistant epilepsy cases.

A new perspective that can be offered is the potential of Valerian extracts as bio-enhancers for antiepileptic drugs. Bioenhancers are substances that enhance the bioavailability and efficacy of drugs by improving their absorption, distribution, metabolism, and elimination. Valerian extracts have been shown to improve the bioavailability of phenytoin and enhance the antiepileptic effects of clonazepam, phenobarbital, and diazepam. This suggests that Valerian extracts act as bio-enhancers for antiepileptic drugs, potentially reducing the required dose and minimizing side effects.

Another perspective that can be offered is the potential of combining Valerian extracts with multiple antiepileptic drugs to achieve a multi-target effect. As mentioned earlier, Valerian extracts contain compounds that can modulate neurotransmitter systems involved in epileptogenesis. The combination of Valerian extracts with multiple antiepileptic drugs may target various pathways involved in epileptogenesis, potentially improving efficacy and reducing side effects.

Conclusion and Future Prospective

In conclusion, the essay comprehensively analyzes *Valeriana officinalis*, shedding light on its profile, phytochemistry, phytopharmacology, and therapeutic effects. The research highlights the complex interplay of multiple compounds in *Valeriana* species' extracts, emphasizing the need for a holistic understanding of its pharmacological activity. This fresh perspective encourages further exploration of Valerian's therapeutic potential, particularly in epilepsy. It opens doors for investigating its mechanisms of action and identifying novel compounds with anticonvulsant properties.

The anticonvulsant effects of the *Valeriana* species' extracts were comprehensively reviewed for the first time in recent years. It's hard to identify explicit assertions well about the herb's anticonvulsant efficacy from the existing evidence because it's now difficult to determine the exact nature of the *Valeriana* species' preparations used to treat seizures in the past. Another issue concerns the need for more evidence for valerian's anticonvulsant effect, based exclusively on case reports with no controlled clinical trials. For this reason, it is recommended to prepare proper drug forms and study its anticonvulsant effects in clinical studies.

In conclusion, *Valeriana* species have been traditionally used for treating epilepsy, and various studies have confirmed their anticonvulsant properties. Isovaleramide, a compound found in valerian, has also been studied for its potential use in clinical trials for epilepsy treatment. While high doses of compounds extracted from *Valeriana* species' roots have been shown to provide potentially valuable amounts of anticonvulsant agents, the therapeutic dose for treating epilepsy and the percentage of the isovaleramide dose converted to isovaleric acid in vivo remain unknown.

The potential of Valerian extracts to act as a natural adjuvant therapy for epilepsy is another exciting avenue of research. Valerian extracts have been shown to have few side effects. They may be helpful with other drugs to improve their efficacy and reduce side effects. Moreover, Valerian extracts may offer a natural alternative to antiepileptic drugs, which can have significant side effects and may not be effective for everyone.

The exclusion of non-English language publications may limit the comprehensiveness of the review. Although the authors mention following the PRISMA guidelines for scoping reviews, the article needs to describe the search strategy, inclusion and exclusion criteria, or the data extraction and synthesis process. This lack of transparency makes it difficult to assess the rigor and reliability of the review process.

To strengthen the findings presented in the article, future research should prioritize conducting well-designed clinical trials to evaluate the efficacy and safety of *Valeriana* species as an anticonvulsant therapy in human subjects. By including a discussion of the results of these trials and their implications, the article can provide a more comprehensive analysis of the practical application of Valerianaceae in clinical settings.

Future research should address the potential adverse effects and safety concerns associated with using *Valeriana* species to provide a balanced assessment. This can be achieved by conducting systematic reviews or meta-analyses that compile and analyze existing literature on the safety profile of Valerianaceae. Incorporating these findings into the article provides a more comprehensive understanding of the risk-benefit profile of *Valeriana* species as an anticonvulsant therapy.

Competing Interests

The author declares no conflict of interest.

Data Availability Statement

Not applicable.

Ethical Approval

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