

VALERIANA OFFICINALIS: A REVIEW OF ITS TRADITIONAL USES, PHYTOCHEMISTRY AND PHARMACOLOGY

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ABSTRACT

Valeriana is a well-known Indian traditional medicinal herb with sleep remedy. It has been used over the years to treat nervine and sedative in hysteria, epilepsy, and sedative in nervous anxiety. It has also been used as an aromatic stimulant and reported some distinctive indications, as well as its use for rheumatism, low-grade fevers, and aphrodisiac. It has been known to grow well in regions of Europe, parts of Asia and North America. This systematic review focuses on the ethnopharmacological uses of Valeriana, including recent advances on the phytochemical and pharmacological study of *Valeriana officinalis*. In addition, future developments and scenarios in the study of the plant have been proposed. Various literature and electronic databases such as PubMed, ScienceDirect, Springer, and Wiley were searched and data obtained. Other online academic libraries such as Google Scholar and ethnopharmacological literature were searched systematically for more information on the plant. In this paper, we have reviewed various research conducted on *V. officinalis* especially in areas of its ethnopharmacological use, phytochemicals, and pharmacology. This plant has been used medicinally for a minimum of 2000 years. It is used in the treatment of brain disorder and also used for the treatment of varied nervous disorders, antispasmodic, anthelmintic, diuretic, diaphoretic, and emmenagogue, and hysteria. More research is needed in the area of pharmacokinetics and toxicology to give further information on the clinical use and control the quality of the plant.

Keywords: *Valeriana officinalis*, Ethnomedicine, Phytochemistry, Neuroprotective.

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INTRODUCTION

Valeriana is a genus of flowering plants in the Caprifoliaceae family, members of which can be normally called as valerians. The name valerian is derived from Valerius, the Latin term “*valere*,” which means health or well-being [1,2]. Valerian consists of the fragments or whole fresh or dried rhizomes, roots, and stolons. There exist about 200 species in Europe, Asia, and North America. Some of the species are *Valeriana officinalis*, *Valeriana jatamansi*, *Valeriana wallichii*, *Valeriana hardwickii*, *Valeriana microphylla*, *Valeriana longiflora*, and *Valeriana quadrangularis*, etc. It has been used medicinally for 2000 years. It absolutely was first used as a treatment for brain disorder within the late 16th century. It is habitually used for the treatment of varied nervous disorders [3], antispasmodic, anthelmintic, diuretic, diaphoretic, and emmenagogue, and hysteria. It has an aromatic stimulant and reported some distinctive indications, as well as its use for rheumatism, low-grade fevers, and aphrodisiac, further as its use in hysteria [4]. Valerian is used as a nervine sedative for the treatment of hysteria, epilepsy and sedative in nervous anxiety [5]. It conjointly used as a cerebral stimulant, analgesic and sedative in nervous irritability, specifically once the condition may be a result of “enfeebled cerebral circulation [6].”

Natural products have upper hand over synthetic drugs because they have fewer side effects and also does not alter physiological and biochemical pathways [7]. Over the years, medicinal plants of the Valeriana genus are shown to treat rheumatism, low-grade fevers, aphrodisiac, nervous disorders, spasmolytic, anthelmintic, diuretic, diaphoretic emmenagogue, and additionally to hysteria [8]. However, the traditional uses of these plants have been recorded primarily in local herbal books or have been passed down orally from one generation to other. The medicinal use of the Valerian, compared to its ornamental and food uses, must be investigated further as it is widespread with known therapeutic efficacy. The compounds and

extracts from *V. officinalis* have exhibited a broad spectrum of biological and pharmacological activities, including antioxidant, antimicrobial, anti-inflammatory, antirheumatic sedative, anxiolytic, tranquilizing, spasmolytic, anticonvulsant, and neuroprotective activities [9-11].

In this review, an attempt was made to present an overall overview of the ethnopharmacological uses of this Indian traditional medicine, its phytochemical properties and pharmacological activities of *V. officinalis*, so the gaps and areas requiring further research works of this plant can be highlighted.

V. officinalis

V. officinalis var. *latifolia* is a perennial herb obtained from the Valeriana genus of the Valerianaceae family found in North America, Europe, and Asia [12]. It is a glabrous or more or less pubescent herb, up to 1.5 m in height. Rootstocks short, sub-erect, hardly thicker than stem, and stoloniferous; stem stolid, erect, and furrowed [13]. *V. officinalis* has pinnately-separated leaves, generally with 6–10 pairs of lance-shaped leaflets and bears numerous small white or pink flowers in a dense head of many stalked clusters. These heads bear small (5 mm) tapered seeds, almost hairless at maturity (Fig. 1) [13-15].

TAXONOMICAL CLASSIFICATION [16]

Kingdom: Plantae
 Unranked: Angiosperms
 Unranked: Eudicots
 Unranked: Asterids
 Order: Dipsacales
 Family: Caprifoliaceae/Valerianaceae
 Genus: Valeriana
 Species: *Officinalis*

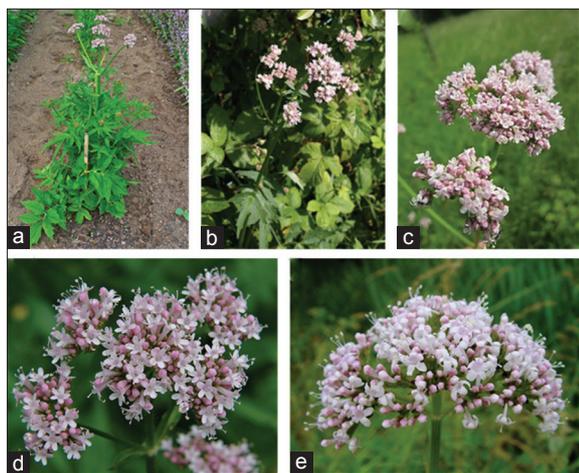


Fig. 1: Morphology of *Valeriana officinalis* (a) whole plant, (b) aerial parts with flower, (c) flower at an early stage, (d) flower and (e) stem [16,17]

Vernacular names [18]

Arabic	Sanballat Web
English	Allheal, English valerian, garden heliotrope, German valerian, great wild valerian, valerian, vandal root
Marathi	Kalavala
Sanskrit	Balahrivera
Tamil	Catamaci, jatamansi, paicavi, takram
Urdu	Balchar, balchhar, bulchar, ikleel-ul-malik, nardin, sumbul-ut-teeb

Common names [19]

English: Valerian, garden heliotrope, common valerian.

Ayurvedic: Tagara, Nata. Baalaka (syn. Udichya, Jala, Barhishtha) is also equated with *Valeriana sp.*

Folk: Sugandhabaalaa, taggar

CHEMICAL CONSTITUENTS

It consists of about 150–200 chemical constituents [20,21], as well as flavonoids with activity on the Central nervous system [22] and lignans. Valerenic acid is regarded as the major constituent [23,24]. The roots and rhizomes of *V. officinalis* have two main groups of constituents: Sesquiterpenes of the volatile oil (valerenic acid and its other derivatives, valeranone, valeranal, and kessyl esters) and valepotriates (valtrate, didrovaltrate, acevaltrate, and isovalerohydroxyvaltrate), an extension to other constituents such as flavonoids, triterpenes, lignans, and alkaloids [25-28]. A wide range of sesquiterpenoids have been discovered from *V. officinalis* including volvalerenals A-F, volvalerenic acids A-D, volvalerelactones A-B, and valeneomerins A-D [29-31].

Traditional uses

In traditional herbal medicine, the roots of *V. officinalis* have long been utilized for sedative and antispasmodic purposes [12,32] and can also be used for curing cardiac arrhythmia [33]. Valerian root has been used for a century as a relaxing and sleep-promoting plant [34,35]. It also used to treat hysteria, hypochondriasis, nervous unrest, and similar emotional states. The juice of fresh drug used as a narcotic in insomnia and anticonvulsive in epilepsy [13]. The root has been medically used to treat insomnia and blood, circulatory, and mental disorders [36]. It can also be used to treat digestive problems and urinary tract infections for at least 1,000 years. It is used as sedative, anxiolytic, antidepressant, antispasmodic, and anti-HIV bioactivities [37-41]. In the United States, it is mainly sold as a sleeping aid, while in Europe it is used for restlessness, tremors, and anxiety [12]. In Brazil, it has been used in conventional medicine for its sedative, anticonvulsant, hypnotic effects, and anxiolytic activity [42].

Phytochemistry

Wang *et al.* isolated Volvalerine A, a novel N-containing bis sesquiterpenoid derivative with a dihydroisoxazole ring and its possible biosynthetic precursor, 1-hydroxy-1,1,1-trimethyldecahydrocyclopropane azulene-10-one from the roots of *V. officinalis* [43]. Han *et al.* isolated valeneomerins A-D, two unique neomerane-type sesquiterpenoids and two newer nor-sesquiterpenoids from the roots of *V. officinalis*. Their structures were characterized by elaborate spectroscopic analysis and Cu K α X-ray crystallography [31]. Mirzaei and Dinpanah examined the applicability of hollow fiber-based liquid phase microextraction for the extraction and pre-concentration of valerenic acid earlier to its identification by reversed-phase high-performance liquid chromatography/ultraviolet [44]. Wang *et al.* isolated volvalerenone A, a new type of mononorsesquiterpenoid with an unprecedented 5/6/6 tricyclic ring system from the roots of *V. officinalis*. A plausible biosynthetic pathway of volvalerenone A was also proposed [45].

Ying *et al.* documented isolation and structural elucidation of two new molecules such as a new sesquiterpene, orivalerianol (4 β , 10 α , 15-trihydroxy-aromadrendane) and a new iridoid, monovalerianester A (aglycone of kanokoside A) collectively with eight known compounds rulepidol, behenic acid, pinoresinol, valerenic acid, β -sitosterol, kanokoside A, prinsepiol-4-O- β -D-glucoside, and 8-hydroxypinoresinol-4-O- β -D-glucoside were attained from the EtOAc extract and n-BuOH extract [46]. Wills and Shohet studied the dried *V. officinalis* powdered root on storage at 5, 14, and 30°C under low, moderate, and high humidity environment for 6 months and the amount of the valerenic acids analyzed on a monthly basis. The concentration of valerenic acid considerably reduced over time and was impacted by temperature and humidity with the loss the greatest at 30°C in low humidity [47]. Safaralie *et al.* examined the extraction of essential oil from *V. officinalis* roots growing wild in Iran by hydrodistillation and supercritical CO₂ extraction. 47 components representing 89.3% and 35 constituents ranging from 86.1% to 95.1% of the oil achieved by hydrodistillation and supercritical CO₂ were identified, respectively [48]. Huang *et al.* evaluated the volatile compounds of the roots of *V. officinalis* utilizing supercritical fluid extraction and headspace solid phase microextraction with gas chromatography-mass spectrometry. The results were compared with those achieved by hydrodistillation. 72 compounds were isolated and identified by gas chromatography-mass spectrometry (GC-MS). The results demonstrated that the major volatile components of *V. officinalis* were completely different from those of *V. officinalis* and diverse with distinctive extraction processes [49].

Hromadkova *et al.* extracted the insoluble plant residues attained after preparation of medicinal tinctures from the roots of *V. officinalis* by standard and ultrasound-assisted extraction with aqueous ethanol. The net yields of extracted polysaccharides were enhanced in the ultrasound extraction procedure [50]. Paul *et al.* isolated and determined the sesquiterpenoid constituents of the essential oils from the liverworts *Frullania tamarisci*, *Frullania fragilifolia*, and angiosperm of *V. officinalis*. From the study, it was found that the compounds present in both the essential oils of the *Frullania* species and *V. officinalis* were enantiomeric to each other [51]. Tori *et al.* isolated valeracetate, a new guaiane-type sesquiterpene and three previously known sesquiterpenes from *V. officinalis* and their structures were determined by spectroscopic techniques [52]. The composition of the steam-distilled oil from the roots of 9-month-old field-grown *V. officinalis* was analyzed and compared with Agrobacterium-mediated transformed roots of the similar species by Gränicher *et al.* Capillary GC and GC-MS reports revealed that normal oil comprised of bornyl acetate (13.3%) and valeranal (12.4%) and the transformed oil contained kessane derivatives, tentatively identified as kessyl alcohol (10.5%), and kessyl acetate (10.4%), as the main constituents [53].

Gränicher *et al.* isolated a new iridoid diester (1R,2S,6S,9S)-5-acetyloxymethyl-9-methyl-3-oxabicyclo [4.3.0] non-4-en-2-yl isovalerate from the hairy roots of *V. officinalis* transformed with *Agrobacterium rhizogenes* R1601. Five valepotriates were isolated and

recognized by means of mass spectrometry and ^1H and ^{13}C nuclear magnetic resonance (NMR) spectrometry [54]. The difference in terpene composition of the leaf essential oil was determined in three populations of *V. officinalis* by Lokar and Moneghini. The GC-MS analysis was used to establish the composition of the terpene volatile fraction of the essential oil, with the detection of 34 components, 31 of which have been known. The greater variances were stated in the percentages of α -pinene, butyl valerate and isobornyl isovalerate among the three populations [55]. Bos *et al.* isolated seven new valerian sesquiterpenoids from a dichloromethane extract of *V. officinalis*. The NMR, infrared (IR) and mass spectral data of the isolated compounds were achieved [56]. Bos *et al.* isolated sesquiterpenoid from *V. officinalis* of which the spectral data (IR, NMR, and mass spectra) were in covenant with those of faurinone. They projected a new structure for faurinone based on ^{13}C NMR and ^1H NMR shift and decoupling assessments [57].

Hendriks *et al.* examined the essential oils of some *V. officinalis* populations collected from 29 localities in the northern part of Netherlands. Using GC-MS, two chemovars could be differentiated based on the existence or absence of valeranone. No differences could be shown in the pattern of the valepotriates which were expected to be the most important pharmacologically active constituents of Valerian [58]. Hazelhoff *et al.* executed an arithmetical correlation between the Soxhlet extraction and the percolation extraction of (iso) valtrate from several Valeriana preparations and it did not show a significant change with respect to their accuracy [59]. Hazelhoff *et al.* determined the composition of the essential oil of subterranean parts of a commercial Valerian strain. GC-MS was performed, and 69 compounds could be identified of which 45 had not been reported the presence of essential oil of European Valerian. Three types of essential oil were distinguished in a comparative investigation of root material from the number of individual plants of *V. officinalis*, namely: Type A: 2.4–4.9% elemol, 6.2–8.7% valeranone, and 3.4–15.9% valeranal; Type B: 9.8–11.7% elemol, 0.3–2.0% valeranal, and no valeranone; Type C: 1.9–2.8% elemol, 16.2–18.1% valeranone, 9.3–10.3% and valeranal [60]. Popov *et al.* isolated a new valepotriate (VII) from *Valeriana officinalis* roots and its structure and stereochemistry determined. Comparison with didrovaltrate was made and an alteration of its C-1 configuration proposed [61]. Johnson and Waller isolated actinidine alkaloid from dried roots of *V. officinalis* by CHCl_3 -MeOH preceded by an Et_2O extraction and followed by a 10% HCl extraction [62]. Torrsell and Wahlberg isolated a crystalline, optically active, quaternary base from the dried roots of *V. officinalis* as the chloride and it was converted to a trifluoroacetate. The structures were revealed by spectroscopic techniques (Fig. 2) [63].

PHARMACOLOGICAL ACTIVITY

Chen *et al.* evaluated *acetylcholinesterase* (AChE) inhibitory activity of isolates, four new sesquiterpenoids and a new monoterpenoid from the root of *V. officinalis* by modified Ellman method *in vitro*. Learning and memory ability of isolate, volvalerenal acid K on mice was evaluated by the Morris water maze. Contents of acetylcholine (ACh), acetylcholine transferase (ChAT) and AChE in mice brains were measured by colorimetry. From this study, it was concluded that volvalerenal acid K can improve the learning and memory abilities of APPswe/PS Δ E9 double-transgenic mice and the mechanism may be related to the regulation of the relative enzyme in the cholinergic system [64]. Torres-Hernández *et al.* demonstrated the PTZ challenge in adult zebrafish for potential antiepileptic drugs. Valerenic acid and *V. officinalis* (both aqueous and ethanolic extracts) increase the latency to PTZ-induced seizure in adult zebrafish in a concentration-dependent manner. The result suggested that Valerenic acid and *V. officinalis* would be possible new therapeutic alternatives for epileptic patients [65]. Nam *et al.* investigated the effects of *V. officinalis* root extracts and its active constituent, valerenic acid on memory function, cell proliferation, neuroblast differentiation, serum corticosterone, and lipid peroxidation (LPO) in adult and aged mice. The administration of valerian root extract and valerenic acid

significantly improved the preferential exploration of new objects in novel object recognition test and the escape latency, swimming speeds, platform crossings, and spatial preference for the target quadrant in Morris water maze test compared to the D-galactose-treated mice. The result concluded that the *V. officinalis* root extract and valerenic acid enhance cognitive function, promote cell proliferation, neuroblast differentiation and reduce serum corticosterone, LPO in aged mice [66].

Shahidi *et al.* evaluated the effect of hydroalcoholic extract of *V. officinalis* on pain modulation and its possible mechanism in mice. Tail-flick and writhing tests were used for estimation of possible modulation of pain. The tail-flick latencies in the valeriana 800 mg/kg, combined valeriana 800 + naloxone, ondansetron, metoclopramide, or scopolamine-treated groups were significantly longer than that in the control group. The numbers of writhings in the Valeriana (800 mg/kg)+ondansetron and metoclopramide treated groups were significantly greater than in the extract (800 mg/kg) group. It was concluded that *V. officinalis* extract possesses a clear analgesic effect and works through the serotonergic and dopaminergic systems [67]. Sudati *et al.* investigated the potential protective effects of *V. officinalis* against the toxicity induced by rotenone in *Drosophila melanogaster*. Rotenone-fed flies had a worse performance in the negative geotaxis assay (i.e., climbing capability) and open-field test (i.e., mobility time) as well as a higher incidence of mortality when compared to control group. *V. officinalis* treatment offered protection against these detrimental effects of rotenone [68]. Pereira *et al.* investigated the possible preventive effects of *V. officinalis*, a medicinal plant widely used to improve disturbances in sleep, against vacuous chewing movements (VCM) in rats [69].

Barton *et al.* evaluated the efficacy of *V. officinalis* supplement for sleep in people with cancer who were undergoing cancer treatment. A supplemental, exploratory analysis revealed that several fatigue endpoints, as measured by the BFI and POMS, were significantly better for those taking valerian over placebo. Exploratory analyses revealed improvement in some secondary outcomes such as fatigue [70]. The effect of valerian extracts on an experimental model of temporal lobe epilepsy was evaluated by Rezvani *et al.* The involvement of adenosine system in the actions of aqueous extract of valerian was also evaluated. The results showed the significant anticonvulsant effect for aqueous but not in petroleum ether extract of valerian [71]. Murphy *et al.* reported behavioral measures of *V. officinalis* and benzodiazepine diazepam and to analyze the chemical composition of *V. officinalis*. Significant reduction of anxious behavior in valerian extracts and valerenic acid exposed subjects when compared to the ethanol control group. This evidence supported *V. officinalis* as a potential alternative to the traditional anxiolytics as measured by the elevated plus maze [72].

Sudati *et al.* studied the protective effect of *V. officinalis* on LPO induced by different pro-oxidant agents with neuropathological importance. Ethanolic extract of valerian (0–60 $\mu\text{g}/\text{ml}$) was tested against quinolinic acid (QA), 3-nitropropionic acid, sodium nitroprusside, and iron sulfate (FeSO_4) and $\text{Fe}^{2+}/\text{EDTA}$ induced LPO in rat brain homogenates. The effect of *V. officinalis* in deoxyribose degradation and reactive oxygen species production were also investigated. The result suggested that *V. officinalis* extract was effective in modulating LPO induced by different pro-oxidant agents and because of that *V. officinalis* extract, functioning as an antioxidant agent, can be beneficial for reducing insomnia complications linked to oxidative stress [73]. Fachinnetto *et al.* examined the effects of *V. officinalis*, a medicinal herb widely used as calming and sleep-promoting, in an animal model of orofacial dyskinesia induced by long-term treatment with haloperidol. Parameters such as VCMs, locomotor activity and plus maze performance were evaluated. Treatment with haloperidol and/or *V. officinalis* decreased the locomotor activity in the open field test. They determined that haloperidol treatment significantly decreased [3H]-dopamine uptake in striatal slices and *V. officinalis* was not able to prevent this effect [74]. Malva *et al.* evaluated the neuroprotective effects of *V. officinalis* against the toxicity induced by amyloid beta

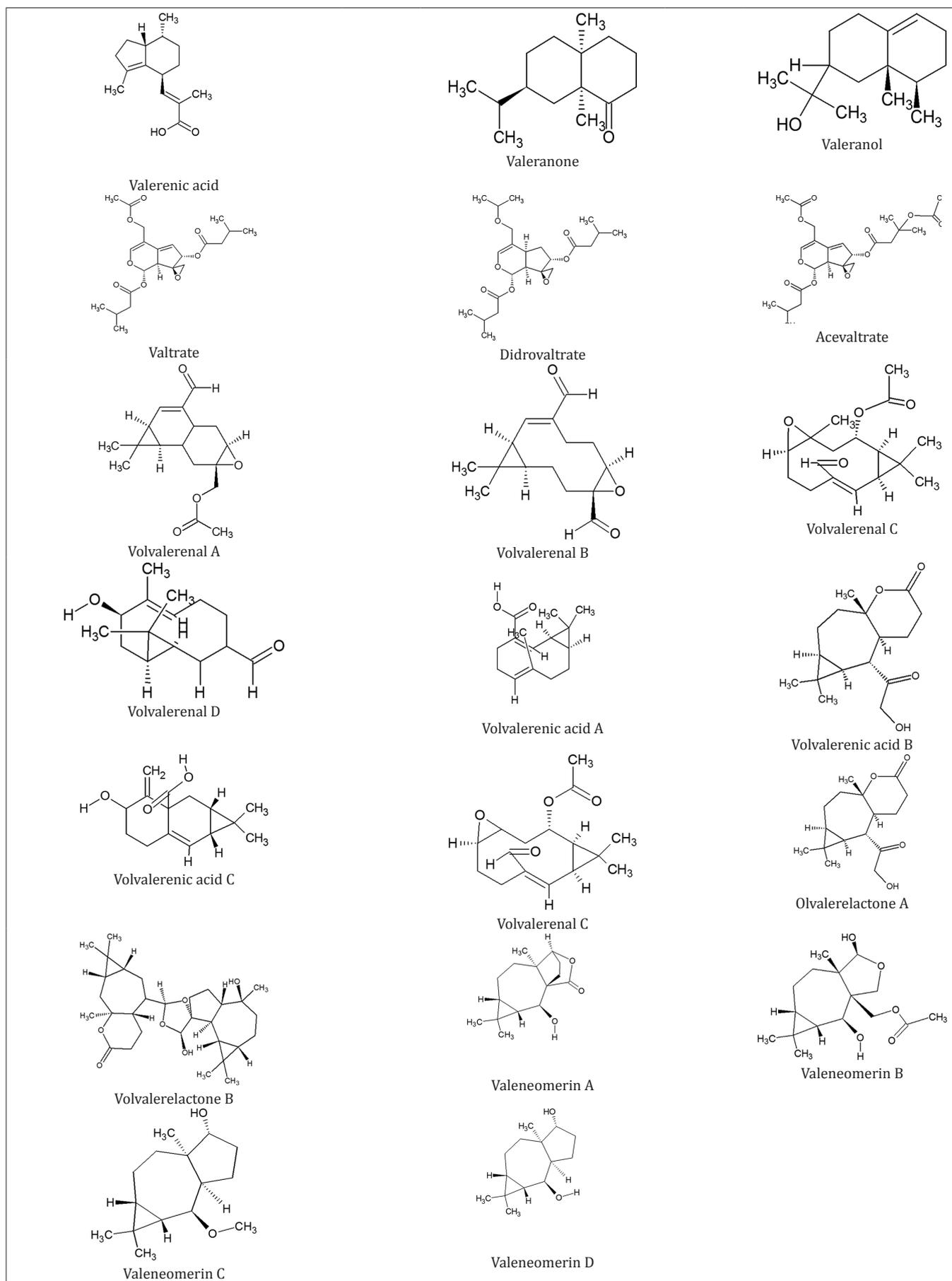


Fig. 2: Chemical constituents of *Valeriana officinalis* [23-29]

peptide 25–35 ($A\beta_{[25-35]}$). Cultured rat hippocampal neurons were exposed to $A\beta_{[25-35]}$ (25 μ M) for 24–48 h, after which morphological and biochemical properties were evaluated. The neuronal injury (decrease in cell reducing capacity and associated neuronal degeneration) evoked by $A\beta$, and prevented by valerian extract. From the study, it concluded that the signaling pathways involving $[Ca^{2+}]_i$ and the redox state of the cells may play a central role in the neuroprotective properties of *V. officinalis* extract against $A\beta$ toxicity [10].

CYTOPROTECTIVE EFFECTS

The potential cytoprotective effects of aqueous extract of *V. officinalis* on rotenone-induced apoptosis in human neuroblastoma SH-SY5Y cells were demonstrated by de Oliveria *et al.* The cytotoxicity, cell viability and analysis of cellular morphology were performed by MTT assay and phase contrast microscopy. Significant changes in the cellular morphology and condensation of the cell body could be observed when cells were treated with 300 nM rotenone for 48 h. The results indicated that neuroprotective action of the *V. officinalis* extracts support for the development of the cytoprotective drug in various therapies [75]. Do *et al.* evaluated pinoselinol-4,40-di-O-b-D-glucoside (PDG) from *V. officinalis* induced calcium mobilization and cell migration through the activation of lysophosphatidic acid (LPA) receptor subtypes. PDG-induced MEF cell migration was attenuated by pretreatment with phosphatidylinositol-3-kinase (PI3K) inhibitor such as LY294002. Cells lacking downstream mediator of PI3K such as Akt1 and Akt2 (DKO cells) showed loss of PDG-induced migration. They concluded that PDG is a strong inducer of cell migration and the pharmacological action of PDG may occur through the activation of an LPA receptor whereby activation of PI3K/Akt signaling pathway mediates PDG-induced MEF cell migration [76].

ANTI CORONARY SPASTIC/ANTIBRONCHOSPASTIC ACTIVITY

Circosta *et al.* were investigated anti coronary spastic, and antibronchospastic activities of ethanolic and aqueous extracts of *Valeriana officinalis* roots in anesthetized guinea-pigs, and the results were correlated with the qualitative/quantitative chemical composition of the extracts. Protective effects were evaluated for orally administered ethanolic and aqueous extracts (50, 100, and 200 mg/kg) against Pitressin-induced coronary spasm and pressor response in guinea-pigs and were compared with those of nifedipine. The protective effects against histamine-induced and Oleaceae antigen challenge induced bronchospasm were also evaluated. The results showed that two valeriana extracts possessed significant anti coronary spastic, antihypertensive, and antibronchospastic properties. This study justified the traditional use of this plant in the treatment of some respiratory and cardiovascular disorders [77].

CONCLUSION

V. officinalis is endemic to many parts of Europe, Asia and North America and are widely used in traditional medicine for various applications. *V. officinalis*, on its own or as part of a polyherbal preparation is a valuable remedy for cancer and neuroprotective disorders. The phytochemical results have indicated a variety of chemical constituents. Pharmacological studies indicated that these plants possessed various biological activities, especially in the areas of antioxidant, anti-inflammatory, anticancer, anticonvulsive, anti-Parkinson's and anti-Alzheimer's disease, etc. Regarding the constituents contributed to therapeutic values, the findings indicated that Valepotriates are major components for the treatment of epilepsy, depressant, Parkinson's disease, and Alzheimer's disease. Although great progress on the phytochemistry and pharmacology of *V. officinalis* have been made, there still need more conclusive studies on the safety, efficacy and *in vivo* toxicity of extracts and pure compounds to gain a better understanding. Collectively, this present review provides systematical information on the ethnopharmacology, phytochemistry, and pharmacology of *V. officinalis*, which supports the further clinical use in modern medicine.

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