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Updating the biological interest of *Valeriana officinalis*

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Abstract. *Valeriana officinalis* L. (Caprifoliaceae) has been traditionally used to treat mild nervous tension and sleep problems. The basis of these activities are mainly attributed to valerenic acid through the modulation of the GABA receptor. Moreover, *V. officinalis* is claimed to have other biological activities such as cardiovascular benefits, anticancer, antimicrobial, and spasmolytic. The current review aims to update the biological and pharmacological studies (*in vitro*, *in vivo*, and clinical trials) of *V. officinalis* and its major secondary metabolites to guide future research.

Databases PubMed, Science Direct, and Scopus were used for literature search, including original papers written in English and published between 2014 and 2020.

There have been identified 33 articles that met the inclusion criteria. Most of these works were performed with *V. officinalis* extracts, and only a few papers (*in vitro* and *in vivo* studies) evaluated the activity of isolated compounds (valerenic acid and volvalerenal acid K). *In vitro* studies focused on studying antioxidant and neuroprotective activity. *In vivo* studies and clinical trials mainly investigated the nervous system activity (anticonvulsant activity, antidepressant, cognitive problems, anxiety, and sleep disorders). Just a few studies were focused on other different activities, highlight effects on symptoms of premenstrual and postmenopausal syndromes.

Valeriana officinalis continues to be one of the medicinal plants most used by today's society for its therapeutic properties and whose biological and pharmacological activities continue to arouse great scientific interest, as evidenced in recent publications. This review shows scientific evidence on the traditional uses of *V. officinalis* on the nervous system.

Keywords: *Valeriana officinalis*; bioactive compounds; biological activity; pharmacology activity; preclinical studies; clinical trials.

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Introduction

Valeriana officinalis L. (Caprifoliaceae family), commonly known as "All-heal" (English), "Herbe aux chats" (French) and "Baldrian" (German), is an herbaceous perennial plant that grows extensively in temperate regions in Europe, Asia and North America (Hamaidia *et al*., 2016; Sundaresan *et al*., 2018) (Figure 1). The name of "*Valeriana*" derives from the Latin word "*valere*" which means to be healthy, strong, or powerful and the Latin word "*officinalis*" ("*officina*"), which refers to monastery pharmacy and apothecaries' shops (Hamaidia *et al*., 2016).

Addressing its chemical composition, there have been identified more than 150 different compounds in *Valeriana officinalis*. The qualitative and quantitative composition varies with the growing environment, climate, plant age, harvest phase and subspecies. The principal chemical constituents are alkaloids (i.e. chatinine, valerine, valerianine and actinidine), organic acids and terpenes (i.e. valerenic acid, isovaleric acid, valeric acid and acetoxyvalerenic) and iridoids (i.e. valepotriate, isovalepotriate), lignanoids (i.e. pinoresinol-4-O-D-glucoside, 8'-hydro-xypinoresinol), flavonoids (i.e. apigenin, luteolin, quercetin) (Patpcka & Jakl, 2010; Wang *et al*., 2010; Chen *et al*., 2013; Wang *et al*., 2013; Chen *et al*., 2015) (Figure 2).

The root of *V. officinalis* has been used since ancient Greece and Rome in traditional medicine until today in modern medicine to improve in the nervous state and to contribute to sleep promotion. The sesquiterpene valerenic acid is the main compound responsible for these activities through GABA receptor modulation (Felgentreff *et al*., 2012). The European Medicine Agency (EMA) based on validated scientific data, reported that the well-established use for dry ethanol (40-70%) extracts of *V. officinalis* in solid oral dosage forms is the relief of mild nervous tension and sleep disorders. Moreover, EMA includes other herbal preparations in *V. officinalis* monography, which are based on traditional use (more than 30 years of use in therapeutics) for relief of mild symptoms of mental stress and to aid sleep (Anon., 2016). Moreover, *V. officinalis* is claimed to have other biological activities such as cardiovascular benefits (reduction in blood pressure and heart rate, antiarrhythmic and regulation of blood lipid levels), anticancer, antimicrobial and spasmolytic (Letchamo *et al*., 2004; Occhiuto *et al*., 2009; Chen *et al*., 2015).

The current review aims to update the biological and pharmacological studies (*in vitro*, *in vivo,* and clinical trials) of *V. officinalis* and its major secondary metabolites to guide future research.

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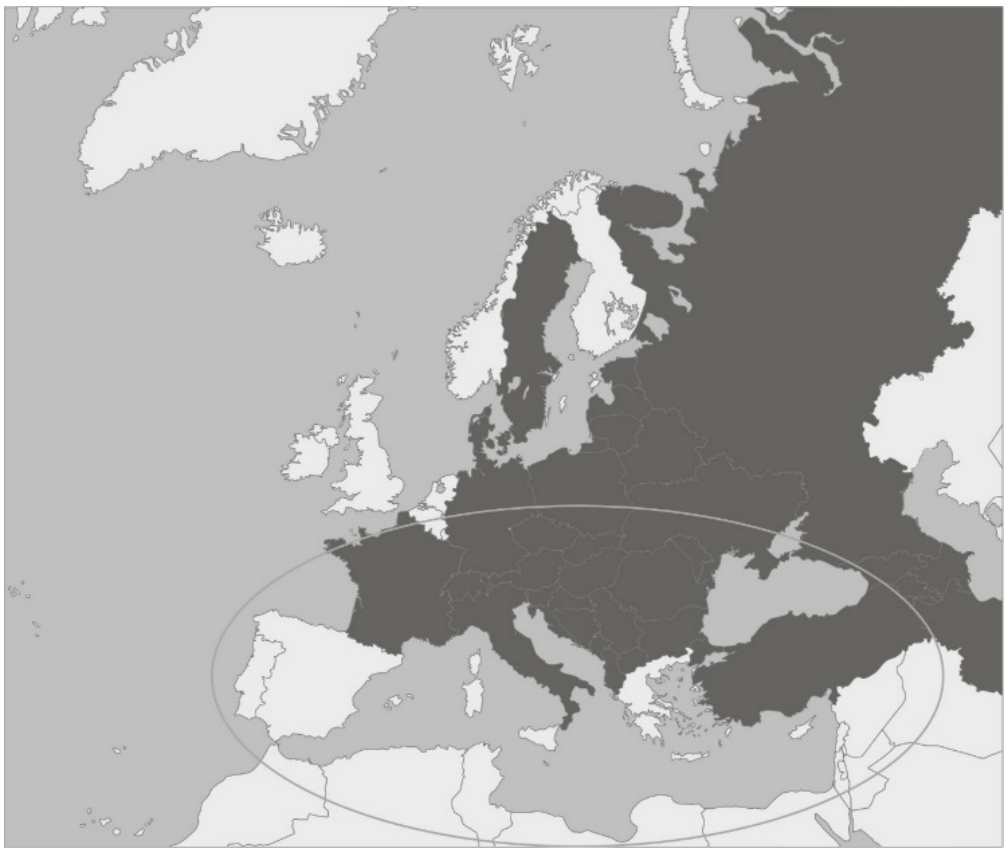

Figure 1. Native distribution of *Valeriana officinalis*.

Methods

This review focused on preclinical and clinical trials on the biological and pharmacological activity of *V. officinalis* and its major bioactive compounds. A literature search was performed in databases PubMed, Science Direct, and Scopus using the keywords *V. officinalis*, valerian, *in vitro, in vivo*, clinical trials, biological, and pharmacology. There were only selected original papers (excluding reviews, case reports, proceedings, editorial/letters, and conferences), written in English and published between 2014 and 2020. In addition, all works on the biological and pharmacological activity of other valerian species different than *V. officinalis* and studies on *V. officinalis* activity combined with other medicinal plant species were excluded.

Manuscripts were selected by two independent researchers who first identified all potential studies in the three cited databases to exclude then duplicates and those papers which did not meet inclusion criteria based on title and abstract analysis and full-text analysis.

Results and Discussion

Initially, we identified 556 studies (259 in PubMed, 37 in Science Direct, and 260 in Scopus). Of these reports, 91 works were excluded because they were duplicated in two or more databases. Of the 465 possible papers, 419 were excluded after analyzing title and abstract for not meeting inclusion criteria, and 13 articles were then excluded after full analysis. Finally, 33 items were included in this review. Figure 3 shows the flowchart of the literature process for the biological and pharmacology activity of *V. officinalis.*

This review consisted of 6 *in vitro* studies, 14 *in vivo* studies (1 of these reports presented *in vitro* and *in vivo* outcomes), and 13 clinical trials. Most of these works were performed with *V. officinalis* extracts, and just 5 (*in vitro* and *in vivo* studies*)* evaluated the biological and pharmacological activity of isolated compounds (valerenic acid, valeric acid, and volvalerenal acid K).

In vitro studies

Table 1 lists six articles with valerian extracts and their isolated compounds. All these works focused on studying antioxidant and neuroprotective activity, except one which aims to evaluate its antidiabetic properties. Four of these studies used chemical *in vitro* assays to measure antioxidant capacity and acetylcholinesterase inhibitory activity (Pilerood & Prakash, 2014; Li *et al*., 2015; Chen *et al*., 2016; Katsarova *et al*., 2018). In the other two *in vitro* studies, cell lines have been employed, particularly, the human neuroblastoma SH-SY5Y cells and the mouse 3T3-L1 preadipocytes (Gonulalan *et al*., 2018; Harada *et al*., 2020).

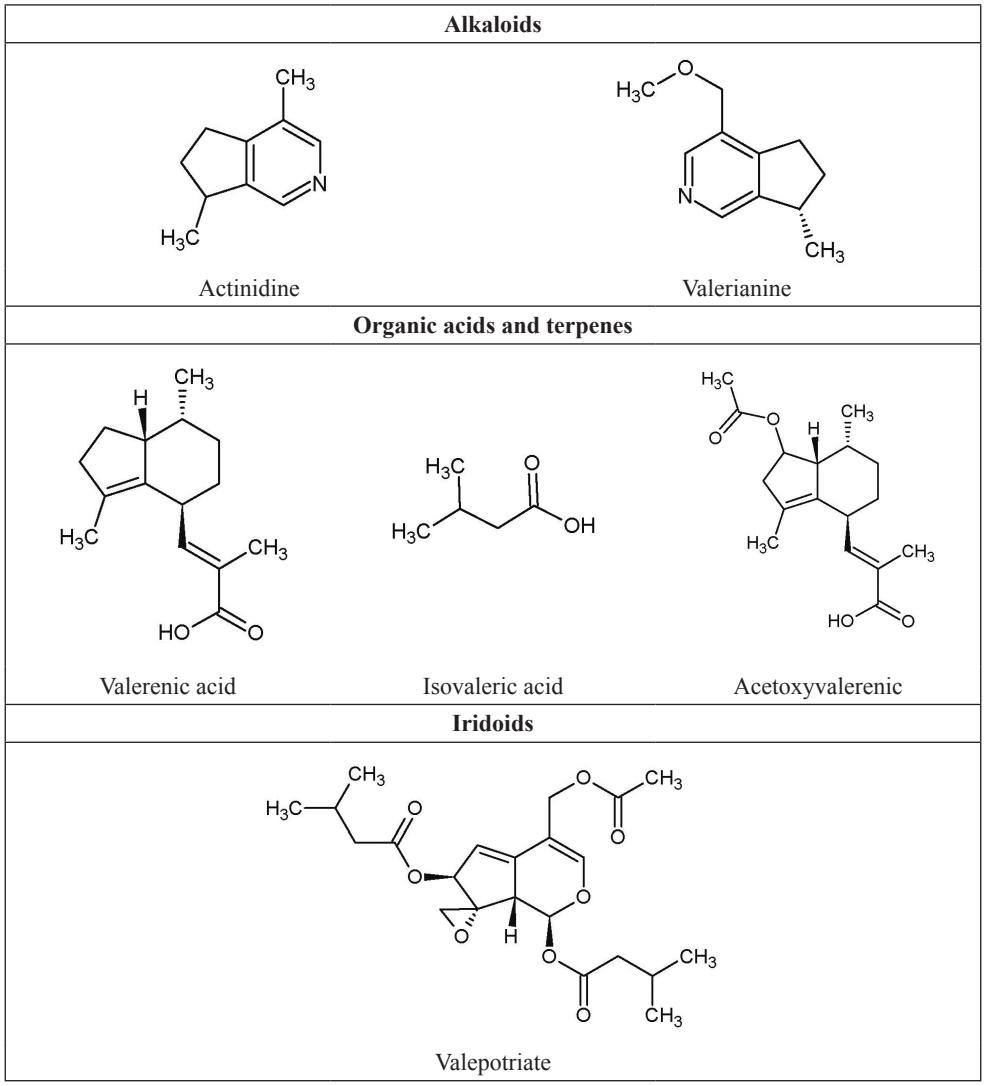

Figure 2. Chemical structures of some principal constituents identified in *Valeriana officinalis*.

Table 1. *In vitro* biological studies for *Valeriana officinalis*

Activity	Extract / isolated compounds	Experimental model	Treatments	Major findings	References
Antidiabetic	*Valeriana officinalis* root methanol extracts	Mouse 3T3-L1 preadipocytes	1, 10, and 100 µg/mL	↑ mRNA levels (PPARγ, CCAAT/enhancer-binding protein α, and adipocyte protein 2)	Harada *et al*., 2020
Antioxidant	*Valeriana officinalis* root extracts	DPPH model Reducing power Total antioxidant method	-	↑ Reducing power (80% methanolic extract) Free radical scavenging (80% methanolic extract)	Pilerood &Prakash, 2014
Antioxidant	*Valeriana officinalis* root extracts	ORAC method HORAC method	-	Low antioxidant activity (ORAC 820.5 µmol TE/g and HORAC 381.6 µmol GAE/g)	Katsarova *et al*., 2017
Antioxidant	*Valeriana officinalis* root ethanolic extracts	DPPH model FRAP method ABTS assay	-	Antioxidant activity (0.2579 mmol Trolox/g)	Li *et al*., 2015
Neuroprotection	*Valeriana officinalis* root extract Methanolic extracts of: • Valerenic acid • Acetoxy valerenic acid • Valerenic acid-free • Acetoxy valerenic acid-free	SH-SY5Y human neuroblastoma cell line	25 µg/mL	↑ BDNF expression	Gonulalan *et al*., 2018
Neuroprotection	Sesquiterpenoids Monoterpenoid	Acetylcholinesterase inhibitory activity	-	Volvalerenal acid K (IC50 0.161 µM)	Chen *et al*., 2016

Antioxidants are compounds that prevent free radical harmful effects by scavenging and metal chelating. There are different *in vitro* tests to evaluate antioxidant activity based on hydrogen atom transfer (i.e. ORAC method), electron transfer reactions (i.e. FRAP assay) and both hydrogen and electrons transfer capacities (i.e. DPPH assay) (Neha *et al*., 2019). Methanolic (80%) and ethanolic (80%) extracts of *V. officinalis* root exhibited highest reducing power activity. Moreover, 80% methanolic extract showed the highest DPPH radical scavenging activity. In another study, *V. officinalis* ethanolic extracts (95%) was effective to scavenge DPPH radical (Li *et al*., 2015). This antioxidant activity was positively correlated with flavonoids and tannin content (Pilerood &Prakash, 2014; Li *et al*., 2015). On the other hand, *V. officinalis* ethanol extracts (40%) showed low antioxidant activity in ORAC and HORAC assays (Katsarova *et al*., 2018).

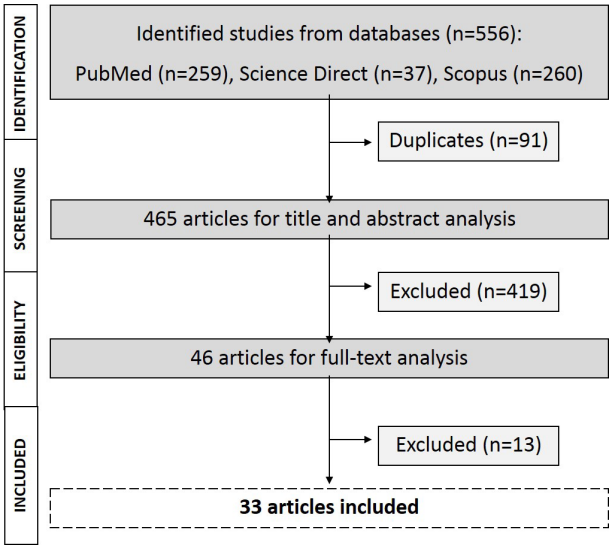

Figure 3. Flowchart of literature review process for biological and pharmacological activity of *Valeriana officinalis*.

In the last six years, the neuroprotective activity of *V. officinalis* extracts and the sesquiterpene volvalerenal acid K has been also studied using *in vitro* techniques. Low levels of Brain-Derived Neurotrophic Factor (BDNF) have been linked to depression. Hence, *V. officinalis* methanolic extract at a concentration of 25 µg/mL increased BDNF level in SH-SY5Y human neuroblastoma cell line. This activity is attributed to valerenic acid (Gonulalan *et al*., 2018). On the other hand, postmortem Alzheimer's disease brains revealed low levels in the neurotransmitter acetylcholine which lead to cognitive impairment and decline. Acetylcholinesterase hydrolyzes acetylcholine, thus targeting this enzyme will be clinically effective in slowing Alzheimer's disease progression (Anand & Singh, 2013). The compound volvalerenal acid K isolated from *V. officinalis* root demonstrated to inhibit acetylcholinesterase activity (IC_{50} value of 0.161 µM), being of interest as anti-Alzheimer agent (Chen *et al*., 2016).

Finally, the methanolic extract of *Valeriana officinalis* root demonstrated to be beneficial against type 2 diabetes by promoting dose-dependently 3T3-L1 adipocytes differentiation; this is related to direct binding to peroxisome proliferator-activated receptor γ (PPARγ) (Harada *et al*., 2020).

In vivo studies

Table 2 summarizes the main results for the fourteen *in vivo* studies. The main investigated activities were analgesic, anticonvulsant, antidepressant, anxiolytic and protective role in neurodegenerative diseases. Regarding animal models, rats and mice (mainly, Wistar and Sprague dawley rats and ICR mice) were the most common to evaluate the activity of valerian. Moreover, gerbils and zebrafish were selected as an experimental model in the other three *in vivo* studies (Torres-Hernández *et al*., 2015; Yoo *et al*., 2015; Torres-Hernández *et al*., 2016). The effect of isolated active compounds (valeric acid, valerenic acid, and volvalerenal acid K) has been investigated in six of the *in vivo* works, whereas the extracts of the root were evaluated in the other nine studies. The doses for both extracts and bioactive compounds were different in all studies.

Acute pain results from activation of nociceptors due to trauma (thermal, mechanical and chemical stimulus) or to biochemical mediators (serotonin, histamine, prostaglandins and arachidonic acid) (Johnson *et al*., 2013). The alcoholic extract of *V. officinalis* root (200 mg/kg and 400 mg/kg) reduced pain score in the acute phase and pain sensitivity in formalin induced pain in Wistar rats and Sprague Dawley rats (Taherianfard & Karamifard, 2018; Zare *et al*., 2018).

Epilepsy is a chronic and severe neurological disorder that consists of having at least two seizures caused by abnormal neuronal activity. Epilepsy affects more than 50 million people worldwide (Quintans *et al*., 2008; GBD 2016 Epilepsy Collaborators, 2019). Valerenic acid and *V. officinalis* extracts (ethanolic and aqueous) increased the latency period to the onset of a seizure and reversed altered swimming behaviors on pentylenetetrazole-induced in zebrafish larval

model epileptic seizures. This anticonvulsant activity seems to be related to *V. officinalis* ability to regulate neural activity (c-fos, npas4a, and bdnf) genes (Torres-Hernández *et al*., 2015; Torres-Hernández *et al*., 2016).

Depression is a common mental disorder that affects more than 264 million people worldwide (GBD 2017 Disease and Injury Incidence and prevalence Collaborators, 2018). Valerenic acid (0.5 mg/kg) and *V. officinalis* root extract alleviated physical and psychological stress in ICR mice by reducing 5-hydroxyindoleacetic acid and 3-methoxy-4-hydroxyphenylethyleneglycol sulfate levels in the hippocampus-amygdala region (Jung *et al*., 2014; Jung *et al*., 2015). These activities are beneficial to treat depression and anxiety. The antidepressant effect has also been demonstrated for *V. officinalis* hydroalcoholic root extract in ovalbumin sensitized Wistar rats as evidenced in an increase in central and peripheral crossing numbers and a decrease in immobility times (Neamati *et al*., 2014).

Alzheimer's disease is the most common neurodegenerative disease. It is estimated that 43.8 million people have dementia (GBD 2016 Dementia Collaborators, 2019). The sesquiterpene volvalerenal acid K improved learning and memory abilities in SPF APPswe/PS1E9 double-transgenic dementia mice by increasing acetylcholine content and acetylcholine transferase and by reducing acetylcholinesterase activity (Chen *et al*., 2016). The hippocampus is related to short-term memory. *V. officinalis* hydroalcoholic extract has been shown to protect against morphology changes (size and number) of cerebral hippocampus astrocytes in rats (Heidarian *et al*., 2020). Parkinson's disease, the second most common degenerative neurological disorder, affects 6.1 million people globally (GBD 2016 Parkinson's Disease Collaborators, 2018). Valerenic acid alleviated 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurotoxicity in C57BL/6 J and CD-1 mice models of Parkinson's disease by reducing pro-inflammatory cytokines (IL-1β, IL-6, TNF-α and IFN-γ) and glial fibrillary acid protein (GFAP) (Rodríguez-Cruz *et al*., 2019).

In addition to all these effects, *V. officinalis* extracts have been investigated as myorelaxant agents and protect against cerebral ischemia. Hence, *V. officinalis* hydroethanolic root extract (2 and 5 g/kg doses) reduced skeletal muscle strength in Swiss mice without the side effect of other myorelaxant agents (muscle tone alteration and endurance decrease) (Caudal *et al*., 2017). Moreover, *V. officinalis* (25 and 100 mg/kg doses) protects against transient cerebral ischemia by decreasing microglial activation and lipid peroxidation in male gerbils (Yoo *et al*., 2015). Furthermore, valeric acid (0.15 mmol/kg) showed a hypotensive effect in Wistar rats, as evidenced by decreased arterial blood pressure and heart rate (Onyszkiewicz *et al*., 2020).

Clinical trials

Most clinical trials conducted in recent years with *V. officinalis* are with extracts and to evaluate different activities on the nervous system. A total of thirteen clinical trials, conducted with 747 patients (average of sample patients was 57, from 20 to 100 individuals) met the inclusion criteria of this review. They included clinical trials mainly originated from Iran (n=8), Brazil, and the USA (n=2). The overall clinical trials were randomized double-blind (except one study) (Jenabi *et al*., 2018) and placebo-controlled trials. The population included in these clinical trials has been varied from healthy volunteers to patients with different base pathologies (i.e., HIV-positive patients, infertile women, patients with acute coronary syndrome). The route of administration of valerian was oral in all studies except for one in which drops of oil (2.5%) (Bagheri-Nesami *et al*., 2015) were administered as massage. The oral doses of valerian ranged from 100 mg/daily to 1,600 mg/daily, being 530 mg the most common dose. Table 3 lists all the studies that meet the inclusion criteria. These studies are arranged alphabetically according to the authors of the investigations.

Anxiety disorders are common prevalent mental disorders (0.9%-28.3%) (Baxter *et al*., 2013). Farah *et al*. (2019) investigated the anti-anxiety effect of *V. officinalis* (100 mg in capsules, 60 minutes before the surgical procedure) and compared its effectiveness with midazolam (15 mg in tablets) in patients with anxiety due to bilateral extraction of mandibular third molars. This study revealed that midazolam is more potent as an anxiolytic drug, but *V. officinalis* causes less adverse effects (sedation and somnolence). Similar results of anti-anxiety properties of *V. officinalis* were observed in patients submitted to impacted lower third molar surgery and treated with valerian (100 mg, 1 hour before the surgical procedure) (Pinheiro *et al*., 2014). Valerian capsules (1,500 mg) has also been shown to significantly reduce anxiety in infertile women who undergo hysterosalpingography (Gharib *et al*., 2015). Moreover, a recent clinical trial revealed that valerian root extract (100 mg, thrice daily for four weeks) has anxiolytic properties by altering functional brain connectivity, as shown in an increase in frontal brain region alpha coherence and a reduction in theta coherence. Coherence in the electrical activity of the brain measures synchrony degree between two or more brain regions to frequency values in a unit of time (Roh *et al*., 2019).

Cognitive problems are more significant in patients with hemodialysis than in the general population. Valerian extract is an agonist of adenosine A1 receptors. This medicinal plant has sedative effects, and it also inhibits cholinergic transmission and increases delta frequency strength in the frontal cortex (Samaei *et al*., 2018). Valerian (capsules, 530 mg, 60 minutes before bed, for one month) could be effective and significantly improve cognitive status; however, no significant changes were observed in the EGG of the hemodialysis patients (Samaei *et al.,* 2018). Moreover, it was demonstrated that *V. officinalis* root extract (1,060 mg/daily each 12 h for eight weeks) reduced odds of cognitive dysfunction in patients scheduled for elective coronary artery bypass graft surgery using cardiopulmonary bypass (Hassani *et al*., 2015). The cognitive status was evaluated in both cited works using the Mini-Mental State Examination (MMSE) questionnaire (11 questions regarding memory and orientation, attention and concentration, language and understanding abilities and visual-spatial abilities; a score of less than nine indicates that the patient has severe cognitive impairment) (Hassani *et al*., 2015; Samaei *et al.,* 2018).

Table 2. *In vivo* biological studies for *Valeriana officinalis*

Activity	Extract / isolated compound	Experimental model	Doses	Major findings	References
Analgesic	Valerian root	Wistar rats Formalin-induced	200 mg/kg of alcoholic extract of valerian root	↓ Pain score in acute phase	Zare *et al*., 2018
Analgesic	*Valeriana officinalis* rhizome extract	Sprague Dawley rats	400 mg/kg	↓ Pain sensitivity	Taherianfard & Karamifard, 2018
Anticonvulsant	Valerenic acid *Valeriana officinalis* extracts (aqueous and ethanolic)	Zebrafish (*Danio rerio*) PTZ-Induced seizures	Valerenic acid (37 µg/ml) Ethanolic valerian extract (0.5 and 1 mg/ml) Aqueous valerian extract (5 mg/ml)	↑ Latency period to the onset of seizure	Torres-Hernández *et al*., 2015
Anticonvulsant	*Valeriana officinalis* aqueous root extract	Zebrafish (*Danio rerio*)	1, 2.5, 5, and 7 mg/ml	Reversion of PTZ-altered swimming behaviors ↑ Neural-activity genes (npas4a and bdnf)	Torres-Hernández *et al*., 2016
Antidepressant	*Valeriana officinalis* hydroalcoholic root extract	Wistar rats	50, 100 and 200 mg/kg	↑ Central and peripheral crossing number ↓ Immobility times	Neamati *et al*., 2014
Antidepressant	*Valeriana officinalis* root extracts	ICR mice	100 mg/kg/0.5 ml	↓ Physical and psychological stress ↓ MHPG-SO4 and 5-HIAA levels	Jung *et al*., 2014
Anxiolytic	Valerenic acid	ICR mice	0.2, 0.5, and 1.0 mg/kg/0.3 mL	↓ Immobility time ↓ Corticosterone levels ↓ Physical and psychological stress response ↓ 5-hydroxyindoleacetic acid and 3-methoxy-4-hydroxy-phenylethyleneglycol sulfate levels	Jung *et al*., 2015
Anxiolytic	Valerenic acid	CD-1 mice	0,5 mg/kg	Anxiolytic effect	Becker *et al*., 2014
Cardioprotective	*Valeriana officinalis* root extract	Male gerbils	25 and 100 mg/kg	Cerebral ischemia protection ↓ Microglial activation ↓ Lipid peroxidation	Yoo *et al*., 2015
Cardioprotective	Valeric acid	Wistar rats	0.15 mmol/kg	↓ Arterial blood pressure ↓ Heart rate	Onyszkiewicz *et al*., 2020
Myorelaxant	*Valeriana officinalis* hydroethanolic root extract	Swiss mice	2 or 5 g/kg	↓ skeletal muscle strength	Caudal *et al*., 2018
Neuroprotection	Valerenic acid	Parkinson's disease model: MPTP-induced mouse C57BL/6 J mice and CD-1 mice	2 mg/kg body weight, *i.p*	↓ Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α and IFN-γ) ↓ GFAP proteins	Rodríguez-Cruz *et al*., 2019
Neuroprotection	Volvalerenal acid K	APPswe/PSΔE9 double-transgenic mice	0.65, 1.30 and 2.60 mg/kg/day	↑ Learning and memory abilities	Chen *et al*., 2016
Neuroprotection	*Valeriana officinalis* hydroalcoholic extract	Sprague dawley rats	300, 400, 600 mg extract daily	↑ Number of astrocytes ↓ Large diameter of astrocytes	Heidarian *et al*., 2020

Insomnia causing absenteeism and social disability affects around one-third of adult people (Bent *et al*., 2006). There are consistent evidence that valerian optimizes the quality of sleep and induces sleep. *V. officinalis* (530 mg, 1 hour before bed, four weeks) improved sleep and anxiety in HIV-positive patients treated with efavirenz (Ahmadi *et al*., 2017). Moreover, the combination of valerian oil 2.5% (2 drops, three nights) improved sleep quality and reduced waking during the night in patients who suffered from acute coronary syndrome (Bagheri-Nesami *et al*., 2015). The sleep status (time and quality) was measured using different techniques such as St. Mary's Hospital Sleep Questionnaire (SMHSQ) (survey with 14 Likert-scale questions and a fill-in-the-blank response) and a validated Persian version of the Pittsburgh Sleep Quality Index (PSQI) (survey with 7 components; a score greater than five indicates that the patient does not sleep long enough and the sleep is not of quality) (Bagheri-Nesami *et al*., 2015; Ahmadi *et al*., 2017). Furthermore, Mineo *et al*. (2017) investigated the effect of a single dose of *V. officinalis* (900 mg; valerenic acid 0.8%) at the cortical level in healthy volunteers using transcranial magnetic stimulation. This study revealed that *V. officinalis* reduced intracortical facilitatory circuits. On the other hand, a dose of 1,600 mg of valerian does not affect drive stimulator performance in healthy volunteers compared to the placebo group (Thomas *et al*., 2016).

Furthermore, a dose of 530 mg of valerian root extraction (2 capsules for one month) resulted in decreasing daily livings, disability, and severity of the tension-type headache. The effect of valerian on headache impact was measured using surveys [headache impact test questionnaire (HIT-6), headache disability inventory (HDI), and Visual Analogue Scale (VAS)] in baseline and one month after the intervention (Azizi *et al*., 2020).

In addition to all these studies, other activities have been studied in humans. Hence, valerian (530 mg, twice per day, two months) reduced the severity and frequency of hot flashes in menopausal women (Jenabi *et al*., 2018). Moreover, valerian (2 capsules daily for three months) reduced emotional, physical, and behavioral symptoms of premenstrual syndrome in women university students (Behboodi Moghadam *et al*., 2016).

Table 3. Clinical trials for *Valeriana officinalis*. Abbreviations are: S. size, sample size.

Study (author, year, country)	Study design	S. size	Population	Intervention	Results
Ahmadi *et al*., 2017 Iran	Randomized, double-blind, placebo	51	HIV-positive patients treated with efavirenz	Intervention group: valerian (530 mg, 1 hour before bed, 4 weeks) Placebo group	↑ Sleep ↓ Anxiety
Azizi *et al*., 2020 Iran	Randomized, double-blind, placebo	88	Tension-type headache	Intervention group: 530 mg of valerian root extraction Placebo group	↓ Disability ↓ Severity score ↓ Daily livings
Bagheri-Nesami *et al*., 2015 Iran	Randomized, double-blind, controlled	90	Patients with acute coronary syndrome	Intervention group: acupressure with valerian oil 2.5% (2 drops, 3 nights) Control group: massage	↑ Sleep quality ↓ Waking
Behboodi Moghadam *et al*., 2016 Iran	Double-blind, placebo	100	Premenstrual syndrome women	Intervention group: valerian (2 capsules daily, 3 months) Placebo group	↓ Emotional, physical and behavioral symptoms
Farah *et al*., 2019 Brazil	Randomized, double-blind, crossover and prospective	20	Anxious patients with an indication for bilateral extraction of mandibular third molars	Intervention group: Valerian (100 mg in capsules, 60 minutes before surgical procedure) Control group: Midazolam (15 mg in tablets, 60 minutes before surgical procedure)	↓ physiological parameters No sedation and less somnolence than midzolam
Gharib *et al*., 2015 Iran	Randomized, double-blind, placebo	64	Infertile women undergoing hysterosalpingography	Intervention group: valeric capsules (1500 mg) Placebo group	↓ Anxiety
Hassani *et al*., 2015 Iran	Randomized, double-blind, placebo	61	Patients scheduled for elective CABG surgery using CPB	Intervention group: valerian capsule (1,060 mg/daily) Placebo group	↓ Odds of cognitive dysfunction
Jenabi *et al.*, 2018 Iran	Randomized, triple-blind, placebo	60	Postmenopausal women	Intervention group: valerian (530 mg, twice per day, two months) Placebo group	↓ Hot flashes (severity and frequency)
Mineo *et al.*, 2017 USA	Randomized, double-blind, placebo, crossover	50	Healthy volunteers	Intervention group: *Valeriana officinalis* extract (900 mg with valerenic acid 0.8%) Placebo group	↓Intracortical facilitation
Pinheiro *et al.*, 2014 Brazil	Randomized, double-blind, placebo	20	Patients submitted to impacted lower third molar surgery	Intervention group: valerian capsule (100 mg) Placebo group	↓ Anxiety
Roh *et al*., 2017 Korea	Randomized, double-blind, placebo, crossover	64	Volunteers suffering psychological stress	Intervention group: valerian root extract (100 mg/thrice daily for 4 weeks) Placebo group	↑ Frontal brain region alpha coherence ↓ Theta coherence
Samaei *et al*., 2018 Iran	Randomized, double-blind, placebo, crossover	39	Hemodialysis patients	Intervention group: valerian capsules (530 mg, 60 min before bed, 1 month) Placebo group	↑ Cognitive status
Thomas *et al.* 2016 USA	Randomized, double-blind, placebo, crossover	40	Healthy adult	Intervention group: valerian (1600 mg) Placebo group	No effect on drive stimulator performance

Regarding adverse effects, only two of the thirteen clinical trials have reported adverse drug reactions (Ahmadi *et al*., 2017; Farah *et al*. (2019). Remarkably, these adverse events were dizziness, somnolence, and nausea. These adverse drug reactions were typed A related to the mechanism of action, dose-related toxicities, and predictable (Iasella *et al.,* 2017).

Finally, no clinically relevant interactions have been reported for valerian root and other drugs that are metabolized by cytochrome P450 isoforms (CYP3A4, CYP2D6, CYP1A2, and CYP2E1) (Anon., 2003; Kelber *et al*., 2014; Anon., 2016).

Conclusions

Valeriana officinalis continues to be one of the medicinal plants most used by today's society for its therapeutic properties and whose biological and pharmacological activities continue to arouse great scientific interest, as evidenced in recent publications. This review shows scientific evidence on the traditional uses of *V. officinalis* on the nervous system. The *in vitro* studies revealed the potential antioxidant activities of *V. officinalis,* which could therapeutically contribute to prevent and protect against oxidative stress-related diseases. Moreover, *in vivo* studies explored its effective activity on different nervous system diseases such as depression, epilepsy, and neurodegenerative disorders. Based on clinical trials, there is consistent evidence of the efficacy of *V. officinalis* in anxiety, cognitive problems, and insomnia without causing side effects. This report highlights the potential biological properties of the compounds volvalerenal acid K and valerenic acid *in vitro* and *in vivo* studies. However, there is a lack of efficacy and safety of these major bioactive compounds in clinical trials. Therefore, future research should be focus on studying the clinical activity of these secondary metabolites as well as investigating new and different biological activities of *V. officinalis*.

References

Ahmadi, M., Khalili, H., Abbasian, L. & Ghaeli, P. 2017. Effect of Valerian in preventing neuropsychiatric adverse effects of efavirenz in HIV-positive patients: A pilot randomized, placebo-controlled clinical trial. Ann. Pharmacother. 51(6): 457–464.

Anand, P. & Singh, B. 2013. A review on cholinesterase inhibitors for Alzheimer's disease. Arch. Pharm. Res. 36(4): 375–399.

Anonymous. 2003. European Scientific Cooperative on Phytotherapy. ESCOP monographs: The Scientific Foundation for Herbal Medicinal Products, 2nd ed. ESCOP, Exeter. Georg Thieme Verlag, Stuttgart. Thieme, New York.

Anonymous. 2016. Committee on Herbal Medicinal Products (HMPC) European Union herbal monograph on Valeriana officinalis L., radix. EMA, HMPC 150848/2015.

Azizi, H., Shojaii, A., Hashem-Dabaghian, F., Noras, M., Boroumand, A., Ebadolahzadeh Haghani, B. & Ghods, R. 2020. Effects of Valeriana officinalis (Valerian) on tension-type headache: A randomized, placebo-controlled, double-blind clinical trial. Avicenna J. Phytomed. 10(3): 297–304.

Bagheri-Nesami, M., Gorji, M.A., Rezaie, S., Pouresmail, Z. & Cherati, J.Y. 2015. Effect of acupressure with valerian oil 2.5% on the quality and quantity of sleep in patients with acute coronary syndrome in a cardiac intensive care unit. J. Tradit. Complement. Med. 5(4): 241–247.

Baxter, A.J., Scott, K.M., Vos, T. & Whiteford, H.A. 2013. Global prevalence of anxiety disorders: a systematic review and meta-regression. Psychol. Med. 43(5): 897–910.

Becker, A., Felgentreff, F., Schröder, H., Meier, B. & Brattström, A. 2014. The anxiolytic effects of a Valerian extract is based on valerenic acid. BMC Complem. Altern. Med. 14: 267.

Behboodi Moghadam, Z., Rezaei, E., Shirood Gholami, R., Kheirkhah, M. & Haghani, H. 2016. The effect of Valerian root extract on the severity of premenstrual syndrome symptoms. J. Tradit. Complement. Med. 6(3): 309–15.

Bent, S., Padula, A., Moore, D., Patterson, M. & Mehling, W. 2006. Valerian for sleep: a systematic review and meta-analysis. Am. J. Med. 119(12): 1005–1012.

Caudal, D., Guinobert, I., Lafoux, A., Bardot, V., Cotte, C., Ripoche, I., Chalard, P. & Huchet, C. 2017. Skeletal muscle relaxant effect of a standardized extract of Valeriana officinalis L. after acute administration in mice. J. Tradit. Complement. Med. 8(2): 335–340.

Chen, H.W., He, X.H., Yuan, R., Wei, B.J., Chen, Z., Dong; J.X. & Wang, J. 2016. Sesquiterpenes and a monoterpenoid with acetylcholinesterase (AchE) inhibitory activity from Valeriana officinalis var. latifolia in vitro and in vivo. Fitoterapia. 110: 142–149.

Chen, H.W., Chen, L., Li, B., Yin, H.L., Tian, Y., Wang, Q., Xiao, Y.H. & Dong, J.X. 2013. Three new germacrane-type sesquiterpenes with NGF-potentiating activity from Valeriana officinalis var. latiofolia. Molecules 18(11): 14138–14147.

Chen, H.W., Wei, B.J., He, X.H., Liu, Y. & Wang, J. 2015. Chemical Components and Cardiovascular Activities of Valeriana spp. Evid.-Based Complement. Altern. Med. 2015: 947619.

Farah, G.J., Ferreira, G.Z., Danieletto-Zanna, C.F., Luppi, C.R. & Jacomacci, W.P. 2019. Assessment of Valeriana officinalis L. (Valerian) for Conscious Sedation of Patients during the Extraction of Impacted Mandibular Third Molars: A Randomized, Split-Mouth, Double-Blind, Crossover Study. J. Oral Maxil. Surg. 77(9): 1796.

Felgentreff, F., Becker, A., Meier, B. & Brattström, A. 2012. Valerian extract characterized by high valerenic acid and low acetoxy valerenic acid contents demonstrates anxiolytic activity. Phytomedicine.19(13): 1216–1222.

GBD 2016 Dementia Collaborators. 2019. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18(1): 88–106.

GBD 2016 Epilepsy Collaborators. 2019. Global, regional, and national burden of epilepsy, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 18(4): 357–375.

GBD 2016 Parkinson's Disease Collaborators. 2018. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 17(11): 939–953.

GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 392(10159): 1789–1858.

Gharib, M., Samani, L.N., Panah, Z.E., Naseri, M., Bahrani, N. & Kiani, K. 2015. The effect of valeric on anxiety severity in women undergoing hysterosalpingography. Glob. J. Health Sci. 7(3): 358–363.

Gonulalan, E.M., Bayazeid, O., Yalcin, F.N. & Demirezer, L.O. 2018. The roles of valerenic acid on BDNF expression in the SH-SY5Y cell. Saudi Pharm. J. 26(7): 960–964.

Hamaidia, M., Barez, P., Carpentier, A. Lebecque, S., Miazek, K., Paul, A., Sriramareddy, S.N., Staumont, B., Danthine, B., Deleu, M., Frederich, M., De Pauw, E., Delaplace, P., Delvigne, F., Goffin, D., Ongena, M., Duysinx, B., Louis, R., Cosse, J.P. & Willems, L. 2016. From Valeriana officinalis to cancer therapy: The success of a bio-sourced compound. Biotechnol. Agron. Soc. 20(S1): 314–320

Harada, K., Kato, Y., Takahashi, J, Imamura, H., Nakamura, N., Nishina, A., Phay, N., Tadaishi, M., Shimizu, M. & Kobayashi-Hattori, K. 2020. The effect of methanolic Valeriana officinalis root extract on adipocyte differentiation and adiponectin production in 3T3-L1 adipocytes. Plant Food. Hum. Nutr. 75(1): 103–109.

Hassani, S., Alipour, A., Darvishi Khezri, H., Firouzian, A., Zeydi, A.E., Baradari, A.G., Ghafari, R., Habibi, W.A., Tahmasebi, H., Alipour, F. & Zadeh, P.E. 2015. Can Valeriana officinalis root extract prevent early postoperative cognitive dysfunction after CABG surgery? A randomized, double-blind, placebo-controlled trial. Psychopharmacol. 232(5): 843–850.

Heidarian, A., Delavioz, H. & Roozbehi, A. Evaluation of the effects of Valeriana officinalis hydroalcoholic extract on the morphology of cerebral hippocampus astrocytes in rats. 2020. Int. J. Pharmaceut. Res. 12(1): 1–5.

Iasella, C.J., Johnson, H.J. & Dunn, M.A. Adverse drug reactions: type A (intrinsic) or type B (idiosyncratic).2017. Clin. Liver Dis. 21(1): 73–87.

Jenabi, E., Shobeiri, F., Hazavehei, S.M.M. & Roshanaei, G. 2018. The effect of Valerian on the severity and frequency of hot flashes: A triple-blind randomized clinical trial. Women Health 58(3): 297–304.

Johnson, Q., Borsheski, R.R. & Reeves-Viets, J.L. 2013. Pain management mini-series. Part I. A review of management of acute pain. Mo. Med. 110(1): 74–79.

Jung, H.Y., Yoo, D.Y., Kim, W., Nam, S.M., Kim, J.W., Choi, J.H., Kwak, Y.G., Yoon, Y.S. & Hwang, I.K. 2014. Valeriana officinalis root extract suppresses physical stress by electric shock and psychological stress by nociceptive stimulation-evoked responses by decreasing the ratio of monoamine neurotransmitters to their metabolites. BMC Complem. Altern. M. 2014 Dec. 11; 14: 476.

Jung, H.Y., Yoo, D.Y., Nam, S.M., Kim, J.W., Choi, J.H., Yoo, M., Lee, S., Yoon, Y.S. & Hwang, I.K. 2015. Valerenic acid protects against physical and psychological stress by reducing the turnover of serotonin and norepinephrine in mouse hippocampus-amygdala region. J. Med. Food. 18(12): 1333–1339.

Katsarova, M., Dimitrova, S., Lukanov, L., Sadakov, S., Denev, P., Plotnikov, E., Kandilarov, I. & Kostadinova, I. 2018. Antioxidant activity and nontoxicity of extracts from Valeriana officinalis, Melissa officinalis, Crataegus monogyna, Hypericum perforatum, Serratula coronata and combinations antistress 1 and antistress 2. Bulg. Chem. 49: 93–98

Kelber, O., Nieber, K., & Kraft, K. 2014. Valerian: no evidence for clinically relevant interactions. Evid.-Based Complement Altern. Med.; 2014: 879396.

Letchamo, W., Ward, W., Heard, B. & Heard, D. Essential oil of Valeriana officinalis L. cultivars and their antimicrobial activity as influenced by harvesting time under commercial organic cultivation. J. Agric. Food. Chem. 2004; 52(12): 3915–3919.

Li, Y., Liu, Y., Xiao, B., Yang, J.I. & Huang, R.Q. 2015. Dynamic comparison of free radical scavenging abilities of Hypericum perforatum L., herba verbenae officinalis, and Valeriana officinalis L. extracts. Phcog. J. 7(3): 198–204.

Mineo, L., Concerto, C., Patel, D. Mayorga, T., Paula, M., Chusid, E., Aguglia, E. & Battaglia, F. 2017. Valeriana officinalis Root Extract Modulates Cortical Excitatory Circuits in Humans. Neuropsychobiology 75(1): 46–51.

Neamati, A., Chaman, F., Hosseini, M. & Boskabady, M.H. 2014. The effects of Valeriana officinalis L. hydroalcoholic extract on depression like behavior in ovalbumin sensitized rats. J. Pharm. Bioallied Sci. 6(2): 97–103.

Neha, K., Haider, M.R., Pathak, A. & Yar, M.S. 2019. Medicinal prospects of antioxidants: A review. Eur. J. Med. Chem. 178: 687–704.

Occhiuto, F., Pino. A., Palumbo, D.R., Samperi, S., De Pasquale, R., Sturlese, E. & Circosta, C. 2009. Relaxing effects of Valeriana officinalis extracts on isolated human non pregnant uterine muscle. J. Pharm. Pharmacol. 61(2): 251–256.

Onyszkiewicz, M., Gawrys-Kopczynska, M., Sałagaj, M., Aleksandrowicz, M., Sawicka, A., Koźniewska, E., Samborowska, E. & Ufnal, M. 2020. Valeric acid lowers arterial blood pressure in rats. Eur. J. Pharmacol. 877: 173086.

Patocka, J. & Jakl, J. 2010. Biomedically relevant chemical constituents of Valeriana officinalis. J. Appl. Biomed. 8: 11–18.

Pilerood, S.A. & Prakash, J. 2014. Evaluation of nutritional composition and antioxidant activity of Borage (Echium amoenum) and Valerian (Valeriana officinalis). J. Food Sci. Tech. Mys. 51(5): 845–854.

Pinheiro, M.L., Alcântara, C.E., de Moraes, M. & de Andrade. E.D. 2014. Valeriana officinalis L. for conscious sedation of patients submitted to impacted lower third molar surgery: A randomized, double-blind, placebo-controlled split-mouth study. J. Pharm. Bioall. Sci. 6(2): 109–114.

Quintans Júnior, L.J., Almeida, J.R.G.S., Lima, J.T., Nunes, X.P., Siqueira, J.S., Gomes de Oliveira, L.E., Almeida, R.N., de Athayde-Filho, P.F. & Barbosa-Filho, J.M. 2008. Plants with anticonvulsant properties: a review. Rev. Bras. Farmacogn. 18: 798–819.

Rodríguez-Cruz, A., Romo-Mancillas, A., Mendiola-Precoma, J., Escobar-Cabrera, J. E., García-Alcocer, G. & Berumen, L. C. 2019. Effect of valerenic acid on neuroinflammation in a MPTP-induced mouse model of Parkinson's disease. IBRO Rep. 8: 28–35.

Roh, D., Jung, J.H., Yoon, K.H., Lee, K.H., Kang, L.Y., Lee, S.K., Shin, K. & Kim, D.H. 2019. Valerian extract alters functional brain connectivity: A randomized double-blind placebo-controlled trial. Phytother. Res. 33(4): 939–948.

Samaei, A., Nobahar, M., Hydarinia-Naieni, Z., Abbas Ali Ebrahimian, A.A.,Tammadon, M.R., Ghorbani, R. & Vafaei, A.A. 2018. Effect of valerian on cognitive disorders and electroencephalography in hemodialysis patients: a randomized, cross over, double-blind clinical trial. BMC Nephrol. 19(1): 379.

Sundaresan, N., Narayanan, K. & Ilango, K. 2018. Valeriana officinalis: A review of its traditional uses, phytochemistry and pharmacology. Asian J. Pharm. Clin. Res. 11(1): 36–41.

Taherianfard, M. & Karamifard, M. 2018. Evaluation of the GABAA receptor on pain sensitivity in male rat pretreated with valeriana officinalis extract using formalin test. Physiol. Pharmacol. 22: 118–123.

Thomas, K., Canedo, J., Perry, P.J., Shadi Doroudgar, D., Lopes, I., Chuang, H.M. & Bohnert, K. 2016. Effects of valerian on subjective sedation, field sobriety testing and driving simulator performance. Accident Anal. Prev. 92: 240–244.

Torres-Hernández, B.A., Colón, L.R., Rosa-Falero, C., Aranza Torrado, A., Miscalichi, N., Ortíz, J.G., González-Sepúlveda, L., Pérez-Ríos, N., Suárez-Pérez, E., Bradsher, J.N. & Behra, M. 2016. Reversal of pentylenetetrazole-altered swimming and neural activity-regulated gene expression in zebrafish larvae by valproic acid and valerian extract. Psychopharmacology 233(13): 2533–2547.

Torres-Hernández, B.A., Del Valle-Mojica, L.M. & Ortíz, J.G. 2015. Valerenic acid and Valeriana officinalis extracts delay onset of Pentylenetetrazole (PTZ)-Induced seizures in adult Danio rerio (Zebrafish). BMC Complem. Altern. Med. 15: 228.

Wang, P.C., Ran, X.H., Luo, H.R., Ma, Q.Y., Liu, Y.Q., Zhou, J. & Zhao, Y.X. 2013. Phenolic compounds from the roots of Valeriana officinalis var. latifolia. J. Braz. Chem. Soc. 24: 1544–1548.

Wang, P.C., Ran, X.H., Chen, R., Lou, H.R., Liu, Y.Q., Zhou, J. & Zhao, Y.X. 2010. Germacrane-type sesquiterpenoids from the roots of Valeriana officinalis var. latifolia. J. Nat. Prod. 73(9): 1563–1567.

Yoo, D.Y., Jung, H.Y., Nam, S.M., Kim, J.W., Choi, J.H., Kwak, Y.G., Yoo, M., Lee, S., Yoon, Y.Y. & Hwang, I.K. 2015. Valeriana officinalis extracts ameliorate neuronal damage by suppressing lipid peroxidation in the gerbil hippocampus following transient cerebral ischemia. J. Med. Food 18(6): 642–647.

Zare, A., Khaksar, Z., Sobhani, Z. & Amini, M. 2018. Analgesic Effect of Valerian Root and Turnip Extracts. World J. Plast. Surg. 7(3): 345–350.