Updating the biological interest of *Valeriana officinalis*

Marta Sánchez†, Elena González Burgos†, Irene Iglesias†, M. Pilar Gómez-Serranillos†

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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 pharmaco-logical 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 volvalerinal 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 pharmaco-logical 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, isovaleriate), lignanoids (i.e. pinoresinol-4-O-D-glucoside, 8’-hydroxy-pinoresinol), 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.
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 *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).
Alkaloids

![Chemical structure of Actinidine and Valerianine.]

Organic acids and terpenes

![Chemical structures of Valerenic acid, Isovaleric acid, and Acetoxyvalerenic acid.]

Iridoids

![Chemical structure of Valepotriate.]

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*      | 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*      | DPPH model            | Reducing power | ↓ Reducing power (80% methanolic extract)                                      | Pilerood & Prakash, 2014 |
| Antioxidant    | *Valeriana officinalis*      | ORAC method           | Total antioxidant method | Low antioxidant activity (ORAC 820.5 µmol TE/g and HORAC 381.6 µmol GAE/g)       | Katsarova *et al.*, 2017 |
| Antioxidant    | *Valeriana officinalis*      | DPPH model            | FRAP method | Antioxidant activity (0.2579 nmol Trolox/g)                                     | Li *et al.*, 2015 |
| Neuroprotection | *Valeriana officinalis*      | SH-SY5Y human neuroblastoma cell line | 25 μg/mL | ↑ BDNF expression                                                               | Gonulalan *et al.*, 2018 |
| Neuroprotection | Sesquiterpenoids             | Acetylcholinesterase inhibitory activity | -         | Volvalerenic 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 ethanol extracts (40%) showed low antioxidant activity in ORAC and HORAC assays (Katsarova et al., 2018).

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 (IC50 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). Valerianic 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-hydroxyphenylethylenglycol 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 APPsw/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%) (Bagherti-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). Valerianic acid (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         | *Valeriana officinalis*   | Sprague Dawley     | 400 mg/kg                                                            | Pain sensitivity                                                                | Taherianfard & Karam, 2018                                                  |
| Analgesic         | *Valeriana officinalis*   | Formalin-induced   | 200 mg/kg of alcoholic extract of valerian root                      | ↓ Pain score in acute phase                                                     | Zare et al., 2018                                                           |
| Analgesic         | *Valeriana officinalis*   | Zebrafish (Danio rerio) | PTZ-Induced seizures (0.5 and 1 mg/ml) | ↑ Latency period to the onset of seizure                                        | Torres-Hernández et al., 2015                                              |
| Anticonvulsant    | *Valeriana officinalis*   | Sprague Dawley     | 1, 2, 5, 7 mg/ml                                                       | Reversion of PTZ-altered swimming behaviors                                      | Torres-Hernández et al., 2016                                              |
| Antidepressant    | *Valeriana officinalis*   | Wistar rats        | 50, 100, 200 mg/kg                                                   | ↑ Central and peripheral crossing number                                         | Neamati et al., 2014                                                       |
| Antidepressant    | *Valeriana officinalis*   | ICR mice           | 100 mg/kg/0.5 ml                                                     | ↓ Immobility times                                                             | Jung et al., 2014                                                          |
| Anxiolytic        | *Valeriana officinalis*   | Zebrafish (Danio rerio) | Ethanol valerian extract (0.5 and 1 mg/ml) | Immobility times                                                                 | Jung et al., 2015                                                          |
| Anxiolytic        | *Valeriana officinalis*   | ICR mice           | 0.2, 0.5 mg/kg/0.3 mL                                                | ↓ Physical and psychological stress                                             | Jung et al., 2015                                                          |
| Anxiolytic        | *Valeriana officinalis*   | CD-1 mice          | 0.5 mg/kg                                                            | ↓ Immobility times                                                             | Becker et al., 2014                                                        |
| Cardioprotective  | *Valeriana officinalis*   | Male gerbils       | 25 mg/kg                                                             | Cerebral ischemia protection                                                   | Yoo et al., 2015                                                           |
| Cardioprotective  | *Valeriana officinalis*   | Wistar rats        | 0.15 mmol/kg                                                        | ↓ Microglial activation                                                        | Onyszczewicz et al., 2020                                                  |
| Myorelaxant       | *Valeriana officinalis*   | Swiss mice         | 2 or 5 mg/kg                                                        | ↓ Arterial blood pressure                                                      | Caudal et al., 2018                                                        |
| Neuroprotection   | *Valeriana officinalis*   | Parkinson’s disease model: MPTP-induced mouse C57BL/6J mice and CD-1 mice | 2 mg/kg body weight, t.p | ↑ Pro-inflammatory cytokines (IL-1β, IL-6, TNF-α and IFN-γ)                     | Rodriguez-Cruz et al., 2019                                               |
| Neuroprotection   | *Valeriana officinalis*   | APPsw/PSEAE9 double-transgenic mice | 0.65, 1.30 and 2.60 mg/kg/day                                      | ↑ Learning and memory abilities                                                | Chen et al., 2016                                                          |
| Neuroprotection   | *Valeriana officinalis*   | Sprague Dawley     | 300, 400, 600 mg extract daily                                      | ↑ Number of astrocytes                                                         | Heidarian et al., 2020                                                     |

Insomnia causing absenteeism and social disability affects around one-third of adult people (Bent et al., 2006). There is 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) | ↑ Sleep, ↓ Anxiety |
| Azizi et al., 2020 Iran       | Randomized, double-blind, placebo | 88      | Tension-type headache | Intervention group: 530 mg of valerian root extraction | ↓ Disability |
| Bagheri-Nesani et al., 2015 Iran | Randomized, double-blind, placebo | 90      | Patients with acute coronary syndrome | Intervention group: acupressure with valerian oil 2.5% (2 drops, 3 nights) | ↓ Sleep quality |
| Behboodi Moghadam et al., 2016 Iran | Double-blind, placebo | 100 | Premenstrual syndrome women | Intervention group: valerian (2 capsules daily, 3 months) | ↓ 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) | ↓ Physiological parameters, No sedation and less somnolence than midazolam |
| Gharib et al., 2015 Iran      | Randomized, double-blind, placebo | 64      | Infertile women undergoing hysterosalpingography | Intervention group: valeric capsules (1500 mg) | ↓ 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) | ↓ 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) | ↓ 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%) | ↓ Intracortical facilitation |
| Pinheiro et al., 2014 Brazil  | Randomized, double-blind, placebo, crossover | 20      | Patients submitted to impacted lower third molar surgery | Intervention group: valerian capsule (100 mg) | ↓ 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) | ↑ Frontal brain region alpha 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) | ↑ Theta coherence |
| Thomas et al. 2016 USA        | Randomized, double-blind, placebo, crossover | 40      | Healthy adult | Intervention group: valerian (1600 mg) | ↑ Cognitive status |

Tables showing the results of clinical trials for Valeriana officinalis.

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; Kellber 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 focused on studying the clinical activity of these secondary metabolites as well as investigating new and different biological activities of V. officinalis.

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