Use of Plant-Derived Natural Products in Sleep Disturbances

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Abstract

Sleep disorders have a high prevalence both in the general population and especially in specific populations such older adults and oncologic patients. Impacting on quality of life, they often translate in drug prescription, with consequent increased risk of drug-drug interactions and adverse drug reactions. In the last years several products derived from plants have been developed with the aim of treating insomnia with lower risk of side effects. Despite several studies have been performed with this aim, the available evidence is inconclusive, and reviews summarizing the most recent evidences on the effectiveness of plant-derived products in treating insomnia are lacking.

This narrative review aims at summarizing the evidences of the mechanism of action, effectiveness and safety of the most commonly used plant-derived products for the treatment of sleep disorders (Valerian, Lemon balm, Passionflower, Chamomile, Hops, and Jujube).

Keywords

Insomnia · Phytotherapy · Valerian · Lemon balm · Passionflower · Chamomile · Hops · Jujube

15.1 Introduction

The term "sleep disorders" refers to a wide variety of disorders including difficulty in falling asleep, insufficient sleep duration, frequent or early awakenings, obstructive sleep apnea, restless legs syndrome, which are often generically referred by patients as "insomnia".

Estimates of prevalence of insomnia are variable due to difference in the definitions used and, in the population, studied. A study published in 2011 reported that from 20% to 41.7% of the general population is dissatisfied with the amount of sleep and reports its sleep as insufficient, with higher prevalence in specific groups, such as older people or shift workers [1].

Several comorbidities are associated with insomnia, and it has been estimated that up to 90% of people with this condition also have conditions causing hypoxemia and dyspnea, gastroesophageal reflux disease, pain conditions, and neurodegenerative [2].

The impact of insomnia on patients' quality of life translates into frequent medical prescrip-

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tions, with a consequent increase in the risk of adverse drug events, drugs/drug interactions, and addiction to some drug classes, such as benzodiazepines [3]. Given these risks, the use of traditional herbal medicine products is appealing, and in the last years several products derived from plants have been developed with the aim of treating insomnia with lower risk of side effects [4].

Despite several studies have been performed to evaluate the effectiveness of herbal products for the treatment of insomnia, the available evidence is inconclusive because of poor methodological quality of the studies included, and the 2017 European guidelines for the diagnosis and treatment of insomnia and the American Academy of Sleep Medicine did not recommend the use of valerian and other phytotherapeutics for the treatment of insomnia [5, 6]. However, several authors support the use of phytotherapy as the first line of treatment or as an adjuvant therapy in association with conventional therapies [7], and about 5% of people with insomnia report to use an alternative medicine medication to treat the disorder [8].

Given these conflicting reports and the lack of recent reviews on the effectiveness of plant-derived products in treating insomnia, in this study we summarized the recent evidences on the use of plant-derived medications for insomnia.

15.2 Methods

This is a narrative review of the current evidences on plant-derived products used for the treatment of insomnia. Studies were retrieved searching the Pubmed database animal studies, observational studies, clinical trials, and reviews published from 2009 to 2019 in English language. The MeSH keywords used were: ("Sleep Disorders" OR "Insomnia" OR "Circadian Rhythm" OR "Sleep Medicine Specialty" OR "Dyssomnias") AND "Phytotherapy". Titles and abstracts of studies matching our search strategy were screened and the full text of potentially eligible ones was evaluated. The bibliography of selected studies was also searched to retrieve additional articles. Most of the screened studies were clinical trials; some reviews were produced on selected compounds, while only few researches were on animal models. We included in the review the phytoterapics with at least two studies on humans available: valerian (*Valeriana officinalis*), chamomile (*Matricaria chamomilla/Matricaria Recutitia*), hops (*Humulus Lupulus*), jujube (*Ziziphus jujuba*), lemon balm (*Melissa officinalis*), and passionflower (*Passiflora incarnata*).

15.3 Valerian (*Valeriana officinalis*)

The medical properties of *Valeriana officinalis* are known since the fourth century BC, when Hippocrates suggested its use in digestive disorders, nausea and menstrual pain. Its properties in the treatment for sleep disorders were described for the first time by Galen in the II century AD, but it was primarily used for this indication in the sixteenth century [9], and only in 2016 this compound has been approved for use and marketing in Europe by the European Medicines Agency (EMA) [10]. In the USA, valerian is marketed as a food supplement and therefore is not regulated as a drug by the Food and Drug Administration.

The exact mechanism of action of valerian is unknown. It contains several substances (alkaloids, terpenes, organic acids, valepotriates, flavonoids) with potential physiological effect. In particular, one alkaloid (actinidine), and two terpenes (valerenic acid and velerenal aldehyde) may modulate GABA-ergic transmission. Actinidine has an allosteric interaction with the GABA receptor through an agonistic action on the benzodiazepine receptors. Valerenic acid interacts with the $GABA_A$ receptor, and its effects are absent in rats with point-mutation of the b3 subunit of the $GABA_A$ receptor, that thus seems to be the target of this substance [11]. This terpene also is a partial agonist of the 5HT receptor [12].

The pharmacological effects of valerian show high inter-individual variability, with considerable inter- and intra-subject variability. Furthermore, peak concentration, area under the curve of concentration, and clearance are inversely related to body weight [13].

In drosophila meganogaster, the addition of valerian extract to the sucrose medium of the fly

bottles induced a decrease of activity during both daytime and nighttime. In the same study, a mixture of valerian and hop (Cascade variety) upregulated the expression of mRNA for GABA receptors and, less strongly, serotonin receptors [14]. In a rodent model of pentobarbital-induced sleep, valerenic acid administration was associated with a reduction of latency sleep time and an increase in total sleep time [15]. A study on aqueous extract of Valeriana wallichii root showed similar results in freely-moving rats [16]. This study also showed a decrease in the monoamine (norepinephrine, serotonine, dopamine and hydroxy-indolacetic acid), levels in the frontal cortex.

With respect to safety, Xu et al. showed that doses up 1200 mg/kg/day did not cause harmful effects in mice and found a DL50 of 2000 mg/kg/day in mice [17]. Thus, recent evidence supports a positive effect of valerian on sleep in different animal models, with a favorable safety profile.

In the last decade, several reviews have been published reporting the effects of valerian in humans [7, 9, 18–22]; the most recent includes 6 randomized controlled trials published between 2009 and 2019. The effect of valerian varied according to the characteristics of the study participants: for example, in a sample of 100 postmenopausal women valerian was effective in improving both subjective and objective (Pittsburgh Sleep Quality Index) indices of sleep quality [23]. Instead, no positive effects were observed in patients with cancer [24] or restless leg syndrome [25].

Valerian has also been studied in association with other herbal remedies. In a randomized clinical trial, 91 patients with primary insomnia were randomized to a standardized mixture of valerian, passionflower, and hop or to zolpidem. Quality in sleep improved in both groups, without between-group differences, and also adverse events were similar in the two groups [26].

All the studies reported showed a good safety profile of valerian, confirming the findings of several other studies published in a time period outside the scope of this review. Furthermore, recently, Thomas et al. showed that a single daily dose of 1600 mg of valerian does not impact driving ability [27]. However, the EMA did not recommend the use of valerian in children <12 years of age and during pregnancy due to lack of clinical data, and warned about the potential to impact driving [10] (Table 15.1).

In conclusion, the studies published on the efficacy of valerian on sleep disorders in the last decade suffer from the same limitation of the rest of the literature on this topic: they are in general small, of medium/low quality, and the results are conflicting. Although part of the discrepancies may be due to differences in the population studied and in the dosage used, the evidence is still too weak to support the use of this plant in treating sleep disorders, and the American Academy of Sleep Medicine does not recommend it for sleep onset or sleep maintenance disturbances [28]. However, given its safety, a trial of valerian may be attempted in people at high risk for adverse drug reaction, such as elderly people at risk for falling.

15.4 Chamomile (*Matricaria chamomilla/Matricaria recutitia*)

Chamomile infusion is commonly used throughout the world. Several flavonoids and other phenolic compounds have been identified in various parts of the chamomile flower head, including apigenin, quercetin, patuletin, and luteolin, with relative concentrations varying within the different flower parts [29–31].

In mice, intra-peritoneal infusion of 360 mg/kg of chamomile induced a 57% reduction of motility without affecting motor coordination [32]. A purified extract containing apigenin (3 mg/kg i.p.) caused an increase of time spent in the open arms of an elevated plus-maze (a sign of reduction in anxiety) [33]. No effects of 10 mg/kg of apigenin were found on training and testing session performance of inhibitory or active avoidance and habituation to an open field, indicating no effect on memory [34]. The site of effect of apigenin is not clear. In a study on ovarictomized rats, inhaled vapours of chamomile oil reduced a stress-induced increase of ACTH and this effect was reversed with addition of a benzodiazepin receptor blocker (flumazenil) [35]. However,

Table 15.1 Mechanism of action and available evidences on the effectiveness of herbal remedies on treating insomnia

Compound	Mechanism of action	Studies on animals	Studies on human
Valerian	Possible modulation of GABAergic transmission by interaction with $GABA_A$ receptor	Effective in different animal models	RCTs available, but all with small sample size and of poor quality; results contrasting Safe
Chamomile	Possible modulation of benzodiazepine receptor	Effective	Small sample size and poor quality; improves sleep quality
Hops	Not clear Possible reduction of melatonin degradation by CYP1A2	Tested together with valerian in Drosophila Melanogaster with effects on locomotor activity	Few studies Small sample size and poor quality Inconclusive results
Jujube	Possible modulation of expression of $GABA_A$ gene	Increases the expression of GABA receptor subunits a1, a 5, b2 in mice	Few studies Small sample size and poor quality Seems to improve insomnia
Lemon balm	Not known	Not available	Only 2 studies Small sample size and poor quality Seems to improve insomnia
Passionflower	Inhibits binding of GABA to $GABA_A$ and $GABA_B$ and inhibits GABA uptake	Not available	Only 2 clinical trials, one of which in combination with other herbal remedies Positive results

apigenin may interact with benzodiazepines receptor differently from benzodiazepines, as suggested by the above-reported study showing no effect on memory and in which the authors also found that, in contrast with diazepam, apigenin had no analgesic effects [34].

In a study on 60 nursing residents randomized to receive 200 mg of chamomile in capsules or a matching placebo, the active treatment group showed better scores at the PSQI compared to the placebo group at the end of a 4-weeks treatment. The difference was still observable at 6 weeks (2 weeks after the end of the treatment) [36]. Comparable results were reported in a similar population by a different research group [37].

The effect of chamomile was also studied in women in the post-partum period. Chang eta al. sequentially allocated 80 women after 6-weeks from delivery into an intervention group which drank a cup of chamomile (teabags with 2 g of dried flower infused in 300 ml of water for 10–15 min) for 14 days or a control group. The 14-item post-partum sleep quality score was used to grade the subjective quality of sleep. Women in the intervention group showed an improvement of physical symptoms associated with sleep disturbances at 2 weeks, with no differences in the other subscales of the PSQS. No differences were observed between the two groups after 4 weeks [38].

In a sample of community-dwelling persons aged 18–65 years with primary insomnia for at least 6 weeks, the effects of 540 mg of chamomile extract were tested in a randomized, placebo-controlled clinical trial. The authors reported only a modest effect on sleep latency and awakenings [39].

These studies, along with other two (one on patients receiving hemodialysis and one in postmanopausal women) were included in a meta-analysis by Hieu et coll., that found an overall beneficial effect of chamomile on sleep quality, but also acknowledged the poor quality of the studies [40] (Table 15.1).

15.5 Hops (*Humulus lupulus*)

Hops has been used in traditional western medicine for the treatment of sleep disturbances due its reported calming and sleep-promoting properties. It has been suggested that it exerts its action by decreasing melatonin degradation by CYP1A2 [41].

As reported elsewhere in this paper, a mixture of valerian and hop of the Cascade variety upregulated the expression of mRNA for GABA receptors and, less strongly, serotonin receptors in drosophila melanogaster, with a reduction of locomotor activity [14]; furthermore a mixture of hops, valerian, and passionflower did not show differences with zolpidem in improving quality of sleep in humans [26].

In patients with primary insomnia, hops in conjunction with polyunsaturated fatty acids was compared to olive oil to evaluate its effects on perceived sleep quality, sleep efficiency measured using actigraphy, and melatonin excretion. The authors found a marked improvement of all outcomes over the study period, but without any difference between the two groups [41].

A larger study on 171 volunteers with mild insomnia investigated the effects of a mixture of hops, casein extract hydrolysate, and *Zizyphus jujube* vs. placebo showed no differences between groups with respect to the primary endpoint (changes in the PSQI). Similarly, no differences were found for secondary endpoints: daytime functioning, physical fatigue, mood and anxiety, cognitive performance, and stress reactivity [14] (Table 15.1).

15.6 Jujube (*Ziziphus jujuba*)

Ziziphus jujuba has been used in Chinese medicine as a sedative, relaxing, and hypnotic agent. Jujube contains several substances that may contribute to these effects, including saponins, alkaloids, and flavonoids. The major active components seem to be the saponin jujuboside A (JuA) [42–44]. In mice, JuA inhibits the locomotory activities [45], and at high doses also inhibits the penicillin-induced hyperactivity of CA1 area in the hyppocampus [42]. It has been hypothesized that JuA exerts its action via the GABAergic system [46]. In vitro, JuA can induce influence the expression of $GABA_A$ □1, □5, and □2 subunit genes; thus, JuA seems to have a mechanism of action different from that of benzodiazepines [47].

A randomized clinical trial comparing a blend of herbs used in Chinese traditional medicine (Suan Zao Ren Tang – SZR – and Zhi Zi Chi Tang – ZZC), that is made by about 20% of jujube, with 0.5 mg of lorazepam enrolled 120 patients with primary insomnia. After 4 weeks of treatment, people taking SZR/ZZC showed a greater reduction in the PSQI score compared to the lorazepam group, the difference was mainly due to an effect on the sleep efficiency subscale [48].

A systematic review also including clinical trials published in Chinese literature underscored the poor methodological quality and the small sample size of the included studies and concluded that there is insufficient evidence to support efficacy of jujube [49] (Table 15.1).

15.7 Lemon Balm (*Melissa officinalis*)

Melissa officinalis has been used over the centuries for treating digestive disorders, infections, and anxiety, and recently it has been shown to have antioxidant properties [50]. Its leaf contains flavonoids (quercitrin, rhamnocitrin, luteolin), polyphenolic compounds (rosmarinic acid, caffeic acid, and protocatechuic acid), monoterpenoid aldehyde, monoterpene glycosides, triterpenes (ursolic and oleanolic acids), sesquiterpenes, tannins, and essential oils (citral), that may contribute to its effects on treating insomnia; however, the exact substances responsible for clinical effects are not known, and no pharmacokinetic nor pharmacodynamic data are available.

Our search strategy did not identify any study on the effect of lemon balm in animals. In humans, this plant (3 g/d) was able to improve sleep quality evaluated using the depression, anxiety and stress scale (DASS-21) test and

Pittsburgh sleep quality index in patients with stable coronary artery disease [51]. In a small pilot study, a group of people with mild-to-moderate anxiety disorders treated with melissa reduced clinician-rated sleep disturbances by 42% [52].

No other studies are available, and therefore no conclusion is possible on the effectiveness of this plant on sleep disturbances (Table 15.1).

15.8 Passionflower (*Passiflora incarnata*)

Passiflora incarnata is credited to have sedative properties and to act as anxiolytic; it is used to treat insomnia and also has spasmolytic effects. *Passiflora* acts by modulating the GABA transmission system, but at variance with valerian, it inhibits the binding of GABA to both $GABA_A$ and $GABA_B$ receptors, and by inhibiting the uptake of GABA [53].

No studies in animal models have been identified in the last decade and only two clinical trial were identified. In the first study, 41 young adults with sleep disturbances were administer passionflower infusion or placebo, with an improvement of sleep quality in the passionflower group [54]. The second study, above mentioned in the "Valerian" section, tested the association of passionflower, valerian and hop in comparison with zolpidem, and showed similar effects in the two treatment arms [26] (Table 15.1).

15.9 Conclusions

Despite the large number of studies published in the latest years, the available evidence on the effectiveness of plant-derived products for the treatment of insomnia remains inconclusive, primarily because of the poor quality and of the small sample size of most of the studies available on this topic. However, globally, these compounds seem to have a very low risk of poor side effects and to be well-tolerated in humans.

Large randomized clinical trials are needed to improve the quality of the available evidences.

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