Medicinal Plants for Insomnia Related to Anxiety: An Updated Review#

Authors
Silvia Borrás[1,2], Isabel Martínez-Solís[2], José Luis Ríos[1]

Affiliations
1 Departament de Farmacologia, Facultat de Farmàcia, Universitat de València, Spain
2 Departamento de Farmacia, Facultad de Ciencias de la Salud, Universidad CEU Cardenal Herrera, Spain

Key words
medicinal plants, essential oils, sleep disorders, insomnia, anxiety, clinical trials

received January 7, 2021
accepted after revision May 9, 2021
published online June 11, 2021

Bibliography
Planta Med 2021; 87: 738–753
DOI 10.1055/a-1510-9826
ISSN 0032-0943

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence
Prof. José Luis Ríos
Departament de Farmacologia, Facultat de Farmàcia, Universitat de València
Av. Vicent Andrés Estellés s/n., 46100 Burjassot, Valencia, Spain
Phone: + 34 963 54 49 73, Fax: + 34 963 54 49 43
jose.l.rios@uv.es

Supplementary material is available under https://doi.org/10.1055/a-1510-9826

ABSTRACT

Sleep disorders are common among the general population and can generate health problems such as insomnia and anxiety. In addition to standard drugs and psychological interventions, there are different complementary plant-based therapies used to treat insomnia and anxiety. This review aimed to find and examine the most recent research on the use of herbal medicines for treating anxiety and insomnia as compiled from clinical trials, as well as to assess the safety and efficacy of these medicines and to elucidate their possible mechanisms of action. The process entailed a search of PubMed, Scopus, and the Cochrane Library databases from 2010 to 2020. The search terms included "sleep disorder", "insomnia", "sedative", "hypnotic", "anxiety", "anxiolytic", and "clinical trial", combined with the search terms "herbs" and "medicinal plants", in addition to individual herbal medicines by both their common and scientific names. This updated review, which focuses mainly on clinical trials, includes research on 23 medicinal plants and their combinations. Essential oils and their associations have also been reviewed. The efficacy of medicinal plants depends on treatment duration, types of study subjects, administration route, and treatment method. More clinical trials with an adequate, standardized design are necessary, as are more preclinical studies to continue studying the mechanisms of action. As a result of our work, we can conclude that the 3 plants with the most potential are valerian, passionflower, and ashwagandha, with the combination of valerian with hops and passionflower giving the best results in the clinical tests.

Introduction

Sleeping is necessary for life, like eating or breathing, and can be described as a reversible state that is easily affected both by the physical environment (even though it does not interact with it) and by age [1]. Different mediators are implicated in the physiology of sleep. Of these, NA, histamine, DA, glutamate, and GABA play a relevant role in the process, but other neurotransmitters are also implicated, such as orexins A and B, adenosine, glycine, ACh, serotonin (5-HT), and melatonin [1–6]. NA is synthesized in different regions of the brain, one of which is the *locus coeruleus*, where it is produced during wakefulness as well as during the sleep cycle; interestingly NA decreases partially in NREM sleep and is absent in REM sleep. In contrast, histamine, which is synthesized in the posterior area of the hypothalamus, specifically in the tuberomammillary nucleus, plays an important role in wakefulness and decreases during NREM sleep [2]. Glutamate, the most important stimulant in the CNS, is the third most relevant stimu-

Dedicated to Professor Arnold Vlietinck on the occasion of his 80th birthday.

ABBREVIATIONS

5-HT	5-hydroxytriptamine, serotonin
ACh	acetylcholine
AChE	acetylcholinesterase
BDNI	brain-derived neurotrophic factor
CNS	central nervous system
DA	dopamine
EPM	elevated plus maze
GABA	gamma-aminobutyric acid
GAD	generalized anxiety disorder
i. p.	intraperitoneally
i. v.	intravenous
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
NA	noradrenaline
NREM	nonrapid eye movement sleep
p. o.	per os, orally
PSQI	Pittsburgh Sleep Quality Index
REM	rapid eye movement sleep

lant neurotransmitter implicated in wakefulness; its activity occurs after stimulation of the ionotropic and metabotropic receptors [3]. The orexins A and B are related to the maintenance of wakefulness; they are synthesized in the hypothalamus and also trigger other systems, such as the noradrenergic, dopaminergic, and histaminergic pathways [4].

Inhibitors of the neurotransmitter system include GABA, adenosine, and glycine. Of these, GABA is the most important because it exerts inhibitory control over both the monoaminergic systems and the orexin system during sleep [5]. The GABA system is implicated in a relevant series of neurophysiological events, including anxiety and sleep, with impairments in GABA modulations producing different neurological and psychological disorders, including insomnia and anxiety [6, 7]. In the case of adenosine, it induces NREM sleep when present in the preoptic area and hypothalamus, whereas glycine favors atonic over REM sleep. ACh plays an important role during REM sleep because anticholinergic activity increases in this phase. In contrast, 5-HT inhibits REM sleep; thus, when the brain stem nucleus is activated, REM sleep decreases [7]. The last neurotransmitter implicated is melatonin, which is released in the absence of light and is essential for sleep regulation and circadian rhythm [2].

Sleep Disorders and Insomnia

Sleep disorders are common in the population and can generate problems with both sleep quality and overall health [8]. The ICSD-3 classifies these problems into 7 categories: insomnia, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement, parasomnias, and other sleep disorders. One of the most common disorders is insomnia, which is defined as "difficulty in falling asleep or maintaining the sleep state during the night" and affects a significant percentage of the general population [9]. The condition is considered chronic when insomnia occurs at least 3 times per week for at least 3 mo. This type of chronic insomnia is estimated to affect 5–10% of the population and is associated with numerous adverse effects on function, health, and quality of life. On the other hand, short-term insomnia manifests itself for less than 3 mo and affects a greater percentage of people–approximately 30% to 50% of the general population [10].

Relationship between Insomnia and Anxiety

Sleep disturbances, especially insomnia, are quite common in people suffering from anxiety, especially GAD, which is a persistent state of anxiety lasting for at least 6 mo and is often a consequence of different psychiatric disorders (e.g., depression or posttraumatic stress disorder). Patients with GAD commonly present with nonspecific somatic symptoms such as insomnia [11]. Based on the available scientific and medical evidence, the sleep disorders linked to mild-moderate GAD are maintenance sleep insomnia and, to a lesser degree, early sleep insomnia [12, 13]. GAD has a prevalence of 4–7% in the general population and is characterized by excessive worry and other physiological symptoms ranging from muscle tension to restlessness and insomnia [14]. Schanzer et al. described GAD as a disabling psychiatric condition encompassing several concurrent disorders, including social phobia, other specific phobias, panic disorder, and major depressive disorder. The pathophysiology of GAD is significantly affected by low levels of GABA and excitatory glutamate neurotransmission. $GABA_A$ receptors are especially concentrated in the medial prefrontal cortex, the amygdala, and the hippocampus, all of which are involved in anxiety and fear responses [15]. Other authors have suggested that there is a bidirectional relationship between anxiety/depression and insomnia, with anxiety and depression being related to future insomnia and insomnia being related to future high anxiety and future high depression [11, 16]. In a recent study by Bragantini et al., difficulties initiating sleep were found to be related to increased anxiety levels [17].

Pharmacological Treatment of Insomnia

Treatment of chronic insomnia often involves prescription drugs such as benzodiazepines and hypnotics, but these have many adverse side effects such as dependency, headaches, nightmares, daytime fatigue, nausea, confusion, and a loss of balance resulting in falls [18]. Other pharmacological treatments such as antipsychotics and antidepressants likewise have significant adverse effects. Even so, they are commonly prescribed "off-label" for chronic insomnia, particularly in later life [19]. In addition, various nonpharmacological approaches are common, including cognitive-behavioral therapy. Having so many options allow people seeking treatment for insomnia to combine pharmacological and nonpharmacological therapies to achieve better sleep [10]. Treatment for GAD is similar; patients can use drugs such as benzodiazepines, antidepressants, and pregabalin (an anticonvulsant), but there are also effective psychological therapies such as behavioral therapy, relaxation response training, mindfulness meditation

training, and cognitive behavioral therapy, which is the most studied and most commonly used [14].

Medicinal Plants in the Treatment of Insomnia

Although pharmacotherapies and psychological interventions are the main treatments for insomnia and sleep disorders, compounds employed in complementary, alternative, and folk medicine have also been used to treat these disorders, albeit mostly by herbalists and indigenous communities. Here it is important to distinguish between the different types of assessments used when discussing these compounds. Thus, for example, whereas traditional knowledge about the historical use of medicinal plants provides valuable insight into their effects, preclinical studies focus on the *in vitro* and *in vivo* (animals) effects to understand and modify the potential applications of these compounds for use in humans. In the case of clinical trials with medicinal plants and their extracts, such studies, along with reviews like this one, provide evidence about how these plants may be used as supplements in humans to induce and maintain sleep during the night [20, 21]. The results obtained to date indicate that the active principles of sedative medicinal plants generally have effects on the GABA system, but other mechanisms are also implicated, including the dopaminergic pathway [6, 22].

This review aimed to find and examine the most recent research on herbal medicines studied for their effects on anxiety and insomnia in human clinical trials, as well as to evaluate their safety and efficacy in treating these pathologies. The methodology involved a language-restricted (English) search of PubMed, Scopus, and the Cochrane Library databases from 2010 to 2020, but certain highlighted papers were also included, mainly preclinical studies. The review centers on clinical data for medicinal plants studied specifically for insomnia and anxiety. The search terms included “insomnia”, “sleep disorders”, “sleep”, “sedative”, “hypnotic”, “anxiety”, “anxiolytic”, and “clinical trial” combined with the search terms “herbs”, “plants”, and “medicinal plants”, in addition to both the common and scientific names of individual herbal medicines. Several preclinical studies were also included to clarify the mechanisms of action of some relevant species. To avoid repetition, the official botanical names [23] of all the plants that appear in this review, as well as the doses and types of tests used, have been included as tables. Thus, ▶ **Table 1** compiles all the protocols and tests used in the clinical trials cited in the text while **Table 1S** (Supporting Information) compiles all the protocols and tests used in the clinical trials cited in **Tables 2S** to **6S** (Supporting Information). ▶ **Table 2** summarizes the species cited in this review, including the binomial botanical name, family, and common names, whereas **Table 2S** (Supporting Information) compiles the principal studies of sedative and anxiolytic-like plants in animals. **Table 3S** (Supporting Information) lists the principal clinical trials cited in the text, including all the experimental data. **Table 4S** (Supporting Information) shows the trials in which a mixture of plants was used and **Table 5S** (Supporting Information) summarizes the trials with only essential oils. Finally, **Table 6S** (Supporting Information) compiles the studies that included mixtures of essential oils.

▶ **Table 1** Rating scales and tests used for clinical studies and cited in this review.

BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
Bf-S	*Befindlichkeitsskala* (sensitivity scale)
DISS	Defined Intensity Stressor Simulation
DSM	Diagnostic and Statistical Manual of Mental Disorders
HAM-A	Hamilton Anxiety Rating Scale
ICSD	International Classification of Sleep Disorders
ISI	Insomnia Severity Index
LSEQ	Leeds Sleep Evaluation Questionnaire
MENQOL	Menopause-Specific Quality of Life Questionnaire
PSQI	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
SMHSQ	St. Mary’s Hospital Sleep Questionnaire
STAI	Spielberger State-Trait Anxiety Inventory
VAS	Visual Analogue Scale

Relevant Species Used to Treat Insomnia

A limited number of species were tested for their sedative and anxiolytic effects in animals. While the results provide some insight into the plants’ active compounds and their potential mechanisms of action, they are inconclusive because some of the tests were carried out with isolated compounds and others with various extracts. Of these, valerian, passionflower, kava, goldshower, ashwagandha, and lemon balm gave the best results, as compiled in **Table 2S** (Supporting Information). In the following paragraphs, medicinal plants are classified according to the relevance of the preclinical and clinical studies performed with them; we then discuss the species cited for their clinical studies only.

Valeriana officinalis

Valerian is probably the species that has been studied the most for its effects on different types of nervous alterations, especially insomnia and anxiety [24]. Previous *in vivo* studies have established the plant’s anxiolytic and antidepressant activities in both mice and rats but not its sedative or myorelaxant properties [25]. Researchers have also elucidated specific pharmacological activities for different compounds from the plant, including the synergistic interactions of different valepotriates [26], along with the allosteric modulation of $GABA_A$ receptors (but not of its analogs and derivatives) by valerenic acid [27] (▶ **Fig. 1**). This latter compound is also responsible for the increase observed in BDNF levels *in vitro* [28]. These results indicate that valerenic acid could be considered the principal active compound of valerian.

Different clinical studies have demonstrated the positive effects of valerian on both the sleep structure and sleep perception of insomnia patients, making this a compound of interest for treating patients with mild psychophysiological insomnia. Indeed,

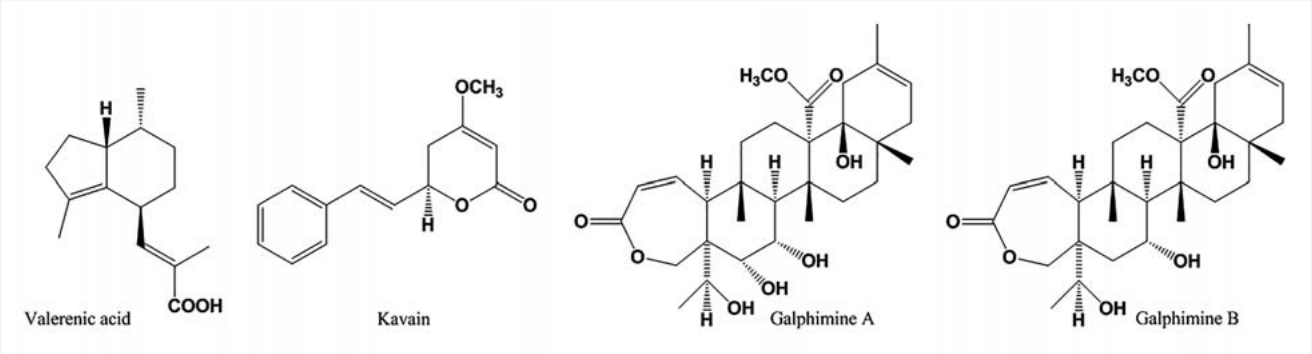
▶ **Table 2** Species cited in the present review: botanical names, family [23], and common names.

Botanical name	Family	Common name
Aloysia polystachya (Griseb.) Moldenke	Verbenaceae	"Burrito", "ka á jaguá"
Caralluma adscendens var. *fimbriata* (Wall.) Gravely & Mayur.	Apocynaceae	"Maakada singi", "Mangana kodu"
Centella asiatica (L.) Urb.	Apiaceae	Gotu cola
Citrus × *aurantium* L.	Rutaceae	Bitter orange, Neroli oil
Citrus limon (L.) Osbeck	Rutaceae	Lemon
Citrus limon (L.) Osbeck (syn: *Citrus* × *bergamia* Risso & Poit.)	Rutaceae	Bergamot
Citrus sinensis (L.) Osbeck	Rutaceae	Sweet orange
Crataegus rhipidophylla Gand. (syn: C. *oxyacantha* L.)	Rosaceae	Hawthorn
Crocus sativus L.	Iridaceae	Saffron
Eschscholzia californica Cham.	Papaveraceae	California poppy
Eucalyptus globulus Labill.	Myrtaceae	Eucalyptus
Foeniculum vulgare Mill.	Apiaceae	Fennel
Galphimia glauca Cav.	Malpighiaceae	Goldshower, "calderona amarilla"
Glycine max (L.) Merr.	Leguminosae	Soya
Humulus lupulus L.	Cannabaceae	Hops
Lactuca sativa L.	Compositae	Lettuce
Lavandula angustifolia Mill.	Lamiaceae	Lavender
Lavandula dentata L.	Lamiaceae	French lavender
Lavandula × *heterophylla* Viv. (syn: *Lavandula* × *hybrida* Balb. ex Ging.)	Lamiaceae	Lavender (hybrida)
Lavandula × *intermedia* Emeric ex Loisel	Lamiaceae	Lavandin super
Lippia alba (Mill.) N. E.Br. ex Britton & P.Wilson	Verbenaceae	Bushy matgrass
Matricaria chamomilla L.	Compositae	Chamomile
Melaleuca alternifolia (Maiden & Betche) Cheel	Myrtaceae	Tea tree
Melissa officinalis L.	Lamiaceae	Lemon balm
Mentha × *piperita* L.	Lamiaceae	Peppermint
Nepeta menthoides Boiss. & Buhse	Lamiaceae	"Ostokhodus"
Passiflora edulis Sims (syn: *Passiflora incarnata* L.)	Passifloraceae	Passionflower
Petasites hybridus (L.) G.Gaertn., B.Mey., & Scherb.	Compositae	Butterbur
Piper methysticum G.Forst.	Piperaceae	Kava
Rosmarinus officinalis L.	Lamiaceae	Rosemary
Scutellaria baicalensis Georgi	Lamiaceae	Baikal skull
Scutellaria lateriflora L.	Lamiaceae	American skullcap
Sedum roseum (L.) Scop. (Syn: *Rhodiola rosea* L.)	Crassulaceae	Golden root
Valeriana officinalis L.	Caprifoliaceae	Valerian
Viola odorata L.	Violaceae	Wood violet or sweet violet
Withania somnifera (L.) Dunal	Solanaceae	Ashwagandha
Ziziphus jujuba var. *spinosa* (Bunge) Hu ex H. F.Chow	Rhamnaceae	Sour date

continued

▶ **Table 2** *Continued*

Botanical name	Family	Common name
Species not declared: possible species used are listed		
Botanical name of species was not cited	Geraniaceae	Geranium
Cananga odorata (Lam.) Hook.f. & Thomson or *Cananga odorata* var. *fruticosa* (Craib) J.Sinclair	Annonaceae	Ylang ylang
Cinnamomum verum J. Presl	Lauraceae	Cinnamon
Citrus paradisi Macfad.	Rutaceae	Grapefruit
Pelargonium hybrids	Geraniaceae	Rose-scented geranium



▶ **Fig. 1** Chemical structure of active component of valerian (valerenic acid), kava (kavain), and goldshower (galphimine A and galphimine B).

Donath et al. [29] analyzed its effects on this disorder using both objective and subjective sleep parameters and found that only patients who had received multiple doses showed a significant increase in sleep. In another clinical trial with patients with non-organic insomnia, Ziegler et al. demonstrated a similar effect when patients received valerian or oxazepam [30]. Other studies did not obtain positive results with similar doses, but these were conducted on a reduced number of patients [31, 32]. In a controlled trial with menopausal women, Taavoni et al. found that valerian had a positive effect on sleep quality in comparison to a placebo [33], but Barton et al. observed no significant improvement in sleep [34]. In patients with obsessive-compulsive disorders, valerian significantly ameliorated anxiety and various other psychiatric symptoms including insomnia, but the effects were not significantly greater than those of the placebo [35]. Another clinical trial evaluated the activity of valerian in patients of both genders, with the results unequivocally demonstrating the remarkable effects of valerian in providing patients with the necessary comfort and relaxation without sedation and with less somnolence than midazolam, which was used as a reference drug [36]. Taking the results of all these clinical trials together, it seems clear that valerian has an anxiolytic effect and, as a consequence, improves both the quality and time of sleep, although more studies are needed before this plant can be recommended in a clinical setting.

Passiflora edulis

The aerial parts of passionflower are widely used to treat sleep disorders and anxiety [37]. Preclinical studies confirmed the anxiolytic and sedative properties in both mice [38, 39] and rats [40]. In the first case, in which the EPM test was used, researchers proposed an anxiolytic-like effect through a $GABA_A$/benzodiazepine receptor antagonist rather than a specific 5-HT_{1A}-antagonist, concluding that passionflower activity in mice may be due to a GABAergic mechanism rather than a serotonergic effect [39]. The same test in rats demonstrated a significant increase in slow-wave sleep and a reduction of REM sleep, along with a decrease in the total time spent in wakefulness [40].

Different clinical trials have confirmed the anxiolytic and sedative effects of passionflower. For example, Akhondzadeh et al. evaluated the efficacy of passionflower in the treatment of GAD, demonstrating that passionflower was indeed an effective treatment therapy [41]. In another study, the results were not significant for anxiety, probably because the dosage was inferior to the adequate dose, but they were positive for sleep quality [42]. In contrast, another trial with pre-operatory patients showed that subjects who took passionflower had a reduction in anxiety levels but experienced no sedation effects [43]. In the case of patients undergoing dental extraction, passionflower had a similar effect to midazolam as an anxiolytic [44]. In the specific case of sleep disorders, Lee et al. demonstrated the positive effects of passion-

flower on objective sleep parameters in adults with insomnia, with improvements in both sleep efficiency and waking after sleep onset [45]. Although the dosages varied in these studies, making comparisons difficult, it seems that passionflower could be useful for treating both anxiety and sleep disorders.

Piper methysticum

Kava is used for treating anxiety, stress, and insomnia and in elevated doses also has anesthetic and hypnotic properties [46,47]. The preclinical assays reviewed here were carried out principally with kavain (▶ **Fig. 1**), which, when tested for its effects on the GABAergic system, was found to improve $GABA_A$ activity. Moreover, the combination of kavain and diazepam produced an even greater enhancement of GABA activity compared to their actions alone [48]. Shinomiya et al. demonstrated that kava improves delta activity during sleep at stages 2–3 and 3–4 [49], while Tsutsui et al. confirmed the hypnotic effect of kavain, finding that, compared to rilmazafone and diphenhydramine, it enhanced sleep quality in sleep-disturbed rats during the sleep-wake cycle. The combination of kavain and rilmazafone reduced sleep latency and awake time and increased NREM sleep time; in contrast, when combined with diphenhydramine, it affected sleep latency but not awake time or NREM sleep [50].

Clinical studies have further demonstrated kava's potential for treating anxiety and sleep disorders in humans. Lehrl, for example, studied the effect of kava on sleep disorders in patients with anxiety, measuring the results with various scales such as the HAM-A, the Bf-S (a self-rated scale of well-being), and the CGI scale. In the first 2, the authors observed a reduction in psychic anxiety and an increase in general well-being [51]. Sarris et al. demonstrated a decrease in the anxiety levels of patients with GAD, above all in participants with high-level anxiety according to the DSM. The results, as measured with HAM-A, showed that the effect in the kava group was associated with GABA transporter polymorphisms [52]. Kutcha et al. likewise demonstrated the efficacy of kava in the treatment of anxiety as measured with HAM-A on volunteers with anxiety disorders, observing a significant enhancement in the high-dose group compared with the low-dose group [53]. Unfortunately, Sarris et al. were unable to confirm this effect in a clinical trial with a longer duration and a larger sample size [54]. Taken together, however, these studies demonstrate that kava generally has anxiolytic and hypnotic effects and can improve sleep quality, especially when the problem is due to anxiety issues.

Galphimia glauca

Goldshower or "calderona amarilla" is a tropical plant of Central America used for treating anxiety and sleep disorders [55]. Many preclinical studies have been performed with enriched extract and with the plant's nor-*seco*-triterpenes, some of which (galphimines A, B [▶ **Fig. 1**], and E) have been described as inhibitors of dopaminergic activity. However, these compounds may also interact with the serotonergic system, which could partly explain their previously described anxiolytic effects [55]. In this context, Herrera-Ruiz et al. tested the anxiolytic properties of goldshower using the EPM test with different sets of mice. They found that the galphimine-rich fraction, galphimine A, and galphimine B showed a higher anxiolytic effect than the placebo, but this effect was modest compared to the standard drug [56]. These same authors [57] studied the effects of a standardized extract using the EPM, the light-dark test, and the forced swimming test in mice and observed an anxiolytic-like effect in the EPM and the light-dark tests; however, no effect was observed in the forced swimming test. This could be due to an interaction of galphimine B with the serotonergic system in the dorsal hippocampus, which modulates the induced response of $5\text{-}HT_{1A}$ receptors in an allosteric manner without affecting the GABAergic system [58]. Avilés-Montes et al. performed another preclinical trial using galphimine A on mice and observed an anxiolytic-like effect with no accompanying sedative effect [59]. The mechanism was elucidated by Santillán-Urquiza et al., who noted that galphimines act in the dopaminergic system but not in the GABAergic system [60]. These same authors also established that the administration route should be oral, although Garige et al. had previously used i. p. administration with similar results [61]. Taken together, these results indicate that *Galphimia glauca* has anxiolytic properties due to its nor-*seco*-triterpenes and galphimines A and B via the serotonergic and dopaminergic systems but not by the GABAergic one.

In addition to the preclinical assays, some relevant trials have also been performed in humans. Especially noteworthy are those carried out by Herrera-Arellano et al., who performed 2 clinical trials comparing goldshower's anxiolytic effects with those of lorazepam but under different conditions. The results for both treatments, as measured with the HAM-A, demonstrated that *Galphimia glauca* exerted anxiolytic effects in patients with GAD, even at different doses and with different treatment times, although the age range was similar [62,63]. In another study, Romero-Cerecero et al. demonstrated the same anxiolytic effect in a study with patients who received either extract or sertraline. Using various scales to measure anxiety, they established that there were no significant differences between groups as measured by the BSPS, which indicates that anxiety decreased in both treated groups [64]. In a second study, these same authors developed a trial comparing the efficacy of a standardized extract of *Galphimia glauca* with that of alprazolam. The results were measured with the Health Scale. The authors observed that the extract of *Galphimia glauca* reduced anxiety levels but did not produce sleepiness during the day, thereby confirming the dopaminergic hypothesis as the mechanism of action for galphimine B [65]. In conclusion, *Galphimia glauca* is an effective anxiolytic that reduces anxiety through a dopaminergic mechanism without causing drowsiness.

Withania somnifera

Ashwagandha is a classic herb used in Ayurvedic medicine [66]. It was evaluated in a previous study by Andrade et al., who investigated its efficacy against anxiety and observed a positive effect vs. placebo [67]. In a subsequent study, Chandrasekhar et al. designed a trial to see if ashwagandha could reduce stress and anxiety and observed similar beneficial results, including improvements in the quality of life, but with no reductions in cortisol levels [68]. Lopresti et al. performed a clinical trial for assessing ashwagandha's effects on stress, anxiety, and hormone production, among other outcomes, in healthy adults. The results of the

HAM-A scale showed a beneficial anxiolytic effect. Likewise, the DASS-21 measure indicated a strong positive trend, with decreases in cortisol and dehydroepiandrosterone levels but no significant increase in testosterone in men [69]. Fuladi et al. suggested that ashwagandha could be used as a complement to selective serotonin reuptake inhibitors in patients with GAD [70]. In the case of patients with schizophrenia, Gannon et al. indicated that ashwagandha could help in the treatment of depression and anxiety [71]. Salve et al. carried out a clinical trial in which patients who received treatment showed improvements in their stress levels and sleep quality as measured by the PSS and HAM-A, as well as in their cortisol levels [72]. A similar trial performed by Langade et al. confirmed that ashwagandha can be used as an anxiolytic as well as for treating insomnia and enhancing sleep quality compared to a placebo [73]. Kelgane et al. studied whether an extract of ashwagandha could be used in the elderly for general health and sleep quality, with the outcomes, as measured with different scales, demonstrating that ashwagandha supplementation could be an effective alternative to counter issues associated with aging, including sleep quality and mental alertness [74]. Deshpande et al. showed improved sleep quality in healthy patients suffering from nonrestorative sleep after treatment with a standardized extract of ashwagandha [75]. In a recent clinical study, Langade et al. verified the use of an extract of ashwagandha both as an anxiolytic and to improve symptoms of insomnia as compared to a placebo [76]. Taken together, these studies show that ashwagandha can be used as an anxiolytic, as well as for treating insomnia and enhancing sleep quality.

Melissa officinalis

Lemon balm is used in folk medicine as a sedative-hypnotic agent for treating insomnia and stress [77], with volatile compounds, triterpenes, and phenolics as the principal active constituents [78]. In one preclinical study, its anti-anxiety effects were associated with the inhibition of GABA transaminase and the consequent increase in cerebral availability of GABA, without impairment to normal activity [79]. This study was complemented with an open-label prospective study performed by the same authors. Indeed, Cases et al. [80] studied the anxiolytic effect of one standardized extract (Cyracos) in healthy volunteers and described its positive effects on symptoms of anxiety and insomnia for patients with mild-to-moderate anxiety. However, this clinical study has severe limitations due to the absence of a placebo or positive control, the low number of volunteers, and the broad age range of the subjects. In another study, Haybar et al. performed a clinical trial in patients with chronic stable angina, observing that treated patients showed significant reductions in their scores for depression, anxiety, stress, and total sleep disturbance in the DASS-21 and PSQI [81]. While more clinical studies with lemon balm are needed to establish clear conclusions about its effects, other studies have examined the potential of mixtures of lemon balm with other plants. These will be discussed below in the section on "Effects of Medicinal Plants in Combination".

Matricaria chamomilla

Chamomile has long been used around the world as a medicinal plant to treat different pathologies and their symptoms, including anxiety and insomnia [82]. In their study of this plant, Amsterdam et al. [83] demonstrated its anxiolytic effect on patients with mild to moderate GAD. Keefe et al. confirmed these anxiolytic properties in patients with moderate GAD but not in patients with severe GAD symptoms [84]. Mao et al. investigated these effects in a similar trial but over a longer period and using different indexes and scales to measure the results. They concluded that chamomile can be used for reducing anxiety in patients with moderate-to-severe GAD without modifying the rate of relapse [85]. Moreover, in an exploratory study, Keefe et al. measured cortisol levels in patients with GAD and demonstrated that an increase in morning salivary cortisol and the diurnal cortisol slope are both related to symptom improvement in chamomile treatment of GAD [86]. Concerning insomnia, chamomile can enhance sleep quality in elderly subjects as demonstrated by Adib-Hajbaghery et al. using the PSQI [87]. Likewise, after drinking a cup of chamomile tea, postnatal women with sleep disorders and symptoms of depression showed an increase in sleep quality and an improvement in their symptoms; however, these effects did not last over an extended period [88]. Chamomile can also be used to ameliorate symptoms of depression, as demonstrated by Amsterdam et al. in a clinical trial that included volunteers with comorbid anxiety and depression [89]. The results suggested that chamomile may be used as an antidepressant in anxious patients with depression to ameliorate the negative symptoms of the disease, including insomnia. In conclusion, chamomile could be a good complementary treatment for sleep disorders, including those due to comorbidities such as anxiety and depression.

Humulus lupulus

Hops, traditionally used for anxiety and mood disorders, were studied by Kyrou et al. in a clinical trial using young subjects that included 2 intervention periods separated by a wash-out period. The researchers noted improvements in the subjects' symptoms of anxiety, stress, and depression, along with the insomnia associated with them [90]. Erkkola et al. performed a clinical trial in healthy postmenopausal women, who often suffer sleep disorders. Although the results were not significant after 8 weeks, at 16 weeks, the treatment was shown to reduce all outcome measures [91]. Nonetheless, the best results were obtained in association with valerian (see the section, "Effects of Medicinal Plants in Combination").

Other species of interest

Carmona et al. performed a phase-2 clinical trial with *Aloysia polystachya* and observed a reduction in anxiety symptoms as measured by HAM-A [92]. *Centella asiatica*, another species that could be used for the treatment of GAD, was tested in patients with this disorder by Jana et al. [93], who observed improvements in levels of anxiety, stress, and depression. *Sedum roseum* was evaluated in a pilot study by Bystritsky et al., who found an anxiolytic effect in volunteers with GAD as demonstrated by reductions in their HAM-A scores; however, it must be noted that the number of participants was exceptionally low [94]. Edwards et al. studied the effects of *Sedum roseum* on students, and the results showed improvements in symptoms of stress [95]. In a similar study, Cropley et al. confirmed the effects of golden root for decreasing

stress and anxiety in subjects with mild anxiety [96]. Different preparations of *Scutellaria laterifolia* were used in a trial conducted by Wolfson et al., who observed an anxiolytic effect, but more studies are needed to confirm this property [97]. In the case of *Scutellaria baicalensis*, no clinical trials have been carried out, but flavonoids (baicalein and wogonin) have previously been cited as being responsible for its anxiolytic and sedative effects [98, 99]. *Nepeta menthoides* was studied by Firoozabadi et al. in a clinical trial with patients suffering from anxiety and symptoms of depression; the results showed a decrease in anxiety symptoms and a significantly lower rate of short-term recurrence of these symptoms after cessation of the intervention [100]. *Rosmarinus officinalis* (rosemary) was studied by Nematolahi et al. in university students to treat memory performance, anxiety, depression, and sleep quality; improvements in all areas were observed [101]. Finally, *Caralluma adscendens* var. *fimbriata* was investigated for the first time by Kell et al. to assess its efficacy in reducing anxiety and stress in patients with mild to moderate anxiety. It is noteworthy that while there were no significant changes in males, the female subjects experienced changes in their cortisol levels [102].

In conclusion, although the number of trials on these plants is quite low, several species have yielded interesting results. These data can thus be considered preliminary, with those studies having positive results pointing the way for future research.

Effects of Medicinal Plants in Combination

Some authors have found that it is possible to obtain better results with a combination of medicinal plants than with only one, an idea also held by practitioners of herbal medicine and phytotherapy (the experimental data are compiled in **Table 4S**, Supporting Information). In this context, Morin et al. performed a study comparing the effects of a mixture of valerian and hops to those of diphenhydramine in patients with mild insomnia vs. a placebo. The combination of medicinal plants improved insomnia as measured by sleep latency, sleep efficiency, and total sleep time and provided enhancements in quality of life [103]. Koetter et al. evaluated the efficacy of a dry extract combination of valerian and hops in patients with nonorganic insomnia and observed that the results were markedly better with the mixture than with valerian alone [104]. Dimpfel et al. demonstrated that a valerian-hops combination improves sleep in patients after receiving only 1 administration [105].

Another typical combination of medicinal plants is valerian and lemon balm. Kennedy et al. studied the effects of this mixture on healthy volunteers suffering from stress induced in a laboratory setting and observed improvements, notably a dose-dependent reduction in anxiety as measured by the DISS [106]. In another study, menopausal women who received essential oil of valerian and lemon balm vs. a placebo presented up to a 5-point reduction in their PSQI scores [107].

Abdellah et al. demonstrated the beneficial effect of a mixture of California poppy and valerian extracts on sleep disorders and anxiety in patients in a primary health care setting [108]. Wheatley studied the effects of kava followed by administration of valerian in patients being treated for stress-induced insomnia, noting improvements in both stress levels and insomnia [109]. Ranjbar et al. carried out a clinical trial in which subjects took lemon balm and *Nepeta menthoides*. The authors found that this combination improved the symptoms of anxiety and depression and reduced insomnia as measured with ISI, BAI, and BDI scores [110].

Maroo et al. demonstrated that administration of NSF-3 (a mixture of valerian, passionflower, and hops) in patients with primary insomnia enhanced total sleep time and latency and decreased both the number of nightly awakenings and the ISI scores [111]. Ze185 (a mixture of valerian, passionflower, lemon balm, and butterbur) reduced the self-reported anxiety response to stress in male test subjects but without affecting any physiological parameters, including salivary cortisol levels due to stress [112]. Hanus et al. combined hawthorn and California poppy to evaluate the effect in patients with mild-to-moderate anxiety disorders associated with functional disturbances. Anxiety levels decreased in both the treatment and placebo groups, but the improvement was greater in the treatment group, as indicated by the HAM-A (both total and somatic) and VAS scores [113]. Scholey et al. demonstrated that LZComplex3, which contains lactium (hydrolyzed milk protein, α-capsazepine enriched), sour date, hops, magnesium, and vitamin B_6, improved sleep quality somewhat, but there were no significant differences between the baseline and endpoint of the primary outcome in patients with insomnia as measured with the PSQI [114]. Dietary supplementation with polyunsaturated fatty acids and hops improved neither sleep quality nor the sleep-wake cycle as measured by the LSEQ in participants with moderate to severe sleep disorders [115]. Finally, in a single-center, single-arm, open-label study in which Lemoine et al. used a combination of medicinal plants (extracts of California poppy, passionflower, and lemon balm) with melatonin and vitamin B_6 in patients with mild-to-moderate insomnia, the results showed improvements in sleep quality [116]. These results justify the use of some combinations of these plants, such as mixtures of valerian and hops or of valerian and passionflower, as sedative agents.

Essential Oils

The essential oil of lavender has been widely used for treating insomnia and anxiety (see experimental data, compiled in **Table 5S**, Supporting Information). Previous reports have suggested that this is mainly due to the regulation of GABAergic neurotransmission, especially with regard to $GABA_A$ receptors, which enhance the inhibitory response of the nervous system [117, 118]. Various clinical trials have confirmed the anxiolytic properties of lavender, as well as its sedative effect. In several of these studies, researchers have opted to use a preparation made from lavender called Silexan. This was the case for Woelk et al., who compared this preparation with lorazepam and observed similar outcomes in subjects with GAD; however, this study did not confirm lavender's sedative properties [119]. Kasper et al. carried out another trial with Silexan, noting that the results demonstrated a clear reduction in the PSQI scores in the Silexan group vs. the placebo group [120]. In another clinical trial, subjects with neurasthenia, posttraumatic stress disorder, or somatization disorder were treated with Silexan, which led to improvements in anxiety levels, sleep disorders, and restlessness [121]. Kasper et al. confirmed the

anxiolytic effect of Silexan in patients with GAD and also demonstrated that Silexan can act as an antidepressant [122]. Kasper et al. performed a clinical study on the ability of Silexan to improve anxiety levels, restlessness, and disturbed sleep patterns with volunteers. They verified the anxiolytic effects as measured with HAM-A; however, no sedative effects were observed (PSQI). These results indicate that Silexan may be administered orally as a treatment for anxiety but not for sedation [123]. Inhalational administration may also be of interest. Indeed, in a study carried out by Chien et al. on midlife premenopausal and postmenopausal women with insomnia who underwent ultrasonic ionizer aromatherapy with essential lavender oil, the authors found that lavender aromatherapy decreased the heart rate while increasing high-frequency standard deviation of the normal-to-normal intervals, along with the square root of the mean-squared differences of successive normal intervals for 30 min in comparison to controls [124]. Another clinical trial was performed by Karan et al. with patients unable to undergo general anesthesia. When these subjects inhaled lavender oil before dental surgery, it reduced anxiety and even decreased the need for antipsychotics [125]. Otaghi et al. performed a similar clinical trial on patients undergoing angiography. Those who received treatment with lavender essential oil and peppermint essential oil before angiography presented no differences in sleep quality [126]. Jokar et al. carried out a clinical trial in menopausal women to assess the effects of lavender oil on menopausal symptoms, especially insomnia, and observed a reduction of symptoms [127]. Another clinical trial with type 2 diabetes patients suffering from insomnia showed that lavender aromatherapy led to an increase in the quality of life through the reduction of insomnia and an increase in mood status [128].

Aromatherapy with lavender essential oil could also be a potential treatment for regulating melatonin levels, especially in older people with various sleep disorders. Velasco-Rodríguez et al. carried out a clinical trial with geriatric patients who inhaled essential lavender oil; the results confirmed that lavender increased blood melatonin levels, thus regulating the circadian cycle in both older adult men and women, which is relevant for treating insomnia. Another possibility for improving sleep disorders and anxiety may be the application of this oil through massage [129]. Ayik et al. demonstrated this in patients undergoing colorectal surgery. Before the operation, patients received a back massage with lavender essential oil (*Lavandula* × *heterophylla*) twice daily. They noted a decrease in both sleep disorders and anxiety as compared to the control group, who received standard nursing care [130].

Neroli oil was tested in pregnant women suffering sleep disturbances; the results showed a reduction of anxiety symptoms [131]. Heydari et al. confirmed that this essential oil can also improve premenstrual syndromes, including insomnia and anxiety, among others [132]. Pimenta et al. showed that bitter orange essential oil (inhalational administration) reduced blood pressure in patients with chronic myeloid leukemia while modifying the excitation of the CNS, thereby reducing insomnia [133]. A similar study carried out by Moslemi et al. showed improvements in patients with acute coronary syndrome who were treated with essential oil [134]. Another recent trial confirmed the anxiolytic effect of bitter orange essential oil in patients undergoing coronary angiography, with a reduction of STAI scores, systolic blood pressure, diastolic blood pressure, and both respiratory and pulse rates [135]. In a clinical trial in elderly patients with heart failure, neroli oil improved sleep quality as measured with SMHSQ [136]. Moreover, aromatherapy with neroli oil can be used in type 2 diabetes patients for decreasing anxiety and fatigue. This same effect was described by Abdollahi et al. in volunteers who inhaled an extract of bitter orange (20% concentration) [137]. The essential oil of sweet orange was studied by Goes et al. in male volunteers subjected to an anxiogenic situation, obtaining positive results [138]. Mirghafourvand et al. carried out a clinical trial with postpartum women and the outcomes, as measured by PSQI, indicated that treatment with orange essential oil increased sleep quality [139].

Ylang-ylang was evaluated in a pilot study, but no differences were observed between groups for either anxiety levels or physiological parameters [140]. Wood violet essential oil was studied in patients with chronic insomnia and the outcomes, as measured by ISI, indicated a reduction in symptoms after treatment [141]. In a subsequent trial, volunteers with chronic insomnia demonstrated that this essential oil is more effective than a placebo in severe insomnia [142]. Another clinical trial in which Shirzadegan et al. studied the effects of geranium aroma on anxiety in subjects with acute myocardial infarction showed a reduction in anxiety levels; unfortunately, there are no other clinical trials on this species reported in the literature [143]. Afrasiabian et al. performed a clinical trial with lemon verbena and observed improvements in insomnia [144]. The essential oil of bushy matgrass may also be a potential treatment for decreasing anxiety. In a preclinical trial carried out by Hatano et al., the authors hypothesized that the component responsible for the plant's anxiolytic effects was carvone [145]. Soto-Vásquez et al. also investigated this plant, noting a reduction in anxiety levels when subjects inhaled the plant's essential oil [146].

Several other clinical trials have examined the potential of various combinations of different types of essential oils for improving sleep disorders and anxiety (**Table 6S**, Supporting Information). In one study, Lee et al. tested the effects of inhalation of an essential oil mixture (lemon, eucalyptus, tea tree, and peppermint) and observed that this aromatherapy reduced stress and depression while improving sleep quality but did not affect the stress index scores [147]. Stevens et al. used a specific mixture (Serenity softgel) containing lavender essential oil, L-theanine, and a blend of lemon balm, passionflower, and chamomile in a group of volunteers and observed significant differences in the treated group as measured with LSEQ [148]. Hur et al. investigated a mixture of essential oils (lavender, geranium, cinnamon, grapefruit, neroli, and ylang-ylang), administered by both inhalation and abdominal massage. The outcomes were satisfactory, with reductions in subjective stress and fatigue, and improvements in sleep quality [149]. Gürler et al. studied the same properties in menopausal women, who inhaled a combination of 2 different oils (lavender and lemon). The results were positive, with a reduction in the total median scores of the PSQI and MENQOL for the aromatherapy group [150]. A combination of lavandin super, bergamot, and ylang-ylang was tested for its effects on the sleep quality of patients in cardiac rehabilitation and found to have significant positive results in the PSQI [151]. Another study compared the effect of lavender and peppermint essential oils (by inhalation) on the

sleep quality of cancer patients; the mean PSQI scores were lower in the lavender and peppermint groups than in the controls, but no differences between the effects of the individual essential oils were observed [152]. Polonini et al. studied the intranasal effect of Pinetonina (a mixture of French lavender and fennel) on stress and chronic stress-induced sleep disorders in volunteers and observed improvements in sleep quality as measured by the PSQI [153]. Lavender and bitter orange improved the sleep quality of postmenopausal women vs. a placebo [154]. The combination of various oils from wood violet, saffron, and lettuce also led to significant reductions in the ISI and PSQI scores in a trial on patients with chronic insomnia [155].

Discussion

Insomnia and anxiety are 2 closely related diseases that affect a large portion of the population, especially in elderly people and women. According to the literature consulted, insomnia is more common in the elderly than in young adults because it is associated with other disorders they tend to suffer from, albeit not with age. Other causes include changes in circadian rhythm or certain medications [156]. Insomnia is more prevalent in women than men (1.5 times), perhaps due to different biological, psychological, and social factors. In fact, 14 to 27 % of women have sleep disorders during pregnancy while 40 to 56 % of menopausal women suffer sleep disturbances [157]. This explains the greater number of clinical trials carried out on these 2 population groups to evaluate the use of various medicinal plants for treating insomnia and anxiety.

At first glance, the results of the different clinical trials seem to disagree on the benefits of these treatments for insomnia and/or anxiety. This is due to various factors, including the use of different types of extracts, the nature of the population group studied, the size of the population sample used in the trial, and the study design. For example, in the various studies on valerian, the protocols used are quite different, and the results vary accordingly. Thus, while valerian improved sleep quality in menopausal women [33], no beneficial effects on insomnia were observed in elderly adults [31, 32]. This could be because different research groups used different specific extracts (see **Table 3S**, Supporting Information). Moreover, Taibi et al. evaluated sleep in the laboratory using self-reported data [32]. In the case of kava, it was shown to improve symptoms of anxiety but only in the elderly [53]. In population groups other than the elderly and menopausal women, similar studies have been carried out with different medicinal plants; for example, both passionflower and goldshower have been tested against these pathologies. Thus, several clinical trials have been carried out with these species to evaluate their efficacy in reducing anxiety and sleep disorders, with 3 specific studies–2 using passionflower [43, 44] and 1 using valerian [36]–assessing the use of these plants to treat anxiety before an intervention. Another widely studied species is chamomile, which can improve moderate GAD, but seems to have little effect on the severe form of the pathology [84]. Still, it showed beneficial results in treating anxiety in postnatal women. Ashwagandha is another species that could be used as an anxiolytic or to improve sleep quality [66].

Another factor affecting the results in this field of study is the complex formulations of the extracts assessed. Because several clinical trials have used a combination of different medicinal plants [104, 107], the results may have been affected by a pharmacokinetic and/or pharmacodynamic synergy, which could lead to both positive and negative interactions between the components [158, 159]. In some cases, synergistic effects can improve the solubility and bioavailability of different active ingredients in plants [160, 161]. For example, the increase in the bioavailability of curcumin in the presence of piperine is well-documented [162].

Concerning the principal mechanisms responsible for the effects of medicinal plants, various studies have implicated the GABAergic pathway as the principal system involved. Indeed, some authors have proposed valerenic acid as the active principle of valerian because it regulates the allosteric $GABA_A$ receptors. In the case of kava, it has a clear active compound, kavain, which enhances the receptor activity of the subunit composition of GABA, especially at receptors $\alpha 4\beta 2\delta$ [48].

Another group of relevant principles on sleep activity and anxiety is flavonoids, which play an important role as $GABA_A$ receptor ligands in the CNS [163]. Of these, amentoflavone (*Ginkgo biloba*), apigenin (*Matricaria chamomilla*), or baicalein (*Scutellaria baicalensis*) is most likely responsible for the sedative properties of these species [163] through a mechanism by which these flavonoids, especially apigenin, act as a noncompetitive antagonist of $GABA_A$ receptors while also enhancing the modulatory action of diazepam on the activation by GABA of $GABA_A$ receptors [164] or that of chrysin (*Passiflora edulis*) as a partial agonist at the benzodiazepine binding site [6]. Other flavonoids, such as kaempferol and quercetin, are transformed into their active metabolites, including hydroxyphenylacetic acid, by the intestinal microflora [6, 165]. The anxiolytic and sedative-like effects of flavonoids such as quercetin, rutin, and isoquercitrin reinforce these studies, but in this case, not only the GABA/benzodiazepine receptors are implicated because the $5\text{-}HT_{1A}$ serotonergic receptors are also involved in this case [166], effects ratified for other flavonoids, such as quercitrin, rutin, kaempferol and tiliroside, which can modify the serotonergic system for inducing their anxiolytic effects by acting directly on the postsynaptic $5\text{-}HT_{2A/2C}$ receptors and also on $5\text{-}HT_{1A}$ [167]. However, the anxiolytic-like effect of rutin in the basolateral amygdala involves $GABA_A$, but the effect was not associated with benzodiazepine receptors [168].

In the case of essential oils, they have also been described as regulators of GABAergic neurotransmission–acting especially on $GABA_A$ receptors–because they seem to enhance the inhibitory response of the nervous system. Still, no specific principles have been described as being responsible for these effects, although several trials have used isolated compounds from essential oils, such as linalool and its oxides [117, 118].

Another interesting aspect of medicinal plants for treating insomnia and anxiety is the potential synergy between synthetic drugs and plant extracts. Indeed, Carrasco et al. described a possible synergy between the active principles of valerian and passionflower with benzodiazepines because these species can enhance the inhibitory activity of benzodiazepines by binding to GABA receptors. Although this causes an interesting enhancement, it can also lead to severe secondary effects [169].

For this reason, Tweddell et al. [170] emphasize the importance of evaluating the efficacy of treatment with medicinal plants in patients treated with benzodiazepines beforehand to avoid adverse interactions.

While studies so far indicate that the GABAergic pathway is the main system affected by different medicinal plants [6], another group of principles has been found to act via the serotonergic and dopaminergic pathways. These include *Galphimia glauca*, which has anxiolytic properties due to galphimines A and B [60–65].

When comparing clinical trials, the study design and the characteristics and size of the population sample are all extremely relevant as they can modify and condition the results obtained, making comparisons between various studies difficult. In the trials analyzed, we observed a great variation in the number of subjects included, as well as the doses employed and the duration of the studies (see **Table 3S**, Supporting Information); also noteworthy is the age range of the subjects in different clinical trials. For example, in one study with only 16 participants, the ages ranged from 22 to 55 years old [29], whereas in another study with 202 patients, the range varied from 18 to 73 years old [30]. Other authors modified their own projects and performed assays first with 34 subjects [64] but then used a greater number of subjects (n = 167) in a second trial [65]. The duration of the studies also varied greatly, with some lasting only 2 weeks [45] whereas others lasted up to 16 weeks [54]. This variability can modify the results because treatments for insomnia and anxiety are not generally short. Likewise, various dosages and routes of administration also need to be highlighted, both in preclinical and clinical studies. For example, the possible routes of administration for preclinical studies in animals are p. o., i. p., or i. v. (see **Table 2S**, Supporting Information), while for clinical studies the administration route is generally oral (see **Table 3S**, Supporting Information).

Another highly relevant aspect of these studies is which plant part and what kind of extract were used in the trials. Indeed, some studies used essential oils to treat insomnia and anxiety, including lavender oil and neroli, along with commercial products such as Silexan (capsules with essential oil of lavender) [119–123]. This influenced the via of administration, with some oils administered by inhalation (lavender oil and neroli) [124–128, 131–136] or intranasal application (a drop of violet essential oil) [141]. Other studies combined aromatherapy with massages, using essential oils in some cases [130, 149].

Taking into account the results found in the literature, the efficacy of medicinal plants, their extracts, and the essential oils obtained from them to treat insomnia and anxiety largely depends on the duration of treatment, the patients involved (number and characteristics), the route of administration, and the treatment method. It is thus necessary to conduct more clinical studies with an adequate study design and more homogeneous trial protocols to compare the results and make a more realistic assessment. More preclinical studies are also of interest because the mechanisms of these plants are mostly unknown. This would also help clarify other relevant aspects, such as appropriate dosages, routes of administration, and safety.

Supporting Information

This section consists of 6 tables. **Table 1S** consists of rating scales and tests used for clinical studies cited in **Tables 3S** to **6S**. **Table 2S** includes the medicinal plant studied for sedative and anxiolytic-like effects in animals. **Table 3S** compiles the data from clinical trials of medicinal plant extracts, including common name, sample/extract studied, doses in mg, time of treatment, administration route, number of patients, clinical protocols, criteria of evaluation, and effects cited in the original paper. **Table 4S** is similar but compiles clinical trials with mixtures of medicinal plants. **Table 5S** summarizes the clinical trials of essential oils of medicinal plants, while **Table 6S** does the same for mixtures of essential oils.

Contributors' Statement

The 3 authors have participated in the preparation of the document jointly. Data collection: S. Borrás; design of the study: I. Martínez, J. L. Ríos; analysis, interpretation and drafting: S. Borrás, I. Martínez, J. L. Ríos; critical revision of the manuscript: I. Martínez, J. L. Ríos.

Acknowledgements

The authors would like to thank Laura Gatzkiewicz for her contribution in the process of improving the language of the text.

Conflict of Interest

The authors declare that they have no conflict of interest

References

[1] Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. J Biol Rhythms 2006; 21: 482–493

[2] Hirshkowitz M, Rose MW, Sharafkhaneh A. Neurotransmitters, Neurochemistry, and clinical Pharmacology of Sleep. In: Chokroverty S, ed. Sleep Disorders Medicine: Basic Science technical Considerations, and clinical Aspects. 3rd ed. Philadelphia: Saunders Elsevier; 2009: 67–79

[3] Ribeiro FM, Vieira LB, Pires RG, Olmo RP, Ferguson SS. Metabotropic glutamate receptors and neurodegenerative diseases. Pharmacol Res 2017; 115: 179–191

[4] Grafe LA, Bhatnagar S. Orexins and stress. Front Neuroendocrinol 2018; 51: 132–145

[5] Szymusiak R, McGinty D. Hypothalamic regulation of sleep and arousal. Ann N Y Acad Sci 2008; 1129: 275–286

[6] Savage K, Firth J, Stough C, Sarris J. GABA-modulating phytomedicines for anxiety: a systematic review of preclinical and clinical evidence. Phytother Res 2018; 32: 3–18

[7] McCarley RW. Neurobiology of REM and NREM sleep. Sleep Med 2007; 8: 302–330

[8] Pavlova MK, Latreille V. Sleep Disorders. Am J Med 2019; 132: 292–299

[9] Sateia MJ. International classification of sleep disorders, third edition: highlights and modifications. Chest 2014; 146: 1387–1394

[10] Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med 2017; 13: 307–349

[11] Kavan MG, Elsasser GN, Barone EJ. Generalized anxiety disorder: practical assessment and management. Am Fam Physician 2009; 79: 785–791

[12] Monti JM, Monti D. Sleep disturbance in generalized anxiety disorder and its treatment. Sleep Med Rev 2000; 4: 263–276

[13] Staner L. Sleep and anxiety disorders. Dialogues Clin Neurosci 2003; 5: 249–258

[14] Hoge EA, Ivkovic A, Fricchione GL. Generalized anxiety disorder: diagnosis and treatment. BMJ 2012; 345: e7500

[15] Schanzer B, Rivas-Grajales AM, Khan A, Mathew SJ. Novel investigational therapeutics for generalized anxiety disorder (GAD). Expert Opin Investig Drugs 2019; 28: 1003–1012

[16] Jansson-Fröjmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. J Psychosom Res 2008; 64: 443–449

[17] Bragantini D, Sivertsen B, Gehrman P, Lydersen S, Güzey IC. Differences in anxiety levels among symptoms of insomnia. The HUNT study. Sleep Health 2019; 5: 370–375

[18] Lie JD, Tu KN, Shen DD, Wong BM. Pharmacological treatment of insomnia. Pharm Therap 2015; 40: 759–771

[19] Sarris J, Byrne GJ. A systematic review of insomnia and complementary medicine. Sleep Med Rev 2011; 15: 99–106

[20] Leach MJ, Page AT. Herbal medicine for insomnia: a systematic review and meta-analysis. Sleep Med Rev 2015; 24: 1–12

[21] Sarris J, McIntyre E, Camfield DA. Plant-based medicines for anxiety disorders, Part 1. CNS Drugs 2013; 27: 207–219

[22] Sarris J, McIntyre E. Herbal Anxiolytics with sedative Actions. In: Camfield D, McIntyre E, Sarris J, eds. Evidence-based herbal and nutritional Treatments for Anxiety in psychiatric Disorders. Stuttgart: Springer; 2017: 11–31

[23] The Plant List. A working list of all known plant species. Royal Botanic Gardens, Kew and Missouri Botanical Garden. Accessed January 11–15, and January 18–22, 2021 at: http://www.theplantlist.org/

[24] Plushner SL. Valerian: *Valeriana officinalis*. Am J Health Syst Pharm 2000; 57: 328, 333, 335

[25] Hattesohl M, Feistel B, Sievers H, Lehnfeld R, Hegger M, Winterhoff H. Extracts of *Valeriana officinalis* L. s.l. show anxiolytic and antidepressant effects but neither sedative nor myorelaxant properties. Phytomedicine 2008; 15: 2–15

[26] Patocka J, Jakl J. Biomedically relevant chemical constituents of *Valeriana officinalis*. J Appl Biomed 2010; 8: 11–18

[27] Felgentreff F, Becker A, Meier B, Brattström A. Valerian extract characterized by high valerenic acid and low acetoxy valerenic acid contents demonstrates anxiolytic activity. Phytomedicine 2012; 19: 1216–1222

[28] Gonulalan EM, Bayazeid O, Yalcin FN, Demirezer LO. The roles of valerenic acid on BDNF expression in the SH-SY5Y cell. Saudi Pharm J 2018; 26: 960–964

[29] Donath F, Quispe S, Diefenbach K, Maurer A, Fietze I, Roots I. Critical evaluation of the effect of valerian extract on sleep structure and sleep quality. Pharmacopsychiatry 2000; 33: 47–53

[30] Ziegler G, Ploch M, Miettinen-Baumann A, Collet W. Efficacy and tolerability of valerian extract LI 156 compared with oxazepam in the treatment of non organic insomnia – a randomized, double-blind, comparative clinical study. Eur J Med Res 2002; 7: 480–486

[31] Diaper A, Hindmarch I. A double-blind, placebo-controlled investigation of the effects of two doses of a valerian preparation on the sleep, cognitive and psychomotor function of sleep-disturbed older adults. Phytother Res 2004; 18: 831–836

[32] Taibi DM, Vitiello MV, Barsness S, Elmer GW, Anderson GD, Landis CA. A randomized clinical trial of valerian fails to improve self-reported, polysomnographic, and actigraphic sleep in older women with insomnia. Sleep Med 2009; 10: 319–328

[33] Taavoni S, Ekbatani N, Kashaniyan M, Haghani H. Effect of valerian on sleep quality in postmenopausal women: a randomized placebo-controlled clinical trial. Menopause 2011; 18: 951–955

[34] Barton DL, Atherton PJ, Bauer BA, Moore DF jr., Mattar BI, Lavasseur BI, Rowland KM jr., Zon RT, Lelindqwister NA, Nagargoje GG, Morgenthaler TI, Sloan JA, Loprinzi CL. The use of *Valeriana officinalis* (Valerian) in improving sleep in patients who are undergoing treatment for cancer: a phase III randomized, placebo-controlled, double-blind study (NCCTG Trial, N01C5). J Support Oncol 2011; 9: 24–31

[35] Roh D, Jung JH, Yoon KH, Lee CH, Kang LY, Lee S, Shin K, Kim DH. Valerian extract alters functional brain connectivity: a randomized double-blind placebo-controlled trial. Phytother Res 2019; 33: 939–948

[36] Farah GJ, Ferreira GZ, Danieletto-Zanna CF, Luppi CR, Jacomacci WP. 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 Maxillofac Surg 2019; 77: 1796.e1–1796.e8

[37] Miroddi M, Calapai G, Navarra M, Minciullo PL, Gangemi S. *Passiflora incarnata* L.: ethnopharmacology, clinical application, safety and evaluation of clinical trials. J Ethnopharmacol 2013; 150: 791–804

[38] Dhawan K, Kumar S, Sharma A. Anti-anxiety studies on extracts of *Passiflora incarnata* Linneaus. J Ethnopharmacol 2001; 78: 165–170

[39] Grundmann O, Wang J, McGregor GP, Butterweck V. Anxiolytic activity of a phytochemically characterized *Passiflora incarnata* extract is mediated via the GABAergic system. Planta Med 2008; 74: 1769–1773

[40] Guerrero FA, Medina GM. Effect of a medicinal plant (*Passiflora incarnata* L.) on sleep. Sleep Sci 2017; 10: 96–100

[41] Akhondzadeh S, Naghavi HR, Vazirian M, Shayeganpour A, Rashidi H, Khani M. Passionflower in the treatment of generalized anxiety: a pilot double-blind randomized controlled trial with oxazepam. J Clin Pharm Ther 2001; 26: 363–367

[42] Ngan A, Conduit R. A double-blind, placebo-controlled investigation of the effects of *Passiflora incarnata* (passionflower) herbal tea on subjective sleep quality. Phytother Res 2011; 25: 1153–1159

[43] Movafegh A, Alizadeh R, Hajimohamadi F, Esfehani F, Nejatfar M. Preoperative oral *Passiflora incarnata* reduces anxiety in ambulatory surgery patients: a double-blind, placebo-controlled study. Anesth Analg 2008; 106: 1728–1732

[44] Dantas LP, de Oliveira-Ribeiro A, de Almeida-Souza LM, Groppo FC. Effects of *Passiflora incarnata* and midazolam for control of anxiety in patients undergoing dental extraction. Med Oral Patol Oral Cir Bucal 2017; 22: 95–101

[45] Lee J, Jung HY, Lee SI, Choi JH, Kim SG. Effects of *Passiflora incarnata* Linnaeus on polysomnographic sleep parameters in subjects with insomnia disorder: a double-blind randomized placebo-controlled study. Int Clin Psychopharmacol 2020; 35: 29–35

[46] Graziano S, Orsolini L, Rotolo MC, Tittarelli R, Schifano F, Pichini S. Herbal highs: review on psychoactive effects and neuropharmacology. Curr Neuropharmacol 2017; 15: 750–761

[47] Salehi B, Zakaria ZA, Gyawali R, Ibrahim SA, Rajkovic J. *Piper* species: a comprehensive review on their phytochemistry, biological activities and applications. Molecules 2019; 24: 1364

[48] Chua HC, Christensen ET, Hoestgaard-Jensen K, Hartiadi LY, Ramzan I, Jensen AA, Absalom NL, Chebib M. Kavain, the major constituent of the anxiolytic kava extract, potentiates $GABA_A$ receptors: functional characteristics and molecular mechanism. PLoS One 2016; 11: e0157700

[49] Shinomiya K, Inoue T, Utsu Y, Tokunaga S, Masuoka T, Ohmori A, Kamei C. Effects of kava-kava extract on the sleep-wake cycle in sleep-disturbed rats. Psychopharmacology (Berl) 2005; 180: 564–569

[50] Tsutsui R, Shinomiya K, Takeda Y, Obara Y, Kitamura Y, Kamei C. Hypnotic. J Pharmacol Sci 2009; 111: 293–298

[51] Lehrl S. Clinical efficacy of kava extract WS 1490 in sleep disturbances associated with anxiety disorders. Results of a multicenter, randomized,

placebo-controlled, double-blind clinical trial. J Affect Disord 2004; 78: 101–110

[52] Sarris J, Stough C, Bousman CA, Wahid ZT, Murray G, Teschke R, Savage KM, Dowell A, Ng C, Schweitzer I. Kava in the treatment of generalized anxiety disorder: a double-blind, randomized, placebo-controlled study. J Clin Psychopharmacol 2013; 33: 643–648

[53] Kuchta K, de Nicola P, Schmidt M. Randomized, dose-controlled double-blind trial: efficacy of an ethanolic kava (*Piper methysticum* rhizome) extract for the treatment of anxiety in elderly patients. Tradit Kampo Med 2018; 5: 3–10

[54] Sarris J, Byrne GJ, Bousman CA, Cribb L, Savage KM, Holmes O, Murphy J, Macdonald P, Short A, Nazareth S, Jennings E, Thomas SR, Ogden E, Chamoli S, Scholey A, Stough C. Kava for generalised anxiety disorder: A 16-week double-blind, randomised, placebo-controlled study. Aust N Z J Psychiatry 2020; 54: 288–297

[55] Sharma A, Angulo-Bejarano PI, Madariaga-Navarrete A, Oza G, Iqbal HMN, Cardoso-Taketa A, Luisa Villarreal M. Multidisciplinary investigations on *Galphimia glauca*: A Mexican medicinal plant with pharmacological potential. Molecules 2018; 23: 2985

[56] Herrera-Ruiz M, González-Cortazar M, Jiménez-Ferrer JE, Zamilpa A, Álvarez L, Ramírez G, Tortoriello J. Anxiolytic effect of natural galphimines from *Galphimia glauca* and their chemical derivatives. J Nat Prod 2006; 69: 59–61

[57] Herrera-Ruiz M, Jiménez-Ferrer JE, De Lima TC, Avilés-Montes D, Pérez-García D, González-Cortazar M, Tortoriello J. Anxiolytic and antidepressant-like activity of a standardized extract from *Galphimia glauca*. Phytomedicine 2006; 13: 23–28

[58] Jiménez-Ferrer JE, Herrera-Ruiz M, Ramírez-García R, Herrera-Arellano A, Tortoriello J. Interaction of the natural anxiolytic galphimine-B with serotonergic drugs on dorsal hippocampus in rats. J Ethnopharmacol 2011; 137: 724–729

[59] Aviles-Montes D, Herrera-Ruiz M, Roman-Ramos R, Jimenez-Ferrer JE, González-Cortazar M, Zamilpa A, Tortoriello J. Pharmacological interaction between galphimine-A, a natural anxiolytic compound and GABAergic drugs. Int J Pharmacol 2015; 11: 944–955

[60] Santillán-Urquiza MA, Herrera-Ruiz M, Zamilpa A, Jiménez-Ferrer E, Román-Ramos R, Tortoriello J. Pharmacological interaction of *Galphimia glauca* extract and natural galphimines with ketamine and haloperidol on different behavioral tests. Biomed Pharmacother 2018; 103: 879–888

[61] Garige BSR, Keshetti S, Vattikuti UMR. *In vivo* study on depressant effects and muscle coordination activity of *Galphimia glauca* stem methanol extract. Pharmacognosy Res 2016; 8: 219–225

[62] Herrera-Arellano A, Jiménez-Ferrer JE, Zamilpa A, Morales-Valdez A, García-Valencia CE, Tortoriello J. Efficacy and tolerability of a standardized herbal product from *Galphimia glauca* on generalized anxiety disorder. A randomized, double-blind clinical trial controlled with lorazepam. Planta Med 2007; 73: 713–717

[63] Herrera-Arellano A, Jiménez-Ferrer JE, Zamilpa A, García-Alonso G, Herrera-Alvarez S, Tortoriello J. Therapeutic effectiveness of *Galphimia glauca* vs. lorazepam in generalized anxiety disorder. A controlled 15-week clinical trial. Planta Med 2012; 78: 1529–1535

[64] Romero-Cerecero O, Islas-Garduño AL, Zamilpa A, Pérez-García MD, Tortoriello J. Therapeutic effectiveness of *Galphimia glauca* in young people with social anxiety disorder: a pilot study. Evid Based Complement Alternat Med 2018; 2018: 1716939

[65] Romero-Cerecero O, Islas-Garduño AL, Zamilpa A, Herrera-Arellano A, Jiménez-Ferrer E, Tortoriello J. Galphimine-B standardized extract versus alprazolam in patients with generalized anxiety disorder: a ten-week, double-blind, randomized clinical trial. Biomed Res Int 2019; 2019: 1037036

[66] Mishra LC, Singh BB, Dagenais S. Scientific basis for the therapeutic use of *Withania somnifera* (ashwagandha): a review. Altern Med Rev 2000; 5: 334–346

[67] Andrade C, Aswath A, Chaturvedi SK, Srinivasa M, Raguram R. A double-blind, placebo-controlled evaluation of the anxiolytic efficacy of an ethanolic extract of *Withania somnifera*. Indian J Psychiatry 2000; 42: 295–301

[68] Chandrasekhar K, Kapoor J, Anishetty S. A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of ashwagandha root in reducing stress and anxiety in adults. Indian J Psychol Med 2012; 34: 255–262

[69] Lopresti AL, Smith SJ, Malvi H, Kodgule R. An investigation into the stress-relieving and pharmacological actions of an ashwagandha (*Withania somnifera*) extract: a randomized, double-blind, placebo-controlled study. Medicine (Baltimore) 2019; 98: 17186

[70] Fuladi S, Emami SA, Mohammadpour AH, Karimani A, Manteghi AA, Sahebkar A. Assessment of *Withania somnifera* root extract efficacy in patients with generalized anxiety disorder: a randomized double-blind placebo-controlled trial. Curr Clin Pharmacol 2020; 15: 1. doi:10.2174/1574884715666200413120413

[71] Gannon JM, Brar J, Rai A, Chengappa KNR. Effects of a standardized extract of *Withania somnifera* (Ashwagandha) on depression and anxiety symptoms in persons with schizophrenia participating in a randomized, placebo-controlled clinical trial. Ann Clin Psychiatry 2019; 31: 123–129

[72] Salve J, Pate S, Debnath K, Langade D. Adaptogenic and anxiolytic effects of ashwagandha root extract in healthy adults: a double-blind, randomized, placebo-controlled clinical study. Cureus 2019; 11: 6466

[73] Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Efficacy and safety of ashwagandha (*Withania somnifera*) root extract in insomnia and anxiety: a double-blind, randomized, placebo-controlled study. Cureus 2019; 11: 5797

[74] Kelgane SB, Salve J, Sampara P, Debnath K. Efficacy and tolerability of ashwagandha root extract in the elderly for improvement of general well-being and sleep: a prospective, randomized, double-blind, placebo-controlled study. Cureus 2020; 12: 7083

[75] Deshpande A, Irani N, Balkrishnan R, Benny IR. A randomized, double blind, placebo controlled study to evaluate the effects of ashwagandha (*Withania somnifera*) extract on sleep quality in healthy adults. Sleep Med 2020; 72: 28–36

[76] Langade D, Thakare V, Kanchi S, Kelgane S. Clinical evaluation of the pharmacological impact of ashwagandha root extract on sleep in healthy volunteers and insomnia patients: a double-blind, randomized, parallel-group, placebo-controlled study. J Ethnopharmacol 2021; 264: 113276

[77] Moradkhani H, Sargsyan E, Bibak H, Naseri B, Sadat-Hosseini M. *Melissa officinalis* L., a valuable medicine plant: a review. J Med Plant Res 2010; 4: 2753–2759

[78] Shakeri A, Sahebkar A, Javadi B. *Melissa officinalis* L.–A review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol 2016; 188: 204–228

[79] Ibarra A, Feuillere N, Roller M, Lesburgere E, Beracochea D. Effects of chronic administration of *Melissa officinalis* L. extract on anxiety-like reactivity and on circadian and exploratory activities in mice. Phytomedicine 2010; 17: 397–403

[80] Cases J, Ibarra A, Feuillère N, Roller M, Sukkar SG. Pilot trial of *Melissa officinalis* L. leaf extract in the treatment of volunteers suffering from mild-to-moderate anxiety disorders and sleep disturbances. Med J Nutrition Metab 2011; 4: 211–218

[81] Haybar H, Javid AZ, Haghighizadeh MH, Valizadeh E, Mohaghegh SM, Mohammadzadeh A. The effects of *Melissa officinalis* supplementation on depression, anxiety, stress, and sleep disorder in patients with chronic stable angina. Clin Nutr ESPEN 2018; 26: 47–52

[82] Srivastava JK, Shankar E, Gupta S. Chamomile: a herbal medicine of the past with bright future. Mol Med Rep 2010; 3: 895–901

[83] Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ, Shults J. A randomized, double-blind, placebo-controlled trial of oral *Matricaria recutita* (chamomile) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol 2009; 29: 378–382

[84] Keefe JR, Mao JJ, Soeller I, Li QS, Amsterdam JD. Short-term open-label chamomile (*Matricaria chamomilla* L.) therapy of moderate to severe generalized anxiety disorder. Phytomedicine 2016; 23: 1699–1705

[85] Mao JJ, Xie SX, Keefe JR, Soeller I, Li QS, Amsterdam JD. Long-term chamomile (*Matricaria chamomilla* L.) treatment for generalized anxiety disorder: a randomized clinical trial. Phytomedicine 2016; 23: 1735–1742

[86] Keefe JR, Guo W, Li QS, Amsterdam JD, Mao JJ. An exploratory study of salivary cortisol changes during chamomile extract therapy of moderate to severe generalized anxiety disorder. J Psychiatr Res 2018; 96: 189–195

[87] Adib-Hajbaghery M, Mousavi SN. The effects of chamomile extract on sleep quality among elderly people: a clinical trial. Complement Ther Med 2017; 35: 109–114

[88] Chang SM, Chen CH. Effects of an intervention with drinking chamomile tea on sleep quality and depression in sleep disturbed postnatal women: a randomized controlled trial. J Adv Nurs 2016; 72: 306–315

[89] Amsterdam JD, Shults J, Soeller I, Mao JJ, Rockwell K, Newberg AB. Chamomile (*Matricaria recutita*) may provide antidepressant activity in anxious, depressed humans: an exploratory study. Altern Ther Health Med 2012; 18: 44–49

[90] Kyrou I, Christou A, Panagiotakos D, Stefanaki C, Skenderi K, Katsana K, Tsigos C. Effects of a hops (*Humulus lupulus* L.) dry extract supplement on self-reported depression, anxiety and stress levels in apparently healthy young adults: a randomized, placebo-controlled, double-blind, crossover pilot study. Hormones (Athens) 2017; 16: 171–180

[91] Erkkola R, Vervarcke S, Vansteelandt S, Rompotti P, De Keukeleire D, Hayrack A. A randomized, double-blind, placebo-controlled, crossover pilot study on the use of a standardized hop extract to alleviate menopausal discomforts. Phytomedicine 2010; 17: 389–396

[92] Carmona F, Coneglian FS, Batista PA, Aragon DC, Angelucci MA, Martinez EZ, Pereira AMS. *Aloysia polystachya* (Griseb.) Moldenke (Verbenaceae) powdered leaves are effective in treating anxiety symptoms: a phase-2, randomized, placebo-controlled clinical trial. J Ethnopharmacol 2019; 242: 112060

[93] Jana U, Sur TK, Maity LN, Debnath PK, Bhattacharyya D. A clinical study on the management of generalized anxiety disorder with *Centella asiatica*. Nepal Med Coll J 2010; 12: 8–11

[94] Bystritsky A, Kerwin L, Feusner JD. A pilot study of *Rhodiola rosea* (Rhodax) for generalized anxiety disorder (GAD). J Altern Complement Med 2008; 14: 175–180

[95] Edwards D, Heufelder A, Zimmermann A. Therapeutic effects and safety of *Rhodiola rosea* extract WS 1375 in subjects with life-stress symptoms–results of an open-label study. Phytother Res 2012; 26: 1220–1225

[96] Cropley M, Banks AP, Boyle J. The effects of *Rhodiola rosea* L. Extract on anxiety, stress, cognition and other mood symptoms. Phytother Res 2015; 29: 1934–1939

[97] Wolfson P, Hoffmann DL. An investigation into the efficacy of *Scutellaria lateriflora* in healthy volunteers. Altern Ther Health Med 2003; 9: 74–78

[98] Hui KM, Huen MS, Wang HY, Zheng H, Sigel E, Baur R, Ren H, Li ZW, Wong JT, Xue H. Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi. Biochem Pharmacol 2002; 64: 1415–1424

[99] De Carvalho RS, Duarte FS, de Lima TC. Involvement of GABAergic non-benzodiazepine sites in the anxiolytic-like and sedative effects of the flavonoid baicalein in mice. Behav Brain Res 2011; 221: 75–82

[100] Firoozabadi A, Kolouri S, Zarshenas MM, Salehi A, Mosavat SH, Dastgheib SA. Efficacy of a freeze-dried aqueous extract of *Nepeta menthoides* Boiss. & Buhse in the treatment of anxiety in patients with depression: a double-blind, randomized, controlled trial. J Herbal Med 2017; 10: 17–23

[101] Nematolahi P, Mehrabani M, Karami-Mohajeri S, Dabaghzadeh F. Effects of *Rosmarinus officinalis* L. on memory performance, anxiety, depression, and sleep quality in university students: a randomized clinical trial. Complement Ther Clin Pract 2018; 30: 24–28

[102] Kell G, Rao A, Katsikitis M. A randomised placebo controlled clinical trial on the efficacy of *Caralluma fimbriata* supplement for reducing anxiety and stress in healthy adults over eight weeks. J Affect Disord 2019; 246: 619–626

[103] Morin CM, Koetter U, Bastien C, Ware JC, Wooten V. Valerian-hops combination and diphenhydramine for treating insomnia: a randomized placebo-controlled clinical trial. Sleep 2005; 28: 1465–1471

[104] Koetter U, Schrader E, Käufeler R, Brattström A. A randomized, double blind, placebo-controlled, prospective clinical study to demonstrate clinical efficacy of a fixed valerian hops extract combination (Ze 91019) in patients suffering from non-organic sleep disorder. Phytother Res 2007; 21: 847–851

[105] Dimpfel W, Suter A. Sleep improving effects of a single dose administration of a valerian/hops fluid extract–a double blind, randomized, placebo-controlled sleep-EEG study in a parallel design using electrohypnograms. Eur J Med Res 2008; 13: 200–204

[106] Kennedy DO, Little W, Haskell CF, Scholey AB. Anxiolytic effects of a combination of *Melissa officinalis* and *Valeriana officinalis* during laboratory induced stress. Phytother Res 2006; 20: 96–102

[107] Taavoni S, Nazem Ekbatani N, Haghani H. Valerian/lemon balm use for sleep disorders during menopause. Complement Ther Clin Pract 2013; 19: 193–196

[108] Abdellah SA, Berlin A, Blondeau C, Guinobert I, Guilbot A, Beck M, Duforez F. A combination of *Eschscholtzia californica* Cham. and *Valeriana officinalis* L. extracts for adjustment insomnia: a prospective observational study. J Tradit Complement Med 2019; 10: 116–123

[109] Wheatley D. Kava and valerian in the treatment of stress-induced insomnia. Phytother Res 2001; 15: 549–551

[110] Ranjbar M, Firoozabadi A, Salehi A, Ghorbanifar Z, Zarshenas MM, Sadeghniiat-Haghighi K, Rezaeizadeh H. Effects of herbal combination (*Melissa officinalis* L. and *Nepeta menthoides* Boiss. & Buhse) on insomnia severity, anxiety and depression in insomniacs: Randomized placebo controlled trial. Integr Med Res 2018; 7: 328–332

[111] Maroo N, Hazra A, Das T. Efficacy and safety of a polyherbal sedative-hypnotic formulation NSF-3 in primary insomnia in comparison to zolpidem: a randomized controlled trial. Indian J Pharmacol 2013; 45: 34–39

[112] Meier S, Haschke M, Zahner C, Kruttschnitt E, Drewe J, Liakoni E, Hammann F, Gaab J. Effects of a fixed herbal drug combination (Ze 185) to an experimental acute stress setting in healthy men–an explorative randomized placebo-controlled double-blind study. Phytomedicine 2018; 39: 85–92

[113] Hanus M, Lafon J, Mathieu M. Double-blind, randomised, placebo-controlled study to evaluate the efficacy and safety of a fixed combination containing two plant extracts (*Crataegus oxyacantha* and *Eschscholtzia californica*) and magnesium in mild-to-moderate anxiety disorders. Curr Med Res Opin 2004; 20: 63–71

[114] Scholey A, Benson S, Gibbs A, Perry N, Sarris J, Murray G. Exploring the effect of Lactium™ and *Zizyphus* Complex on sleep quality: a double-blind, randomized placebo-controlled trial. Nutrients 2017; 9: 154

[115] Cornu C, Remontet L, Noel-Baron F, Nicolas A, Feugier-Favier N, Roy P, Claustrat B, Saadatian-Elahi M, Kassaï B. A dietary supplement to improve the quality of sleep: a randomized placebo controlled trial. BMC Complement Altern Med 2010; 22: 10: 29

[116] Lemoine P, Bablon JC, da Silva C. A combination of melatonin, vitamin B_6 and medicinal plants in the treatment of mild-to-moderate insomnia: A prospective pilot study. Complement Ther Med 2019; 45: 104–108

[117] Woronuk G, Demissie Z, Rheault M, Mahmoud S. Biosynthesis and therapeutic properties of *Lavandula* essential oil constituents. Planta Med 2011; 77: 7–15

[118] Koulivand PH, Khaleghi Ghadiri M, Gorji A. Lavender and the nervous system. Evid Based Complement Alternat Med 2013; 2013: 681304

[119] Woelk H, Schläfke S. A multi-center, double-blind, randomised study of the lavender oil preparation silexan in comparison to lorazepam for generalized anxiety disorder. Phytomedicine 2010; 17: 94–99

[120] Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Dienel A, Schläfke S. Silexan, an orally administered *Lavandula* oil preparation, is effective in the treatment of 'subsyndromal' anxiety disorder: a randomized, double-blind, placebo controlled trial. Int Clin Psychopharmacol 2010; 25: 277–287

[121] Uehleke B, Schaper S, Dienel A, Schlaefke S, Stange R. Phase II trial on the effects of Silexan in patients with neurasthenia, post-traumatic stress disorder or somatization disorder. Phytomedicine 2012; 19: 665–671

[122] Kasper S, Gastpar M, Müller WE, Volz HP, Möller HJ, Schläfke S, Dienel A. Lavender oil preparation Silexan is effective in generalized anxiety disorder–a randomized, double-blind comparison to placebo and paroxetine. Int J Neuropsychopharmacol 2014; 17: 859–869

[123] Kasper S, Anghelescu I, Dienel A. Efficacy of orally administered Silexan in patients with anxiety-related restlessness and disturbed sleep–a randomized, placebo-controlled trial. Eur Neuropsychopharmacol 2015; 25: 1960–1967

[124] Chien LW, Cheng SL, Liu CF. The effect of lavender aromatherapy on autonomic nervous system in midlife women with insomnia. Evid Based Complement Alternat Med 2012; 2012: 740813

[125] Karan NB. Influence of lavender oil inhalation on vital signs and anxiety: a randomized clinical trial. Physiol Behav 2019; 211: 112676

[126] Otaghi M, Qavam S, Norozi S, Borji M, Moradi M. Investigating the effect of lavender essential oil on sleep quality in patients candidates for angiography. Biomed Pharmacol J 2017; 10: 473–478

[127] Jokar M, Zahraseifi, Baradaranfard F, Khalili M, Bakhtiari S. The effects of lavender aromatherapy on menopausal symptoms: a single-blind placebo-controlled clinical trial. Int J Pham Res 2018; 10: 182–188

[128] Nasiri Lari Z, Hajimonfarednejad M, Riasatian M, Abolhassanzadeh Z, Iraji A, Vojoud M, Heydari M, Shams M. Efficacy of inhaled *Lavandula angustifolia* Mill. Essential oil on sleep quality, quality of life and metabolic control in patients with diabetes mellitus type II and insomnia. J Ethnopharmacol 2020; 251: 112560

[129] Velasco-Rodríguez R, Pérez-Hernández MG, Maturano-Melgoza JA, Hilerio-López ÁG, Monroy-Rojas A, Arana-Gómez B, Vásquez C. The effect of aromatherapy with lavender (*Lavandula angustifolia*) on serum melatonin levels. Complement Ther Med 2019; 47: 102208

[130] Ayik C, Özden D. The effects of preoperative aromatherapy massage on anxiety and sleep quality of colorectal surgery patients: a randomized controlled study. Complement Ther Med 2018; 36: 93–99

[131] Namazi M, Amir Ali Akbari S, Mojab F, Talebi A, Alavi Majd H, Jannesari S. Aromatherapy with *Citrus aurantium* oil and anxiety during the first stage of labor. Iran Red Crescent Med J 2014; 16: e18371

[132] Heydari N, Abootalebi M, Jamalimoghadam N, Kasraeian M, Emamghoreishi M, Akbarzadeh M. Investigation of the effect of aromatherapy with *Citrus aurantium* blossom essential oil on premenstrual syndrome in university students: a clinical trial study. Complement Ther Clin Pract 2018; 32: 1–5

[133] Pimenta FC, Alves MF, Pimenta MB, Melo SA, de Almeida AA, Leite JR, Pordeus LC, Diniz MF, de Almeida RN. Anxiolytic effect of *Citrus aurantium* L. on patients with chronic myeloid leukemia. Phytother Res 2016; 30: 613–617

[134] Moslemi F, Alijaniha F, Naseri M, Kazemnejad A, Charkhkar M, Heidari MR. *Citrus aurantium* aroma for anxiety in patients with acute coronary syndrome: a double-blind placebo-controlled trial. J Altern Complement Med 2019; 25: 833–839

[135] Moradi K, Ashtarian H, Danzima NY, Saeedi H, Bijan B, Akbari F, Mohammadi MM. Essential oil from *Citrus aurantium* alleviates anxiety of patients undergoing coronary angiography: a single-blind, randomized controlled trial. Chin J Integr Med 2021; 27: 177–182

[136] Arabfirouzjaei Z, Ilali E, Taraghi Z, Mohammadpour RA, Amin K, Habibi E. The effect of *Citrus aurantium* aroma on sleep quality in the elderly with heart failure. JBUMS 2019; 21: 181–187

[137] Abdollahi F, Mobadery T. The effect of aromatherapy with bitter orange (*Citrus aurantium*) extract on anxiety and fatigue in type 2 diabetic patients. Adv Integr Med 2020; 7: 3–7

[138] Goes TC, Antunes FD, Alves PB, Teixeira-Silva F. Effect of sweet orange aroma on experimental anxiety in humans. J Altern Complement Med 2012; 18: 798–804

[139] Mirghafourvand M, Mohammad-Alizadeh Charandabi S, Hakimi S, Khodaie L, Galeshi M. Effect of orange peel essential oil on postpartum sleep quality: a randomized controlled clinical trial. Eur J Integr Med 2016; 8: 62–66

[140] Gnatta JR, Piason PP, Lopes CL, Rogenski NM, Silva MJ. Aromatherapy with ylang for anxiety and self-esteem: a pilot study. Rev Esc Enferm USP 2014; 48: 492–499

[141] Feyzabadi Z, Jafari F, Kamali SH, Ashayeri H, Badiee Aval S, Esfahani MM, Sadeghpour O. Efficacy of *Viola odorata* in treatment of chronic insomnia. Iran Red Crescent Med J 2014; 16: e17511

[142] Feyzabadi Z, Rezaeitalab F, Badiee S, Taghipour A, Moharari F, Soltanifar A, Ahmadpour MR. Efficacy of violet oil, a traditional Iranian formula, in patients with chronic insomnia: a randomized, double-blind, placebo-controlled study. J Ethnopharmacol 2018; 25: 22–28

[143] Shirzadegan R, Gholami M, Hasanvand S, Birjandi M, Beiranvand A. Effects of geranium aroma on anxiety among patients with acute myocardial infarction: a triple-blind randomized clinical trial. Complement Ther Clin Pract 2017; 29: 201–206

[144] Afrasiabian F, Mirabzadeh Ardakani M, Rahmani K, Azadi NA, Alemohammad ZB, Bidaki R, Karimi M, Emtiazy M, Hashempur MH. *Aloysia citriodora* Palau (lemon verbena) for insomnia patients: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. Phytother Res 2019; 33: 350–359

[145] Hatano VY, Torricelli AS, Giassi AC, Coslope LA, Viana MB. Anxiolytic effects of repeated treatment with an essential oil from *Lippia alba* and (R)-(−)-carvone in the elevated T-maze. Braz J Med Biol Res 2012; 45: 238–243

[146] Soto-Vásquez MR, Alvarado-García PAA. Anxiolytic-like effect of *Lippia alba* essential oil: A randomized, placebo-controlled trial. J Complement Med Res 2018; 7: 101–107

[147] Lee M, Lim S, Song J, Kim M, Hur M. The effects of aromatherapy essential oil inhalation on stress, sleep quality and immunity in healthy adults: randomized controlled trial. Eur J Integr Med 2017; 12: 79–86

[148] Stevens N, Dorsett J, DaBell A, Eggett DL, Han X, Parker TL. Subjective assessment of the effects of an herbal supplement containing lavender essential oil on sleep quality: a randomized, double-blind, placebo-controlled crossover study. Cogent Medicine 2017; 4: 1380871

[149] Hur MH, Hong JH, Yeo S. Effects of aromatherapy on stress, fructosamine, fatigue, and sleep quality in prediabetic middle-aged women: a randomised controlled trial. Eur J Integr Med 2019; 31: 100978

[150] Gürler M, Kızılırmak A, Baser M. The effect of aromatherapy on sleep and quality of life in menopausal women with sleeping problems: a non-randomized, placebo-controlled trial. Complement Med Res 2020; 9: 1–10

[151] McDonnell B, Newcomb P. Trial of essential oils to improve sleep for patients in cardiac rehabilitation. J Altern Complement Med 2019; 25: 1193–1199

[152] Hamzeh S, Safari-Faramani R, Khatony A. Effects of aromatherapy with lavender and peppermint essential oils on the sleep quality of cancer patients: a randomized controlled trial. Evid Based Complement Alternat Med 2020; 2020: 7480204

[153] Polonini H, Mesquita D, Lanine J, Dijkers E, Gkinis S, Raposo NRB, Brandão MAF, Ferreira ADO. Intranasal use of lavender and fennel decreases salivary cortisol levels and improves quality of sleep: a double-blind randomized clinical trial. Eur J Integr Med 2020; 34: 101015

[154] Kamalifard M, Farshbaf-Khalili A, Namadian M, Ranjbar Y, Herizchi S. Comparison of the effect of lavender and bitter orange on sleep quality in postmenopausal women: a triple-blind, randomized, controlled clinical trial. Women Health 2018; 58: 851–865

[155] Taherzadeh Z, Khaluyan H, Iranshahy M, Rezaeitalab F, Eshaghi Ghalibaf MH, Javadi B. Evaluation of sedative effects of an intranasal dosage form containing saffron, lettuce seeds and sweet violet in primary chronic insomnia: a randomized, double-dummy, double-blind placebo controlled clinical trial. J Ethnopharmacol 2020; 262: 113116

[156] Ancoli-Israel S. Sleep and its disorders in aging populations. Sleep Med 2009; 10 (Suppl 1): S7–S11

[157] Suh S, Cho N, Zhang J. Sex differences in insomnia: from epidemiology and etiology to intervention. Curr Psychiatry Rep 2018; 20: 69

[158] Williamson E. Synergy and other interactions in phytomedicines. Phytomedicine 2001; 8: 401–409

[159] Spinella M. The importance of pharmacological synergy in psychoactive herbal medicines. Altern Med Rev 2002; 7: 130–137

[160] Wagner H, Ulrich-Merzenich G. Synergy research: approaching a new generation of phytopharmaceuticals. Phytomedicine 2009; 16: 97–110

[161] Wagner H. Synergy research: approaching a new generation of phytopharmaceuticals. Fitoterapia 2011; 82: 34–37

[162] Bhutani MK, Bishnoi M, Kulkarni SK. Anti-depressant like effect of curcumin and its combination with piperine in unpredictable chronic stress-induced behavioral, biochemical and neurochemical changes. Pharmacol Biochem Behav 2009; 92: 39–43

[163] Wasowski C, Marder M. Flavonoids as $GABA_A$ receptor ligands: The whole story? Br J Pharmacol 2011; 163: 234–245

[164] Campbell EL, Chebib M, Johnston GA. The dietary flavonoids apigenin and (−)-epigallocatechin gallate enhance the positive modulation by diazepam of the activation by GABA of recombinant $GABA_A$ receptors. Biochem Pharmacol 2004; 68: 1631–1638

[165] Vissiennon C, Nieber K, Kelber O, Butterweck V. Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin–are they prodrugs? J Nutr Biochem 2012; 23: 733–740

[166] Aguirre-Hernández E, González-Trujano ME, Terrazas T, Herrera-Santoyo J, Guevara-Fefer P. Anxiolytic and sedative-like effects of flavonoids from *Tilia americana* var. *mexicana*: GABAergic and serotonergic participation. Salud Mental 2016; 39: 37–46

[167] Noguerón-Merino MC, Jiménez-Ferrer E, Román-Ramos R, Zamilpa A, Tortoriello J, Herrera-Ruiz M. Interactions of a standardized flavonoid fraction from *Tilia americana* with serotoninergic drugs in elevated plus maze. J Ethnopharmacol 2015; 164: 319–327

[168] Hernández-León A, González-Trujano ME, Fernández-Guasti A. The anxiolytic-like effect of rutin in rats involves $GABA_A$ receptors in the basolateral amygdala. Behav Pharmacol 2017; 28: 303–312

[169] Carrasco MC, Vallejo JR, Pardo-de-Santayana M, Peral D, Martín MA, Altimiras J. Interactions of *Valeriana officinalis* L. and *Passiflora incarnata* L. in a patient treated with lorazepam. Phytother Res 2009; 23: 1795–1796

[170] Tweddell P, Boyle C. Potential interactions with herbal medications and midazolam. Dent Update 2009; 36: 175–178