

## REVIEW

# Therapeutic potential of hypnotic herbal medicines: A comprehensive review

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## Abstract

Insomnia affects millions of people worldwide, prompting considerable interest in herbal remedies for its treatment. This review aims to assess the therapeutic potential of such remedies for insomnia by analyzing current scientific evidence. The analysis identified several herbs, including *Rosmarinus officinalis*, *Crocus sativus*, *Rosa damascena*, *Curcuma longa*, *Valeriana officinalis*, *Lactuca sativa*, *Portulaca oleracea*, *Citrus aurantium*, *Lippia citriodora*, and *Melissa officinalis*, which show promise in improving overall sleep time, reducing sleep latency, and enhancing sleep quality. These plants act on the central nervous system, particularly the serotonergic and gamma-aminobutyric acid (GABA)ergic systems, promoting sedation and relaxation. However, further research is necessary to fully understand their mechanisms of action, optimal dosages, and treatment protocols. Combining herbal medicines with conventional treatments may offer an effective natural alternative for those seeking medication. Nevertheless, individuals should consult their healthcare provider before using herbal remedies for insomnia. While this review provides evidence supporting their use, additional high-quality studies are needed to firmly establish their clinical efficacy.

## KEYWORDS

gamma-aminobutyric acid, lettuce, *Melissa*, *Rosmarinus*, sleep, valerian

## 1 | INTRODUCTION

Sleep is a fundamental biological function that is shared by all living species, accounting for one-third of human life. Sleep deprivation has been related to a variety of physiological system dysfunctions, including endocrine and metabolic functioning, higher cortical cognitive processes, and neurological disorders. Sleep problems can manifest as complaints of insufficient sleep, excessive drowsiness, or abnormal sleep movements (Pavlova & Latreille, 2019). Sleep disorders are a

group of disorders that disrupt the typical sleep rhythm. They are a common difficulty in therapeutic practice and affect people's emotional, mental, physical, and social well-being by depriving them of adequate and restorative sleep. In addition, these disorders have far-reaching effects on the quality and safety of life and general health (Karna et al., 2020).

Sleep disorders are divided into several categories, with insomnia, circadian rhythm abnormalities, and obstructive sleep apnea receiving the most attention (Zhao et al., 2020). Insomnia is a sleep-related disorder characterized by difficulty initiating or maintaining sleep (Riemann et al., 2023). Circadian sleep rhythm disorders are persistent disturbances of the sleep-wake cycle that last for at least 1 month. These abnormalities are caused either by changes in the circadian timing system or by an imbalance between a person's natural circadian rhythm and the sleep-wake times dictated by school or work. As a

**Abbreviations:** 5-HT<sub>2b</sub>, 5-hydroxytryptamine 2B receptor; 5-HT<sub>5a</sub>, 5-hydroxytryptamine 5A receptor; EEG, electroencephalogram; GABA, gamma-aminobutyric acid; GABA<sub>A</sub>, γ-Aminobutyric acid type A; GABRB3, gamma-aminobutyric acid type A receptor subunit beta3; GAD, glutamic acid decarboxylase; H1R, histamine H1 receptor; HT1A, 5-hydroxytryptamine receptor 1A; mRNA, messenger ribonucleic acid; NREM, non-rapid eye movement; REM, rapid eye movement; SOD, superoxide dismutase.

result, people who suffer from circadian rhythm sleep disorders have difficulty falling asleep and waking up (Zee et al., 2013). Obstructive sleep apnea is the repetitive narrowing or closing of the upper airway during sleep caused by the relaxation of the muscles in the throat (pharyngeal muscles) (Pham et al., 2022). As well as affecting productivity and quality of life, sleep disorders are also associated with a higher risk of physical and mental health problems. They are a risk factor for a variety of illnesses, including type 2 diabetes, hypertension, and cardiovascular disease. Furthermore, children's sleep health has been linked to their physiological and psychological well-being, cognitive development, and behaviors (Gangwisch, 2014; Hysing et al., 2018; Zhao et al., 2020).

Sleep disorders have complicated and multiple underlying mechanisms that involve a variety of physiological, psychological, and environmental components (Liu et al., 2018). Additionally, lifestyle factors such as stress, diet, and physical activity can contribute to sleep disorders. Psychological factors such as anxiety and depression can also disrupt sleep (Sejbuk et al., 2022). Understanding the underlying mechanisms of sleep disorders is crucial in developing effective treatment strategies (Faulkner & Bee, 2016).

Sleep disorders have a wide range of physiological underlying causes that can involve several bodily systems, including the central nervous system, respiratory system, and cardiovascular system. Sleep onset and maintenance can be affected by abnormalities in neurotransmitter modulation, such as the gamma-aminobutyric acid (GABA)ergic system (Sejbuk et al., 2022). Airway blockage during sleep can cause obstructive sleep apnea, resulting in disrupted breathing and sleep fragmentation (Slowik et al., 2022). Sleep quality and duration can also be affected by cardiovascular disease and metabolic disorders (Sejbuk et al., 2022). The development of focused therapies for the management of sleep disorders can benefit from understanding the physiological mechanisms underlying these conditions.

Although drugs such as benzodiazepines, zolpidem, and melatonin are currently used to treat sleep disorders, their efficacy and undesirable side effects (dizziness, confusion, incoordination, memory problems, and muscle weakness; Capiu et al., 2023; Edinoff et al., 2021) should be critically evaluated. Therefore, it is important to investigate the need for novel drugs for the treatment of sleep disorders. Complementary and alternative medicine approaches, including the use of herbal medicines, have shown promise as complementary therapies for sleep disorders, particularly insomnia, and have the potential to improve sleep quality and duration. Several herbal medicines, such as *Rosmarinus officinalis*, *Crocus sativus*, *Rosa damascena*, *Curcuma longa*, *Valeriana officinalis*, *Lactuca sativa*, *Portulaca oleracea*, *Citrus aurantium*, *Lippia citriodora*, *Echium italicum*, and *Melissa officinalis* have demonstrated sleep-promoting properties in both preclinical and clinical studies based on various mechanisms including regulation of the serotonergic, nitroergic, and GABAergic systems (Bruni et al., 2021; Hosseinzadeh et al., 2012; Ishola et al., 2020; Shi et al., 2014).

Therefore the investigation of herbal medicines with sleep-promoting properties could be a helpful strategy to develop effective sleep-promoting methods with likely favorable safety profiles.

The present article provides a complete overview of medicinal plants, focusing on their physio-pharmacological mechanisms of action and scientific evidence for their sleep-promoting effects. By evaluating existing data, this review aims to contribute to the search for herbal medicines that balance efficacy and safety in the treatment of sleep disorders (insomnia, sleep disturbances, sleep quality and duration). However, further studies are required to conclusively determine the safety and therapeutic effect of the plants.

## 2 | METHODS

As a comprehensive review, our objective was to provide a comprehensive overview and analysis of the available literature on the topic. We conducted a thorough search on Google Scholar, PubMed, and Scopus using relevant keywords related to sleep disorders, herbal medicine, and complementary medicine. The keywords used included "sleep," "sleep disorders," "insomnia," "hypnotic," "sleep disturbances," "sleep quality," "sleep latency," "sleep duration," "sleep aids," "sleep remedies," "medicinal Plant," "herbs," "botany," "pharmacognosy," "phytotherapy," "naturopathy," "plants medicinal," "herbal drugs," "herbal medicine," "herbal remedy," "herbal preparations," "herbal product," "herbal," "traditional medicine," "Unani medicine," "complementary medicine," "alternative medicine," "ethnomedicine," "phytochemical," "phytochemical," "botanical," "Phytomedicine," and "natural product." The search was conducted without any time constraints to ensure a comprehensive inclusion of relevant studies (Figure 1).

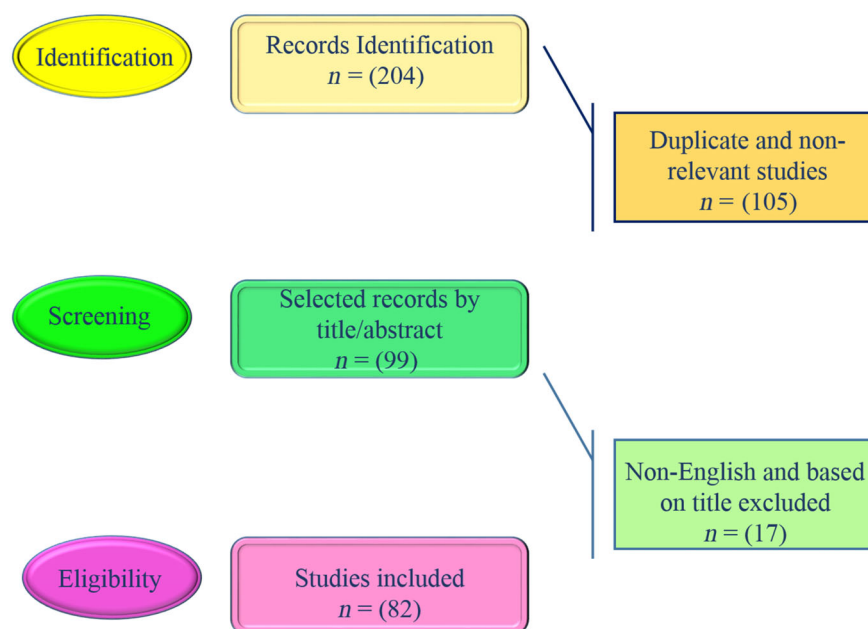
## 3 | HERBAL SLEEP-INDUCING MEDICINES

Folk medicine has long recognized the sleep-inducing properties of various plants, and modern researchers are now investigating and characterizing these plants and their components for their potential in treating sleep disorders. This section aims to provide a review of the mechanism of action of several medicinal plants that possess sleep-inducing properties.

### 3.1 | *Rosmarinus officinalis* (rosemary)

Rosemary, *R. officinalis* (Labiatae) as it is scientifically known, has long been used in folk medicine to treat several conditions, including depression, dysmenorrhea, epilepsy, headache, hysteria, nervous agitation, stomachache, rheumatic pain, physical and mental exhaustion, and spasms (Rahbardar & Hosseinzadeh, 2020). The medicinal advantages of several types of rosemary extracts and their main chemical components, such as rosmarinic acid, carnosol, and carnosic acid have attracted increasing scientific interest in recent years. Numerous studies have shown that rosemary and its compounds have a wide range of therapeutic benefits, including anti-inflammatory

**FIGURE 1** The diagram of the search strategy.



(Rahbardar et al., 2017), antinociceptive (Ghasemzadeh et al., 2016), antioxidant (Nakisa & Ghasemzadeh, 2022; Rahbardar et al., 2018), antiapoptotic (Ghasemzadeh et al., 2016), antidote (Alavi et al., 2021), antirheumatic (Nakisa & Rahbardar, 2022), antidepressant (Rahbardar & Hosseinzadeh, 2021), cardioprotective (Ghasemzadeh Rahbardar et al., 2024; Rahbardar et al., 2022), and neuroprotective effects (Ghasemzadeh Rahbardar et al., 2022; Ghasemzadeh Rahbardar & Hosseinzadeh, 2020).

### 3.1.1 | In vivo/in vitro

A study examined the hypnotic mechanism of rosmarinic acid on rodents and primary cultured hypothalamic cells of rats. The obtained data of the in vivo part of the study demonstrated that rosmarinic acid attenuated locomotor activity and sleep latency in mice while increasing total sleep time in animals received pentobarbital. Rosmarinic acid could also reduce rapid eye movement (REM) sleep as well as sleep/wake cycles, and enhance the total and non-REM (NREM) sleep in rats. Analyzing the power density of NREM sleep demonstrated that rosmarinic acid decreased  $\alpha$ -waves and increased  $\delta$ -waves. This compound also augmented glutamic acid decarboxylase (GAD)65/67 protein expression and GABA<sub>A</sub> receptors subunits except the  $\beta_1$  subunit. The results of the in vitro part of the study illustrated that rosmarinic acid significantly amplified intracellular  $\text{Cl}^-$  influx in the primary cultured hypothalamic cells of rats (Kwon et al., 2017) (Figures 2 and 3).

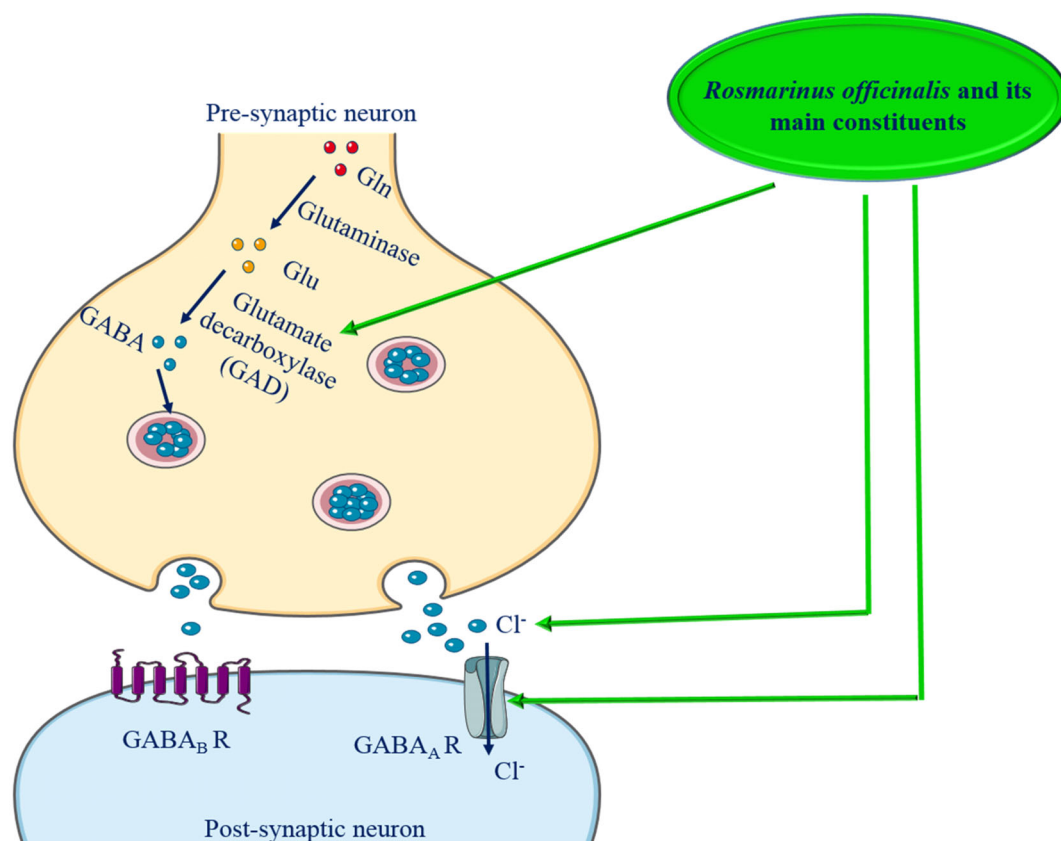
An in vivo research reported that the administration of rosmarinic acid to mice exhibited direct binding and acted as an agonist for the adenosine A<sub>1</sub> receptor (A<sub>1</sub>R) (adenosine has depressant effects via its A<sub>1</sub> receptor and can be considered as an anxiolytic, anticonvulsant, and neuroprotective agent (Higgins et al., 1994)). It was also indicated that rosmarinic acid has a significant impact on decreasing sleep fragmentation and onset latency to NREM sleep. Moreover, rosmarinic

acid decreases neuronal activity in regions of the brain responsible for promoting wakefulness, such as the lateral hypothalamus and the basal forebrain, while increasing activity in the ventrolateral preoptic nucleus, an area that promotes sleep (Kim et al., 2022).

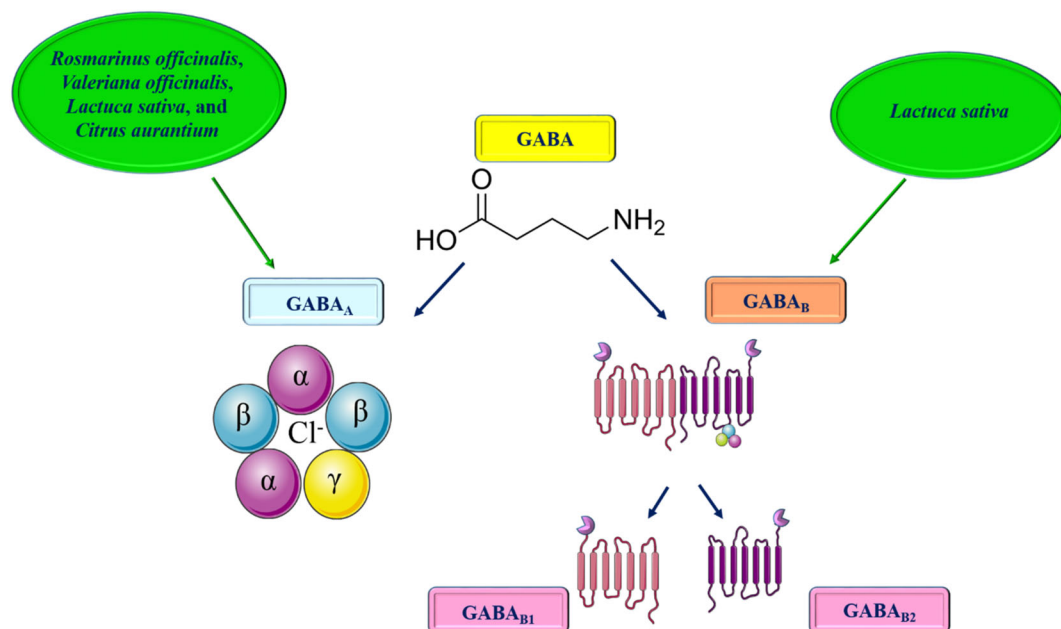
### 3.1.2 | Clinical trial

A clinical trial examined the potential effects of *R. officinalis* on drug abusers and the data disclosed that dried leaves of *R. officinalis* could increase daily sleep duration and decrease insomnia in comparison with the control group (Solhi et al., 2013). In another clinical trial that was carried out on university students, dried powder of aerial parts of *R. officinalis* pointedly improved sleep quality and attenuated sleep latency (Nematollahi et al., 2018). Moreover, the obtained data from another clinical trial revealed that aromatherapy with essential oils of *R. officinalis* enhanced sleep quality in young healthy volunteers (Alvarado-García et al., 2023) (Table 1).

In brief, these investigations indicate that rosmarinic acid has a hypnotic effect, which may be attributable to its ability to increase total and NREM sleep, decrease sleep fragmentation and onset latency, and decrease REM sleep and sleep/wake cycles. These effects could be attributed to its competence to boost intracellular  $\text{Cl}^-$  influx as well as GAD65/67 protein production and GABA<sub>A</sub> receptor subunits. Furthermore, rosmarinic acid was discovered to be an A<sub>1</sub>R agonist, which lowered neuronal activity in wake-promoting brain areas while increasing activity in sleep-promoting brain regions. Clinical research has also shown that *R. officinalis* can increase sleep quality and duration, making it a prospective treatment agent for insomnia. However, more in vivo investigations and clinical trials are needed to determine the precise underlying mechanisms and efficacy of rosemary and its primary constituents' hypnotic effects.



**FIGURE 2** The proposed mechanism of neuroprotective action of safranal, *Rosmarinus officinalis* and its main components. Source: Images from [smart.servier.com](https://smart.servier.com).



**FIGURE 3** The symbolic molecular structure of GABA receptors and the herbal medicines affect them. GABA<sub>A</sub>. Source: Images from [smart.servier.com](https://smart.servier.com).

**TABLE 1** The effect of *Rosmarinus officinalis* and *Crocus sativus* on sleep.

Compound/extract	Study design	Doses/duration	Results	References
<i>R. officinalis</i> (Rosemary)				
In vivo/In vitro				
Rosmarinic acid	In vivo, rodents	0.5, 1, and 2 mg/kg, p.o.	↑ Total sleep time, the number of mice falling asleep, NREM sleep in rats, $\delta$ -waves, GABA <sub>A</sub> receptors subunits except for $\beta_1$ subunit, protein expression of GAD65/67 ↓ Sleep latency, REM sleep, counts of sleep/wake cycles, $\alpha$ -waves	(Kwon et al., 2017)
	In vitro, primary cultured hypothalamic cells of rats	0.1, 1.0 and 10 $\mu$ g/mL	↑ Intracellular Cl <sup>-</sup> influx	
Rosmarinic acid	In vivo, Male ICR mice and male C57BL/6 mice	1, 3, 10, and 30 mg/kg, 30 min before pentobarbital injection, p.o.	- Has direct binding activity and agonistic activity for A <sub>1</sub> R ↑ Neuronal activity in the ventrolateral preoptic nucleus ↓ Onset latency to NREM sleep, sleep fragmentation, neuronal activity in wake-promoting brain regions (lateral hypothalamus and basal forebrain)	(Kim et al., 2022)
Clinical trial				
Dried leaves of <i>R. officinalis</i>	Clinical trial, 81 drug abusers	300 mg, first 3 days: 16 capsules/day, days 4–7: 12 capsules/day, the second week: 8 capsules/day	↑ Duration of sleep ↓ Insomnia	(Solhi et al., 2013)
Dried powder of aerial parts of <i>R. officinalis</i>	Clinical trial, 68 university students	500 mg, twice daily, 1 month	↑ Sleep quality ↓ Sleep latency	(Nematollahi et al., 2018)
Essential oils of <i>R. officinalis</i>	Clinical trial, 81 undergraduate students	Two drops of essential oils of <i>R. officinalis</i> on a cotton ball, 30 min, 4 weeks	↑ Sleep quality	(Alvarado-García et al., 2023)
<i>C. sativus</i> (Saffron)				
In vivo				
<i>C. sativus</i> aqueous extract, crocin, and safranal	In vivo, male mice	<i>C. sativus</i> aqueous extract: 56, 80, 320, and 560 mg/kg, i.p. Crocin: 50, 200 and 600 mg/kg, i.p. Safranal: 0.05, 0.15, and 0.35 mL/kg, i.p.	↑ <i>C. sativus</i> (0.56 g/kg): the total sleep time - Crocin: no hypnotic effect ↑ Safranal: the total sleep time dose-dependently	(Hosseinzadeh & Noraei, 2009)
Crocin and crocetin	In vivo, male mice	Crocin: 30 and 100 mg/kg, i.p. Crocetin: 100 mg/kg, i.p.	- No change in the amount of REM sleep ↑ The total time of NREM sleep	(Masaki et al., 2012)
Clinical trial				
<i>C. sativus</i> capsule	Clinical trial, 50 diabetic patients	300 mg, 7 days, p.o.	↑ Quality of sleep	(Dehghanmehr et al., 2017; Shahdadi et al., 2017)
affron®	Clinical trial, 128 participants with self-reporting low mood	22, 28 mg/day, 4 weeks, p.o.	- No significant improvement in sleep quality	(Kell et al., 2017)

(Continues)

TABLE 1 (Continued)

Compound/extract	Study design	Doses/duration	Results	References
Crocetin	Clinical trial, 30 healthy adult	7.5 mg/day, 14 days, p.o.	– No significant changes in sleep efficiency, sleep latency, total sleep time, and wake after sleep onset	(Umigai et al., 2018)
<i>C. sativus</i> alcoholic extract	Clinical trial, 54 outpatients with comorbid depression–anxiety	30 mg/day, 8 weeks, p.o.	↓ Sleep disturbance	(Milajerdi et al., 2018)
Crocin	Clinical trial, 50 patients under methadone maintenance treatment	30 mg/day, 8 weeks, p.o.	↑ Sleep quality	(Khalatbari-Mohseni et al., 2019)
affron®	Clinical trial, 63 healthy adults with self-reported sleep problems	14 mg, twice daily, 28 days, p.o.	↑ Sleep quality, total sleep time, mood on awakening, alertness on awakening ↓ Sleep latency, number of awakenings after sleep onset	(Lopresti et al., 2020)
affron®	Clinical trial, 120 adults with unsatisfactory sleep	14 or 28 mg, 28 days, p.o.	↑ Sleep quality, evening melatonin concentrations	(Lopresti et al., 2021)
Saffr'Activ®	Clinical trial, 66 subjects with mild to moderate sleep disorder associated with anxiety	15.5 mg/day, 6 weeks, p.o.	↑ Ease of getting to sleep, sleep quality, sleep duration ↓ Sleep latency	(Pachikian et al., 2021)
<i>C. sativus</i> powder	Clinical trial, 70 diabetic patients	100 mg/day, 8 weeks, p.o.	↑ Sleep quality	(Tajaddini et al., 2021)
affron®	Clinical trial, 62 healthy recreationally active adults	28 mg, 6 weeks, p.o.	– No significant changes in total sleep time and sleep efficiency	(Lopresti & Smith, 2022)
Saffr'Activ®	Clinical trial, individuals with attention deficit/hyperactivity disorder	30 mg/day, 3 months, p.o.	↑ Sleep duration ↓ Sleep latency	(Blasco-Fontecilla et al., 2022)

Abbreviations: GABA<sub>A</sub>,  $\gamma$ -Aminobutyric acid type A; GAD, glutamic acid decarboxylase; NREM, non-REM; REM: rapid eye movement.

### 3.2 | *Crocus sativus* (saffron)

*Crocus sativus* (saffron) is a member of the Iridaceae family and is extensively used as a spice and coloring component in a variety of foods and cosmetic applications. While it is grown throughout the world, it is most popular in Iran, France, Italy, and Spain (Ghasemzadeh Rahbardar & Hosseinzadeh, 2023). Saffron stigma contains several components that have been found through phytochemical studies, including crocin, crocetin, picrocrocin, and safranal (Alavizadeh & Hosseinzadeh, 2014; Boskabady et al., 2010; Boskabady, Rahbardar, & Jafari, 2011). Besides the phytochemicals mentioned earlier, saffron also contains a variety of other nutrients. These include proteins, amino acids, minerals, anthocyanins, gums, carbohydrates, flavonoids, and vitamins such as riboflavin and thiamine (Khoshandam et al., 2022). Saffron has been used by traditional medicine for several therapeutic benefits, including as an expectorant, aphrodisiac, anti-spasmodic, and stomachache treatment. Additionally, it has been used to treat insomnia, depression, and anxiety (Hosseini et al., 2018). Furthermore, in traditional medicine, saffron has often been used as a sleep aid due to its calming and relaxing effects (Lopresti et al., 2020; Mollazadeh et al., 2015). Several bioactive compounds, including crocin and safranal, are thought to enhance the

levels of certain neurotransmitters in the brain, such as serotonin, or affect benzodiazepine binding sites of the GABA<sub>A</sub> receptor complex (Sadeghnia et al., 2008; Siddiqui et al., 2022). In traditional Persian medicine, saffron has been recommended as a natural remedy for insomnia and sleep disturbances (Taherzadeh et al., 2020). Recent pharmacological research has demonstrated that saffron stigma possesses several beneficial effects, including anxiolytic (Hosseinzadeh & Noraei, 2009; Pitsikas & Tarantilis, 2020), antinociceptive (Hosseinzadeh & Shariaty, 2007; Hosseinzadeh & Younesi, 2002), anticonvulsant (Hosseinzadeh & Khosravan, 2002), antidepressant (Ghasemi et al., 2015; Hosseinzadeh et al., 2004), neuroprotective (Bedrood et al., 2023) properties that are based on its antioxidant (Hosseinzadeh et al., 2008; Hosseinzadeh et al., 2009; Kiashemshaki et al., 2021), anti-inflammatory (Vafaeipour et al., 2023), and antiapoptotic (Mohammadzadeh et al., 2022; Rajabian et al., 2023) properties.

#### 3.2.1 | In vivo

In a study, *C. sativus* aqueous extract, crocin, or safranal was administered to mice 30 min after the injection of sodium pentobarbital. The results illustrated that *C. sativus* aqueous extract at the dose of



0.56 g/kg significantly increased the total sleep time. Crocin had no hypnotic effects on the administered doses, but safranal could enhance the total sleep time dose independently (Hosseinzadeh & Noraei, 2009). The findings of another study indicated that intraperitoneal injection of crocin or crocetin enhanced the total time of NREM sleep in mice, while they had no significant effect on the total time of REM sleep in these animals (Masaki et al., 2012).

### 3.2.2 | Clinical trial

The results of a clinical trial demonstrated that the administration of saffron capsules could remarkably increase sleep quality in diabetic patients (Dehghanmehr et al., 2017; Shahdadi et al., 2017). Furthermore, it has been shown that the administration of an alcoholic extract of saffron to outpatients with comorbid depression-anxiety reduced sleep disturbances for 8 weeks (Milajerdi et al., 2018). Besides, crocin was administered to individuals receiving methadone maintenance treatment during a clinical trial, and it improved their sleep quality (Khalatbari-Mohseni et al., 2019). It was observed that the administration of affron<sup>®</sup> to healthy adults with self-reported sleep problems pointedly increased sleep quality and total sleep time, improved mood on awakening, and enhanced alertness on awakening. It also attenuated sleep latency and the number of awakenings after sleep onset (Lopresti et al., 2020). In another clinical trial on adults with unsatisfactory sleep, affron<sup>®</sup> prescription for 28 days could significantly increase sleep quality as well as evening melatonin concentrations (Lopresti et al., 2021). Likewise, Saffr'Activ<sup>®</sup>, an extract from *C. sativus*, was administered to individuals experiencing mild to moderate sleep disorder with anxiety. As a result, the extract improved their ability to fall asleep easily, increased the quality and duration of sleep, and reduced their sleep latency (Pachikian et al., 2021). Saffron powder has been shown to enhance sleep quality in patients with type 2 diabetes (Tajaddini et al., 2021). Another clinical trial reported that the administration of standardized *C. sativus* (affron<sup>®</sup>) to healthy recreationally active adults had no significant effect on total sleep time and sleep efficiency (Lopresti & Smith, 2022). The apparent contradiction between this study and other studies that reported the hypnotic effects of saffron might be attributed to differences in the study populations, saffron dosages, and the methodology used. The positive effects of saffron in this context may not necessarily translate to healthy individuals. Moreover, the saffron formulations used in these studies may have differed in terms of dosage, purity, and bioavailability. It has also been observed that the administering of Saffr'Activ<sup>®</sup> to individuals with attention deficit/hyperactivity disorder led to an increase in sleep duration and a decrease in sleep latency (Blasco-Fontecilla et al., 2022) (Table 1).

Briefly, the administration of *C. sativus* extract, crocin, and safranal has been shown to have varying effects on sleep in rodents, with safranal having a dose-dependent hypnotic effect and crocin having no significant effect. Clinical trials have demonstrated that saffron in various forms, including capsules, extracts, and powders, can improve sleep quality and duration in individuals with diabetes, comorbid

depression anxiety, methadone maintenance treatment, and self-reported sleep problems. However, the effects of saffron on total sleep time and efficiency in healthy individuals remain inconclusive. Further research is needed to establish the optimal dosages and formulations of saffron for improving sleep and to determine its safety and efficacy in different populations.

### 3.3 | *Rosa damascena* (damask rose)

*Rosa damascena* (damask rose) is a tall shrub with stunning and vivid flowers (Boskabady, Vatanprast, et al., 2011). It includes beneficial constituents such as carotenoids, citric acid, flavonoids, malic acid, pectin, tannin, and vitamins A, B1, B2, B3, C, and K. Studies have also shown that the plant has sedative and hypnotic properties (Mokhtari et al., 2023). It has been discovered that this plant has a variety of medical characteristics, including anti-inflammatory, analgesic, anti-headache, muscle relaxation, inotropic and chronotropic effects (Boskabady, Vatanprast, et al., 2011), sedative and hypnotic properties (Mokhtari et al., 2023), as well as anticonvulsant effects (Hosseini, Ghasemzadeh Rahbardar, et al., 2011).

#### 3.3.1 | In vivo

The findings of an in vivo study demonstrated that the administration of ethanoic and aqueous extracts of *R. damascena* could significantly increase the sleeping time in mice, but the chloroformic extract had no hypnotic effect (Rakhshandah & Hosseini, 2006).

#### 3.3.2 | Clinical trial

It has been reported that aromatherapy with *R. damascena* oil could improve sleep quality in critical care unit (CCU) patients (Hajibagheri et al., 2014). Furthermore, the results of a clinical trial indicated that oral administration of *R. damascena* extract on patients undergoing angiography did not affect sleep parameters in comparison to the placebo group. But, it could enhance sleep quality before and after intervention (Babaei et al., 2016). Assessing the effect of aromatherapy with *R. damascena* oil on children with sleep disorders illustrated that it decreased resistance to sleep, waking up during the night, nightmares, and difficulty waking in the morning, while it did not affect daytime sleeping and fatigue (Keyhanmehr et al., 2018). Inhaling *R. damascena* essential oil in cancer patients could pointedly increase sleep duration and quality, while it decreased sleep latency (Heydarirad et al., 2019). It has been shown that aromatherapy with *R. damascena* essential oil could improve sleep quality and reduce daytime sleepiness in patients with chronic renal failure (Jodaki et al., 2021). Another study evaluated the effect of inhaling *R. damascena* essential oil on elderly people. The data revealed that this compound did not affect sleep disturbance, but it remarkably improved sleep quality and sleep efficacy. It also decreases daytime

dysfunction (problems that a person has throughout the day as a result of sleeplessness). The authors reported that the efficiency of *R. damascena* essential oil was more than *C. aurantium* (Khalili et al., 2021). The probable effects of *R. damascena* aromatherapy were assessed in a clinical trial carried out on operating room personnel during the COVID-19 pandemic. The findings revealed that *R. damascena* oil was successful in increasing sleep quality in comparison with the placebo group (Mahdood et al., 2022). Another recent clinical trial reported that aromatherapy with *R. damascena* essential oil increased sleep quality in burn patients (Mokhtari et al., 2023).

Finally, it has been shown that *R. damascena* has potential hypnotic effects in both animal and human studies. Aromatherapy with *R. damascena* essential oil has been found to improve sleep quality and reduce sleep disturbances in various patient populations, including critical care unit patients, cancer patients, and elderly individuals (Table 2). However, depending on the route of administration and the patient group, the effects of *R. damascena* on sleep parameters may differ. More research is required to determine the mechanisms of action and effective dosages of *R. damascena* for enhancing sleep quality in various patient populations.

### 3.4 | *Curcuma longa* (turmeric)

Turmeric, also known as *C. longa*, is a member of the ginger family, Zingiberaceae, and is a perennial, flowering, rhizomatous plant, and herbaceous that is native to Southeast Asia and India. The roots of turmeric are commonly used as a spice in cooking and have attracted considerable attention from the culinary, scientific, and medical communities. Curcumin, sourced from *C. longa*, has been known for its therapeutic effects for centuries, but its underlying mechanisms and key components have only recently been studied. In traditional medicine, turmeric is prescribed to treat liver problems, respiratory disorders, anorexia, sinusitis, and allergies (Razavi et al., 2021). At present, turmeric has been found to possess a variety of properties, such as hypnotic (Um et al., 2021), anxiolytic and antidepressant (Ceremuga et al., 2017), renoprotective (Hosseini et al., 2024), and neuroprotective (Abass et al., 2020) properties. Furthermore, numerous studies have demonstrated the anti-inflammatory (Liu et al., 2022) and antioxidant (Ghasemzadeh Rahbardar & Hosseinzadeh, 2024; Razavi & Hosseinzadeh, 2020) properties of turmeric.

#### 3.4.1 | In vivo

*Curcuma longa* rhizome was found to have hypnotic effects by interacting with the GABAergic and nitrgic systems. The co-administration of *C. longa* with midazolam was observed to enhance barbiturate-induced hypnosis (Ishola et al., 2020). In mice, ingesting turmeric extract increased NREM duration without delta activity, decreased sleep latency, and inhibited H<sub>1</sub>R agonist-induced rise in action potentials in the hypothalamic neurons (Um et al., 2021). Moreover, the administration of curcuminoids (curcumin,

demethoxycurcumin, and bisdemethoxycurcumin) to mice in pentobarbital-induced sleep test modulated H<sub>1</sub>R activity, enhanced sleep duration, and NREM duration. They also decreased sleep latency without altering the REM and delta activity (Um et al., 2022).

#### 3.4.2 | Clinical trial

The results of a clinical trial illustrated that the administration of curcumin preparation (Longvida®) to healthy older people had no significant effect on sleep parameters (Cox et al., 2020).

To sum up, it has been found that turmeric has hypnotic effects in mice through interacting with the GABAergic and nitrgic systems, which can enhance sleep duration and decrease sleep latency. However, a clinical trial on healthy older individuals did not reveal any appreciable effects on sleep metrics. To completely comprehend the possible advantages of turmeric for sleep, more study is required.

### 3.5 | *Valeriana officinalis* (valerian)

*Valeriana officinalis* L., known as Valeriana, is a Caprifoliaceae family plant. It grows naturally in temperate parts of Europe, Asia, and North America (Azizi et al., 2020). Traditional herbal therapy has employed the roots of *V. officinalis* as a sedative, anti-spasmodic, anxiolytic, antiemetic, and antidepressant, as well as to treat cardiac arrhythmia and sleep problems (Azizi et al., 2020; Mulyawan et al., 2020a; Rajabalizadeh et al., 2022). Glutamate, valepotriates, hydroxy pinosresinol, alkaloids (catinidin, actinidin, valerian, and valerianin), and volatile oil (valerinic acid, sesquiterpenes, and monoterpene bornyl acetate) are all components of *V. officinalis*. In GABAergic neurons, glutamine is transformed into GABA after crossing the blood-brain barrier. The main ingredient in *V. officinalis* is valerenic acid, which slows the breakdown of GABA in the brain caused by catabolism enzymes and causes sleepiness (Mulyawan et al., 2020a).

#### 3.5.1 | In vitro/in vivo

The findings of a study illustrated that *V. officinalis* extracts (50%, 100% methanol, petroleum ether, as well as dichloromethane) and valerenic acid have a strong binding affinity to the 5-HT<sub>5a</sub> receptor (Dietz et al., 2005). The oral administration of *V. officinalis* root ethanolic extract to rats improved sleep quality as well as delta activity during NREM and reduced sleep latency. Although it displayed no significant effect on total times of wakefulness, NREM, and REM sleep (Shinomiya et al., 2005). The results of an in vivo investigation revealed that inhalation of *V. officinalis* root odor could increase sleep duration and GABA activity, while it decreased sleep latency as well as GABA transaminase activity in rats (Komori et al., 2006). The oral administration of *V. officinalis* ethanolic extract to rats resulted in decreased sleep latency. However, it showed no remarkable effect on total times of wakefulness, delta activity, NREM and REM sleep



**TABLE 2** The effect of *Rosa damascena* and *Curcuma longa* on sleep.

Compound/extract	Study design	Doses/duration	Results	References
<i>R. damascena</i> (Damask Rose)				
In vivo				
Ethanollic, aqueous and chloroformic extracts of <i>R. damascena</i>	In vivo, mice	100, 500 and 1000 mg/kg, i.p.	Ethanollic and aqueous extracts: ↑ Sleeping time Chloroformic extract: no hypnotic effect	(Rakhshandah & Hosseini, 2006)
Clinical trial				
<i>R. damascena</i> essential oil	Clinical trial, 60 CCU patients	3 drops, 4 nights	↑ Sleep quality	(Hajibagheri et al., 2014)
<i>R. damascena</i> extract	Clinical trial, 90 patients undergoing angiography	15 drops every 8 h, p.o.	↑ Sleep quality	(Babaei et al., 2016)
<i>R. damascena</i> essential oil	Clinical trial, 30 children with sleep disorder	5 drops, 2 weeks	– No effect on daytime sleeping and fatigue ↓ Resistance to sleep, waking up during the night, nightmare, difficulty waking in the morning	(Keyhanmehr et al., 2018)
<i>R. damascena</i> essential oil	Clinical trial, 54 cancer patients	5 drops of 5% and 10%, 2 weeks	↑ Sleep quality, sleep duration ↓ Sleep latency	(Heydarirad et al., 2019)
<i>R. damascena</i> essential oil	Clinical trial, 40 patients with chronic renal failure	3 drops with concentrations of 10%, a month	↑ Sleep quality ↓ Daytime sleepiness	(Jodaki et al., 2021)
<i>R. damascena</i> essential oil	Clinical trial, 60 elderly people	3 drops, 3 nights	– No effect on sleep disturbance ↑ Sleep quality, sleep efficacy ↓ Daytime dysfunction	(Khalili et al., 2021)
<i>R. damascena</i> oil	Clinical trial, 80 operating room personnel	5 drops (0.34 mL), 31 days	↑ Sleep quality	(Mahdood et al., 2022)
<i>R. damascena</i> oil	Clinical trial, 60 burn patients	5 drops of 40% <i>R. damascena</i> oil, 3 nights	↑ Sleep quality	(Mokhtari et al., 2023)
<i>C. longa</i> (Turmeric)				
In vivo				
<i>C. longa</i> rhizome	In vivo, mice	100, 200, 400 mg/kg, p.o.	– The highest level of hypnosis potentiation: 100 mg/kg – The hypnotic effects were reversed by flumazenil or N <sup>G</sup> -nitro-L-arginine pre-treatment	(Ishola et al., 2020)
<i>C. longa</i> ethanol aqueous solution	In vivo, male C57BL/6N mice	10–100 mg/kg, p.o.	– Inhibited H <sub>1</sub> R agonist-induced increase in action potentials in the hypothalamic neurons ↑ NREM duration without delta activity ↓ Sleep latency	(Um et al., 2021)
Curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin)	In vivo, mice		– Modulated H <sub>1</sub> R activity ↑ Sleep duration, NREM duration ↓ Sleep latency without altering the REM and delta activity	(Um et al., 2022)
Clinical trial				
Curcumin preparation (Longvida®)	Clinical trial, 80 healthy older people	400 mg/day containing 80 mg curcumin, 12 weeks, p.o.	– No significant effect on sleep	(Cox et al., 2020)

Abbreviations: H<sub>1</sub>R, histamine H1 receptor; NREM, non-rapid eye movement; REM: rapid eye movement.

(Tokunaga et al., 2007). The obtained data of another in vivo study illustrated that receiving *V. officinalis* (aqueous extract, valerian compound preparation, aqueous extract and ethyl acetate extraction phase, water extract of valerian n-butanol phase) pointedly increased sleep duration and decreased sleep latency in mice (Zhao et al., 2015). In another investigation, the comparative analysis of the sedative effects of *V. officinalis* extract and melatonin was conducted using multiple parameters, including locomotor activity, performance index, body wall contractions, and displacement velocity in *Drosophila melanogaster* flies and larvae. The data demonstrated that exposure to *V. officinalis* root aqueous extract resulted in a significant increase in locomotor activity, performance index, body wall contractions, and displacement velocity compared to the effects observed with melatonin. These findings indicated that the sedative effects of *V. officinalis* root extract were superior to those of melatonin in the tested model system (Cheuczuk et al., 2017). Furthermore, *V. officinalis* ethanolic extract could enhance sleep duration and NREM period and attenuate sleep latency in rodents. The authors claimed that valerenic acid significantly contributed to the binding activity of the extract on the GABA receptor (Choi et al., 2018). It has been reported that oral administration of *V. officinalis* dry root or rhizome to mice increased gamma-aminobutyric acid type A receptor subunit beta3 (GABRB3), the gene that encodes the GABA<sub>A</sub> receptor  $\beta_3$  subunit, gene mRNA expression (Mulyawan et al., 2020b). The oral administration of *V. officinalis* hydroalcoholic extract suffering from neuropathic pain decreased REM sleep, increased NREM sleep, the density and frequency of sleep spindle, as well as sleep quality (Soltani et al., 2021).

### 3.5.2 | Clinical trial

It has been reported that administration of the aqueous extract of *V. officinalis* root to men increased sleep quality and decreased sleep latency, while it did not affect dream recall, night awakenings, or somnolence the next morning (MUNOZ-BOX, 1982). The administration of *V. officinalis* root extract to men with mild insomnia decreased sleep latency in comparison with the placebo group (Leathwood & Chauffard, 1985). Another study investigated the effects of *V. officinalis* root extract on sleep in two groups of young, healthy participants—one group slept at home, and the other in a sleep laboratory. Both doses of valerian extract reduced perceived sleep latency and wake time after sleep onset, with increased motor activity in the middle third of the night. However, only the higher dose was tested in the sleep laboratory, and no significant differences from placebo were found. Nevertheless, the changes in sleep measures and motor activity were consistent with those observed at home (Balderer & Borbély, 1985). Moreover, the administration of Nature's Way (*V. officinalis* root) to Hispanic symptomatic volunteers for 2 weeks decreased insomnia. Nature's Way also showed a time-dependent or dose-response relationship in ameliorating insomnia (Dominguez et al., 2000). Likewise, it has been demonstrated that *V. officinalis* could reduce insomnia in patients with stress-induced insomnia (Wheatley, 2001). It has been indicated that a single-dose oral

prescription of *V. officinalis* to healthy elderly had no sedative effect (Glass et al., 2003). Furthermore, the single dose administration of *V. officinalis* dry root ethanolic extract to sleep-disturbed individuals did not affect psychometric measure and electroencephalogram (EEG) parameters (Diaper & Hindmarch, 2004). An internet-based clinical trial assessed the effect of *V. officinalis* on insomnia and reported that this plant had no significant effect in ameliorating insomnia (Jacobs et al., 2005). Pure *V. officinalis* extract was also unsuccessful in reducing insomnia in non-organic insomnia (Koetter et al., 2007). Another clinical trial examined the effect of a single dose or 2-week administration of Nature's Resource® (*V. officinalis* root extract) in older women with insomnia. The data displayed that Nature's Resource® did not have any significant effect on sleep latency, self-rated sleep quality, sleep efficiency, and wake after sleep onset (Taibi et al., 2009). Besides, *V. officinalis* pure ground raw root could not significantly improve sleep in patients undergoing cancer treatment, but it ameliorated the secondary outcomes and decreased fatigue endpoints, drowsiness, and trouble with sleep (Barton et al., 2011). However, it has been shown that *V. officinalis* root extract to postmenopausal women with insomnia significantly increased sleep quality (Taavoni et al., 2011). Likewise, findings of another clinical trial on hemodialysis patients disclosed that *V. officinalis* dried root could remarkably improve sleep quality in these patients (Tammadon et al., 2021) (Table 3).

Finally, data from in vitro, in vivo, and clinical investigations suggests that *V. officinalis* has potential sleep-enhancing properties. In vitro investigations revealed that *V. officinalis* extracts and valerenic acid have a high affinity for the 5-HT<sub>5A</sub> receptor, indicating a probable mechanism of action. Following oral treatment or inhalation of *V. officinalis* extracts, in vivo experiments demonstrated increases in sleep quality, delta activity during NREM sleep, and reduced sleep latency. Increased GABA activity and decreased GABA transaminase activity were linked to these effects. Clinical trials reported conflicting findings, with some demonstrating beneficial effects on sleep quality and decreased sleep latency while others found no considerable changes over placebo. It is important to note that the results of clinical trials differed according to elements including dosage, administration time, and the population being studied. Therefore, the exact underlying mechanisms of action of *V. officinalis* must be clarified, and the best dosage and formulation for improving sleep in various populations must be identified. Despite the contradictory results, the total body of research points to *V. officinalis* as a potential herbal treatment for sleep-related problems. However, care should be taken when using it, and healthcare specialists should be consulted for detailed advice.

### 3.6 | *Lactuca sativa* (lettuce)

Lettuce, scientifically known as *L. sativa* L., is a popular vegetable from the Asteraceae family that is cultivated all over the world (Ahn et al., 2023; Shi et al., 2022). Aside from nutritional use, lettuce has received attention for its potential benefits in the treatment of

**TABLE 3** The effect of *Valeriana officinalis* on sleep.

Compound/extract	Study design	Doses/duration	Results	References
<i>V. officinalis</i> (Valerian)				
In vitro				
<i>V. officinalis</i> extracts and valerenic acid	In vitro, CHO-K1 cell	50 µg/mL	<ul style="list-style-type: none"> <li>– Strong binding affinity to the 5-HT<sub>5a</sub> receptor</li> <li>– Weak binding affinity to the 5-HT<sub>2b</sub> and the serotonin transporter</li> </ul>	(Dietz et al., 2005)
In vivo				
<i>V. officinalis</i> root ethanolic extract	In vivo, male Wistar rats	1000 and 3000 mg/kg, p.o.	<ul style="list-style-type: none"> <li>– No effect on total times of wakefulness, NREM, REM sleep</li> <li>↑ Sleep quality, delta activity during NREM</li> <li>↓ Sleep latency</li> </ul>	(Shinomiya et al., 2005)
<i>V. officinalis</i> root odor	In vivo, male Wistar rats		<ul style="list-style-type: none"> <li>↑ Sleep duration, GABA activity</li> <li>↓ Sleep latency, GABA transaminase activity</li> </ul>	(Komori et al., 2006)
<i>V. officinalis</i> ethanolic extract	In vivo, male Wistar rats	300 and 1000 mg/kg, p.o.	<ul style="list-style-type: none"> <li>– No effect on total times of wakefulness, NREM, REM sleep, delta activity</li> <li>↓ Sleep latency</li> </ul>	(Tokunaga et al., 2007)
<i>V. officinalis</i> (aqueous extract, valerian compound preparation, aqueous extract and ethyl acetate extraction phase, water extract of valerian n-butanol phase)	In vivo, ICR mice	<i>V. officinalis</i> (aqueous extract, valerian compound preparation): 200 mg/kg, 10 days, i.g. Aqueous extract and ethyl acetate extraction phase: 10 mg/kg, 10 days, i.g. Water extract of valerian n-butanol Phase: 25 mg/kg, 10 days, i.g.	<ul style="list-style-type: none"> <li>↑ Sleep duration</li> <li>↓ Sleep latency</li> </ul>	(Zhao et al., 2015)
<i>V. officinalis</i> root aqueous extract	In vivo, Canton-S flies	1, 2.5, 5, and 10 mg/mL, 15 min	<ul style="list-style-type: none"> <li>↓ Locomotor activity, performance index, body wall contractions, displacement velocity</li> </ul>	(Cheuczuk et al., 2017)
<i>V. officinalis</i> ethanolic extract	In vivo, ICR mice and Sprague-Dawley rats	160 mg/kg, p.o.	<ul style="list-style-type: none"> <li>↑ Sleep duration, NREM</li> <li>↓ Sleep latency</li> </ul>	(Choi et al., 2018)
<i>V. officinalis</i> dry root or rhizome	In vivo, male BALB/c mice	2.5 mg/10 g, 5 mg/10 g, 7 days, p.o.	<ul style="list-style-type: none"> <li>↑ GABRB3 gene mRNA expression</li> </ul>	(Mulyawan et al., 2020b)
<i>V. officinalis</i> hydroalcoholic extract	In vivo, male Wistar rats	400 mg/kg, 3 weeks, p.o.	<ul style="list-style-type: none"> <li>↑ NREM sleep, sleep spindle density and frequency, sleep quality</li> <li>↓ REM sleep</li> </ul>	(Soltani et al., 2021)
Clinical trial				
<i>V. officinalis</i> root aqueous extract	Clinical trial, 128 men	400 mg, p.o.	<ul style="list-style-type: none"> <li>– No effect on dream recall, night awakenings, somnolence the next morning</li> <li>↑ Sleep quality</li> <li>↓ Sleep latency</li> </ul>	(MUNOZ-BOX, 1982)
<i>V. officinalis</i> root aqueous extract	Clinical trial, 8 men with mild insomnia	450 or 900 mg	<ul style="list-style-type: none"> <li>↓ Sleep latency</li> </ul>	(Leathwood & Chauffard, 1985)
		450 and 900 mg	<ul style="list-style-type: none"> <li>↓ Sleep latency</li> </ul>	

(Continues)

TABLE 3 (Continued)

Compound/extract	Study design	Doses/duration	Results	References
<i>V. officinalis</i> root aqueous extract	Clinical trial, 18 healthy young subjects			(Balderer & Borbély, 1985)
Nature's Way ( <i>V. officinalis</i> root)	Clinical trial, 23 male and female Hispanic symptomatic volunteers	470 mg, 2 weeks, p.o.	↓ Insomnia	(Dominguez et al., 2000)
<i>V. officinalis</i>	Clinical trial, 24 patients with stress-induced insomnia	600 mg, 6 weeks, p.o.	↓ Insomnia	(Wheatley, 2001)
<i>V. officinalis</i>	Clinical trial, 14 healthy elderly	400 and 800 mg, p.o.	– No sedative effect	(Glass et al., 2003)
<i>V. officinalis</i> dry root ethanolic extract	Clinical trial, 16 sleep disturbed participants	300 and 600 mg, single dose, p.o.	– No effect on EEG parameter or psychometric measure	(Diaper & Hindmarch, 2004)
<i>V. officinalis</i>	Clinical trial, 391 individuals with anxiety or insomnia	2 capsules (each containing 3.2 mg of valerenic acids; 1% valerenic acid in extract), 28 days, p.o.	– No significant effect on insomnia	(Jacobs et al., 2005)
Pure <i>V. officinalis</i> extract	Clinical trial, 30 non-organic insomnia	500 mg, 4 weeks, p.o.	– No effect on sleep latency	(Koetter et al., 2007)
Nature's Resource® ( <i>V. officinalis</i> root extract)	Clinical trial, 16 older women with insomnia	300 mg, single dose or 2 weeks, p.o.	– No effect on sleep latency, self-rated sleep quality, sleep efficiency, and wake after sleep onset	(Taibi et al., 2009)
<i>V. officinalis</i> pure ground raw root	Clinical trial, 227 people undergoing cancer treatment	450 mg, 8 weeks, p.o.	↓ Fatigue endpoints, drowsiness, trouble with sleep	(Barton et al., 2011)
<i>V. officinalis</i> root extract	Clinical trial, 100 postmenopausal women with insomnia	530 mg, twice a day, 4 weeks, p.o.	↑ Sleep quality	(Taavoni et al., 2011)
<i>V. officinalis</i> dried root	Clinical trial, hemodialysis patients	530 mg, a month, p.o.	↑ Sleep quality	(Tammadon et al., 2021)

Abbreviations: 5-HT<sub>2b</sub>, 5-hydroxytryptamine 2B receptor; 5-HT<sub>5a</sub>, 5-hydroxytryptamine 5A receptor; EEG, electroencephalogram; GABA, gamma-aminobutyric acid; GABRB3, gamma-aminobutyric acid type A receptor subunit beta3; mRNA, messenger ribonucleic acid; NREM, non-rapid eye movement; REM: rapid eye movement.

anxiety, insomnia, oxidative damage, cancer, and neurodegenerative diseases (Ahn et al., 2023; Harsha & Anilakumar, 2013). When the stems and leaves of lettuce are cut, a bitter-tasting latex is produced, which contains lactucin, an alkaloid known for its nerve stabilization and insomnia-relieving properties. Notably, lettuce contains quercetin-3-glucuronide that interacts with GABA receptors, contributing to various physiological effects such as sedation, improvement of sleep, and anticonvulsant activity (Wesołowska et al., 2006).

### 3.6.1 | In vivo

A group of researchers examined the hypnotic effects of *L. sativa* hydroalcoholic extract, water fraction, ethyl acetate fraction, and n-butanol fraction on pentobarbital-induced sleep in mice. The data revealed that the *L. sativa* hydroalcoholic extract increased sleep duration and n-butanol fraction enhanced the duration of sleep and

reduced sleep latency that was comparable to diazepam effects (Ghorbani et al., 2013). The administration of *L. sativa* seed and leaf ethanolic extracts to mice has been shown to increase sleep duration (Kim et al., 2017). A pentobarbital-induced sleep test in rodents showed that the oral administration of *L. sativa* leaf ethanolic extract remarkably enhanced sleep duration, NREM sleep, and delta wave. It also lessened sleep latency in animals. The extract also displayed affinity to the GABA<sub>A</sub>-benzodiazepine receptor (Hong et al., 2018). The administration of *L. sativa* leaf ethanolic extract to rodents in pentobarbital-induced sleep test caused an increase in sleep duration, NREM sleep, besides a reduction in sleep latency, REM sleep, and the binding of [<sup>3</sup>H]-flumazenil. The findings also confirmed the affinity of lactucin and lactucopicrin to the GABA<sub>A</sub>-benzodiazepine receptor (Kim et al., 2019). An in vivo study evaluated the hypnotic effect of *L. sativa* leaf ethanolic extract on sleep disturbance control in oxidative stress-induced vertebrate and invertebrate models. Exposing *D. melanogaster* that experienced vibration stress to *L. sativa* leaf

**TABLE 4** The effect of *Lactuca sativa* and *Portulaca oleracea* on sleep.

Compound/extract	Study design	Doses/duration	Results	References
<i>L. sativa</i> (Lettuce)				
In vivo				
<i>L. sativa</i> hydroalcoholic extract, water fraction, ethyl acetate fraction, and n-butanol fraction	In vivo, male albino mice	<i>L. sativa</i> hydroalcoholic extract: 50, 100, 200, 400 mg/kg, i.p. Water fraction, ethyl acetate fraction, and n-butanol fraction: 200 mg/kg, i.p.	<i>L. sativa</i> hydroalcoholic extract: ↑ Sleep duration n-butanol fraction: ↑ Sleep duration ↓ Sleep latency	(Ghorbani et al., 2013)
<i>L. sativa</i> seed and leaf ethanolic extracts	In vivo, ICR mice	80 and 160 mg/kg, p.o.	↑ Sleep duration	(Kim et al., 2017)
<i>L. sativa</i> leaf ethanolic extract	In vivo, male ICR mice and Sprague–Dawley rats	80, 100, 120, 140, and 160 mg/kg, p.o.	↑ Sleep duration, NREM, delta wave ↓ Sleep latency	(Hong et al., 2018)
<i>L. sativa</i> leaf ethanolic extract	In vivo, ICR mice and Sprague–Dawley rats	80, 100, 120, and 160 mg/kg, p.o.	↑ Sleep duration, NREM sleep ↓ Sleep latency, REM sleep	(Kim et al., 2019)
<i>L. sativa</i> leaf ethanolic extract	In vivo, <i>Drosophila melanogaster</i> , male Sprague–Dawley rats and ICR mice	<i>Drosophila melanogaster</i> : 0.5 and 1%, 14 days Rats: 80 and 120 mg/kg, 9 days, p.o. Mice: <i>L. sativa</i> leaf ethanolic extract: 80, 120 mg/kg Quercetin-3-glucuronide: 5, 10, 20 mg/kg	↑ Sleep duration, gene expression of SOD ↑ Sleep quality, NREM sleep, expression levels of GABA <sub>A</sub> receptor ↑ Sleep duration ↓ Sleep latency	(Jo et al., 2021)
<i>L. sativa</i> leaf extract	In vivo, male ICR mice and Sprague–Dawley rats	50, 80, 100, and 150 mg/kg, p.o.	↑ Sleep duration, NREM movement, delta waves, gene and protein expression of GABA <sub>A</sub> , GABA <sub>B</sub> , and 5-HT1A ↓ Awake time increased by caffeine administration	(Ahn et al., 2023)
Clinical trial				
<i>L. sativa</i> seed oil	Clinical trial, 60 individuals with insomnia with or without anxiety	1000 mg, a week	↓ Sleeping difficulty	(Yakoot et al., 2011)
<i>L. sativa</i> seeds	Clinical trial, 100 pregnant women with insomnia	1000 mg, 2 weeks, p.o.	↑ Sleep quality ↓ Insomnia	(Pour et al., 2018)
<i>L. sativa</i> seed oil	Clinical trial, 67 children with sleep disorders	7 drops on temporal areas and forehead, 3 weeks	↓ Bedtime issues, excessive daytime sleepiness, night awakenings, problems in regularity and duration of sleep	(Ranjbar et al., 2020)
<i>L. sativa</i> seed syrup	Clinical trial, 50 patients with breast cancer with sleep disorders or insomnia	5 mL twice daily, 4 weeks	↑ Sleep quality, sleep duration, habitual sleep efficacy ↓ Sleep disturbance	(Mosavat et al., 2022)
<i>P. oleracea</i> (Purslane)				
In vivo				
<i>P. oleracea</i> aqueous decoction extract	In vivo, male albino mice	25, 50, and 75 mg/kg, i.p.	↑ Sleep duration	(Miladi-Gorji et al., 2011)
<i>P. oleracea</i> hydroalcoholic extract, ethyl acetate fraction, N hexane	In vivo, mice	<i>P. oleracea</i> hydroalcoholic extract: 12.5, 25, 50, 75, and 100 mg/kg, i.p.	↑ Sleep duration ↓ Sleep latency  All fractions: ↑ Sleep duration	(Hamed et al., 2019)

(Continues)

TABLE 4 (Continued)

Compound/extract	Study design	Doses/duration	Results	References
fraction, water fraction		Ethyl acetate fraction, N hexane fraction, water fraction: 25 mg/kg, i.p.	N hexane fraction: ↓ Sleep latency	

Abbreviations: GABA, gamma-aminobutyric acid; HT1A, 5-hydroxytryptamine receptor 1A; NREM, non-rapid eye movement; REM, rapid eye movement; SOD, superoxide dismutase.

ethanolic extract resulted in increased sleep duration and gene expression of SOD. Besides, the administration of *L. sativa* leaf ethanolic extract to rats increased sleep quality, NREM sleep, and expression levels of the GABA<sub>A</sub> receptor. Moreover, receiving *L. sativa* leaf ethanolic extract and quercetin-3-glucuronide in mice in pentobarbital-induced sleep tests improved sleep duration and attenuated sleep latency (Jo et al., 2021). The hypnotic effect of *L. sativa* leaf extract was examined in rodents and it was observed that the extract enhanced sleep duration, NREM movement, as well as delta waves, and attenuated awake time augmented as a result of caffeine administration. Besides, the extract increased gene and protein expression of GABA<sub>A</sub>, GABA<sub>B</sub>, and 5-hydroxytryptamine receptor 1A (5-HT<sub>1A</sub>) (Ahn et al., 2023) (Figure 3).

### 3.6.2 | Clinical trial

A clinical trial examined the effect of *L. sativa* seed oil on individuals with insomnia and found that it could significantly reduce sleep difficulties (Yakoot et al., 2011). The findings of a clinical trial indicated that the administration of *L. sativa* seeds to pregnant women with insomnia could successfully decrease insomnia and improve sleep quality (Pour et al., 2018) (Table 4). Using *L. sativa* seed oil in children with sleep disorders resulted in reduced bedtime issues, excessive daytime sleepiness, night awakenings, and problems in regularity and duration of sleep (Ranjbar et al., 2020). Evaluating the effect of *L. sativa* seed syrup in breast cancer patients indicated that the syrup could remarkably increase sleep quality, sleep duration, habitual sleep efficacy, and reduce sleep disturbance (Mosavat et al., 2022).

In summary, research on *L. sativa* studies has shown its potential as a natural remedy for improving sleep. In animal models, *L. sativa* extracts, notably the leaf and seed extracts, displayed hypnotic effects by increasing sleep duration, decreasing sleep latency, and improving sleep quality. The extracts increased the expression of sleep-related genes and receptors, as well as their affinity for the GABA<sub>A</sub>-benzodiazepine receptor. Clinical investigations involving people suffering from insomnia and sleep problems have also found that *L. sativa* supplementation improves sleep quality and reduces sleep difficulties. These findings indicate that *L. sativa* has potential as a natural sleep aid, but more research is needed to better understand its mechanisms of action, as well as to discover ideal dosages and long-term effects.

## 3.7 | *Portulaca oleracea* (purslane)

Purslane (*P. oleracea* L.), a member of the Portulacaceae Juss family, is a plant found worldwide, primarily in tropical and subtropical regions. Since ancient times, *P. oleracea* has been used in traditional cuisine and folk medicine as a vermifuge, antiseptic, and febrifuge, as well as in the treatment of headache, cough, burns, arthritis, shortness of breath, and intestine, stomach, and liver disorders in many parts of the world. Previous studies have highlighted the pharmacological effects of *P. oleracea*, which include analgesic, antidepressant, anxiolytic, and antiepileptic (Forouzanfar et al., 2019; Jalali & Ghasemzadeh, 2022; Jalali & Ghasemzadeh, 2023).

### 3.7.1 | In vivo

The administration of *P. oleracea* aqueous decoction extract to mice could significantly increase sleep duration (Miladi-Gorji et al., 2011). The hypnotic effects of *P. oleracea* hydroalcoholic extract, ethyl acetate fraction, N hexane fraction, and water fraction were assessed in mice receiving pentobarbital. The findings illustrated that *P. oleracea* hydroalcoholic extract could pointedly improve sleep duration and attenuate sleep latency. Moreover, all fractions enhanced sleep duration, however, only the n-hexane fraction was successful in reducing sleep latency (Hamed et al., 2019) (Table 4).

These findings suggest that *P. oleracea* may have the potential as a natural sleep aid although further exploration is required in sleep-related research.

## 3.8 | *Citrus aurantium* (sour orange)

Sour orange, formally known as *C. aurantium*, is a fragrant tree that grows to a height of about five meters and is found all over the world. *C. aurantium* components such as the peel, blossoms, and leaves are frequently used for their beneficial benefits (Hosseini, Pkan, et al., 2011).

### 3.8.1 | In vitro/in vivo

The administration of *C. aurantium* peel essential oil, hexanic, and dichloromethane fractions to mice resulted in an increased duration



**TABLE 5** The effect of *Citrus aurantium*, *Melissa officinalis*, and *Lippia citriodora* on sleep.

Compound/extract	Study design	Doses/duration	Results	References
C. aurantium (Sour orange)				
In vitro/In vivo				
C. aurantium peel essential oil, hexanic and dichloromethane fractions	In vivo, Swiss male mice	0.5 or 1.0 g/kg	↑ Sleep duration	(Carvalho-Freitas & Costa, 2002)
C. aurantium flowers aqueous extract	In vivo, male NMRI rats	62.5, 125, 250 mg/kg, i.p.	↑ Sleep duration ↓ Locomotor activity, the onset of sleep, the firing rate of basolateral amygdale neurons	(Motaghi et al., 2016)
C. aurantium flowers essential oil	In vitro, SH-SY5Y cells	2.5 and 5 µL/mL	↑ Cl <sup>-</sup> influx	(Liang et al., 2021)
	In vivo, ICR mice	40, 80, and 120 mg/kg, 14 days, p.o./i.p.	↑ Sleep duration ↓ Sleep latency, locomotor activity	
Clinical trial				
C. aurantium essential oil	Clinical trial, 60 elderly people	3 drops, 3 nights	↑ Sleep quality	(Khalili et al., 2021)
C. aurantium essential oil	Clinical trial, 80 postmenopausal women with sleep disturbances	2 drops, twice a day, for 4 consecutive days in a week, 4 weeks	↑ Sleep quality, sleep duration ↓ Sleep disturbances, sleep latency	(Abbaspoor et al., 2022)
C. aurantium essential oil	Clinical trial, 68 pregnant women with sleep disorders	5 drops, twice a day, every day, a month	↑ Sleep quality	(Mohammadi et al., 2022)
C. aurantium blossom distillate	Clinical trial, 60 mothers in neonatal intensive care unit-admitted infants	100 mL, three times a day, 7 days	↓ Sleep disorder score	(Dehghan et al., 2023)
M. officinalis (Lemon balm)				
Clinical trial				
Cyracos® (M. officinalis extract)	Clinical trial, 20 volunteers with anxiety disorders and sleep disturbances	600 mg, 15 days, p.o.	↓ Insomnia	(Cases et al., 2011)
M. officinalis syrup	Clinical trial, 40 patients with chronic heart failure	12 mL, 4 weeks, p.o.	↑ Sleep duration ↓ Sleep latency	(Aliakbari, 2018)
M. officinalis aerial parts	Clinical trial, 80 patients with chronic stable angina	3 g, 8 weeks, p.o.	↓ Sleep disturbance	(Haybar et al., 2018)
M. officinalis essence	Clinical trial, 100 females with premenstrual syndrome	600 mg, twice a day, 3 months (during menstrual cycle), p.o.	↓ Sleeping disorder	(Heydari et al., 2018)
M. officinalis dried leaf powder	Clinical trial, 80 in-patients underwent coronary artery bypass surgery	500 mg, three times a day, 7 days, p.o.	↑ Sleep quality	(Soltanpour et al., 2019)
M. officinalis hydroalcoholic extract	Clinical trial, 60 patients with type 2 diabetes mellitus and symptoms of depression	700 mg, 12 weeks, p.o.	– No significant effect on sleep quality	(Safari et al., 2023)
L. citriodora (lemon verbena)				
In vivo				
L. citriodora leaves ethanolic and aqueous extracts and verbascoside	In vivo, male mice	L. citriodora ethanolic and aqueous extracts: 50, 100, and 200 mg/kg, i.p. Verbascoside: 25, 50, and 100 mg/kg, i.p.	↑ Sleeping time ↓ Sleep latency	(Razavi et al., 2017)
L. citriodora leaves ethanolic extract	In vivo, male ICR mice	25, 50, and 100 mg/kg	↑ Relaxation	(Sabti et al., 2019)

(Continues)

TABLE 5 (Continued)

Compound/extract	Study design	Doses/duration	Results	References
Clinical trial				
<i>L. citriodora</i> leaves ethanolic extract	Clinical trial, 40 patients with stress and poor sleep quality	400 mg, 8 weeks, p.o.	↑ Feeling better rested, duration of deep sleep and REM, sleep quality	(Martínez- Rodríguez et al., 2022)

of sleep (Carvalho-Freitas & Costa, 2002). It has been reported that intraperitoneal administration of *C. aurantium* flowers aqueous extract to rats enhanced sleep duration, attenuated locomotor activity and the onset of sleep. It also reduced the firing rate of basolateral amygdale neurons (Motaghi et al., 2016). A study evaluated the effect of exposing SH-SY5Y cells to *C. aurantium* flowers essential oil increased  $\text{Cl}^-$  influx and this effect could be blocked by the antagonists of the  $\text{GABA}_A$  receptor. The in vivo part of the research examined the effect of *C. aurantium* flowers essential oil on mice. The findings showed that the essential oil augmented the sleep duration and reduced sleep latency as well as locomotor activity in animals (Liang et al., 2021) (Table 5).

### 3.8.2 | Clinical trial

It has been shown that aromatherapy with *C. aurantium* essential oil in elderly people increases the quality of sleep (Khalili et al., 2021). Another clinical trial examined the effect of aromatherapy with *C. aurantium* essential oil in postmenopausal women with sleep disturbances. The findings displayed that the essential oil pointedly enhanced sleep quality and duration, while it decreased sleep disturbances and sleep latency (Abbaspoor et al., 2022). Similarly, it has been demonstrated that using *C. aurantium* essential oil for aromatherapy in pregnant women with sleep disorders could remarkably improve their sleep quality (Mohammadi et al., 2022). Furthermore, a recent clinical trial reported that the administration of *C. aurantium* blossom distillate to mothers with neonatal intensive care unit-admitted infants reduced sleep disorder scores in comparison with the mothers in the placebo group (Dehghan et al., 2023).

Finally, both in vitro and in vivo investigations have indicated that *C. aurantium* extracts and essential oils can increase sleep duration, reduce sleep latency, and mitigate sleep disorders in several laboratory methods. Clinical research with *C. aurantium* essential oil has further confirmed its effectiveness in improving sleep quality. These results suggest that the essential oil of *C. aurantium* flowers may interact with several neurotransmitter systems involved in sleep regulation. The observed increase in  $\text{Cl}^-$  influx and its blockade by  $\text{GABA}_A$  receptor antagonists indicate a possible interaction with the  $\text{GABA}_A$ ergic system, which is known to play a crucial role in promoting sleep. Additionally, the reduction in locomotor activity suggests a possible modulation of the serotonergic system, which is involved in the regulation of wakefulness and arousal. Furthermore, the biological significance of these findings lies in the potential therapeutic importance of the

essential oil of *C. aurantium* flowers as a natural sleep aid. The ability to prolong sleep duration and shorten sleep latency underscores its potential as an alternative or supplement to conventional sleep medications. However, it is important to point out that further research is needed to elucidate the exact mechanisms of action and to fully understand the interactions of *C. aurantium* flower essential oil with the serotonergic,  $\text{GABA}_A$ ergic, and nitrenergic systems. Additionally, the specific components of the essential oil responsible for the observed effects should be identified to determine their biological significance and possible therapeutic applications.

## 3.9 | *Melissa officinalis* (lemon balm)

*Melissa officinalis*, sometimes known as lemon balm, is a medicinal plant in the Lamiaceae family. The plant contains a variety of bioactive compounds including flavonoids, volatile oils, and phenolic acids. Lemon balm has antioxidant, neuroprotective, anxiolytic, and spasmolytic effects (Virchea et al., 2021; Reddy et al., 2019).

### 3.9.1 | Clinical trial

The prescription of Cyracos® (*M. officinalis* extract) to volunteers with anxiety disorders and sleep disturbances could pointedly reduce their insomnia (Cases et al., 2011). It has been shown that the administration of *M. officinalis* syrup to patients with chronic heart failure increased their sleep duration and decreased their sleep latency versus the placebo group (Aliakbari, 2018). Moreover, it has been disclosed that the supplementation of *M. officinalis* aerial parts to patients with chronic stable angina significantly reduced their sleep disturbances (Haybar et al., 2018). Taking *M. officinalis* essence capsules could significantly reduce sleeping disorders in females with premenstrual syndrome (Heydari et al., 2018). In another clinical trial, patients who underwent coronary artery bypass surgery were administered *M. officinalis* dried leaf powder capsules for a week. The results of the study showed a significant improvement in their sleep quality (Soltanpour et al., 2019). In contradiction to other investigations, a clinical trial reported that *M. officinalis* hydroalcoholic extract had no significant effect on sleep quality in patients with type 2 diabetes mellitus and symptoms of depression (Safari et al., 2023).

In summary, *M. officinalis* has demonstrated potential effects in enhancing sleep efficiency and lowering sleep disturbances in a variety of individuals. Studies have shown it to be useful in lengthening

sleep duration, decreasing sleep latency, and treating sleeping disorders. Moreover, the inconsistency in the findings of these studies on the effects of *M. officinalis* on sleep quality could be attributed to a variety of factors, including differences in study design, such as differences in sample size, duration of intervention, dosage, and administration methods. However, more research is needed to fully understand its probable benefits and limitations in promoting healthy sleep patterns.

### 3.10 | *Lippia citriodora* (lemon verbena)

*Lippia citriodora* (lemon balm), a member of the Verbenaceae family, is a plant native to South America. The leaves of this plant possess a lemon-like fragrance and are commonly used in beverages and food. Lemon verbena has a long history in traditional medicine where it has been utilized for treating a range of disorders such as digestive issues, fever, skin infections, and colds (Amin et al., 2018). Furthermore, *L. citriodora* has been employed for its anti-spasmodic, anti-pyretic, and sedative properties. The primary constituents of this popular herb consist of flavonoids, iridoids, phenolic acids, and phenylpropanoids, with verbascoside being particularly noteworthy due to its potent antioxidant effects. Extracts derived from *L. citriodora* and verbascoside exhibit diverse pharmacological effects including antioxidant, analgesic, memory enhancing, and neuroprotective properties (Amin et al., 2016; Amin et al., 2018; Tandisehpanah et al., 2022).

#### 3.10.1 | In vivo

It has been illustrated that the administration of *L. citriodora* ethanolic and aqueous extracts and verbascoside to mice increased sleeping time and reduced sleep latency. These effects were reversed by flumazenil (Razavi et al., 2017). Likewise, *L. citriodora* ethanolic extract could significantly induce relaxation in mice by modulating cyclic adenosine monophosphate (cAMP) and calcium (Sabti et al., 2019).

#### 3.10.2 | Clinical trial

Taking *L. citriodora* leaves ethanolic-aqueous extract resulted in increased feeling of better rested, enhanced duration of deep sleep and REM, as well as sleep quality in patients with poor sleep quality and stress (Martínez-Rodríguez et al., 2022).

In summary, studies have demonstrated the potential benefits of *L. citriodora* and verbascoside in enhancing sleep-related parameters both in animal models and human subjects by increasing sleeping time and relaxation, besides decreasing sleep latency. These effects might be induced by modulating cAMP and calcium levels as well as GABA receptors. These findings highlight the potential of *L. citriodora* as a natural agent for sleep-related concerns, demanding further research and exploration of its therapeutic applications.

## 4 | CONCLUSION

In conclusion, our review of the literature indicates that herbal medicines may have some benefits in treating insomnia when compared to currently used drugs. Some herbs that have shown promise in this regard include *L. sativa*, *C. aurantium*, *M. officinalis*, *R. damascena*, *R. officinalis*, *C. sativus*, *C. longa*, *V. officinalis*, and *L. citriodora*. There are several underlying mechanisms in which these plants exert their hypnotic effects including interaction with the nitrenergic and GABAergic system and other neurotransmitter pathways that are important in regulating sleep and stimulating delta activity during NREM sleep by interacting with the 5-HT<sub>5a</sub> receptor.

One of the potential benefits of herbal medicines is its natural and alternative approach to treating insomnia. Compared to currently used medications, herbal medicines may offer a safer profile with fewer side effects. In addition, herbal remedies often have a long history and may offer a holistic approach to sleep health. However, it is important to note that while these herbal remedies show promising results, it is important to seek medical advice before using them for sleep-related problems. Further research, including well-designed clinical trials and in-depth mechanistic studies, is needed to confirm their efficacy, determine optimal dosing and ensure their safety in different populations.

By advancing our understanding of the mechanisms and potential benefits of herbal interventions, we pave the way for evidence-based herbal treatments that can complement existing approaches to insomnia management. However, further high-quality studies are needed to firmly establish the clinical efficacy of the plants.

## 5 | FUTURE DIRECTIONS

Despite the promising findings regarding the therapeutic potential of herbal medicines for insomnia, several areas require further exploration. Future research should focus on the multiple aspects to enhance our understanding and utilization of herbal interventions in this field, including: (1) Identifying the key molecular mechanisms that will help elucidate the precise interactions of these herbs with neurotransmitter systems, receptors, and signaling pathways involved in sleep regulation. (2) Conducting clinical trials that involve diverse populations and utilize methodologies to establish the optimal dosages, treatment durations, and potential interactions with conventional medications. (3) Quality control measures, including identification of bioactive compounds and assessment of purity, should be implemented to guarantee the safety and efficacy of herbal products used for insomnia. (4) Understanding the pharmacokinetic and pharmacodynamic interactions will help healthcare professionals in prescribing appropriate combinations or adjusting dosages to prevent unfavorable complications. (5) Comprehensive safety assessments are necessary to determine the long-term effects and potential risks associated with the prolonged use of herbal medicines for insomnia. This includes monitoring for any adverse events, evaluating potential toxicity, and

assessing herb-drug interactions in specific populations such as pregnant women, children, and elderly individuals. (6) Determining the synergistic effects and optimizing the combination of herbal remedies with existing treatments will contribute to more comprehensive and effective management strategies.

## AUTHOR CONTRIBUTIONS

**Mahboobeh Ghasemzadeh Rahbardar:** Data curation; investigation; writing – original draft. **Hossein Hosseinzadeh:** Conceptualization; supervision; writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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