

ORIGINAL ARTICLE

A review of available herbal medicine options for the treatment of chronic insomniaZOHREH POURSALEH ¹, MAHMOOD KHODADOOST ^{1*}, ENSIEH VAHEDI ², MOHAMMAD MAHDI AHMADIAN-ATTARI ³, MAHDI JAFARI ⁴, ERFAN POURSALEH ^{5,6}¹Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran²Chemical Injuries Research Center, Systems Biology and Poisonings Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran³Evidence-based Phytotherapy and Complementary Medicine Research Center, Alborz University of Medical Sciences, Karaj, Iran⁴Department of Clinical Psychology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran⁵Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran⁶Young Researchers and Elite Club, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran*Corresponding Author: Mahmood Khodadoost, Associate professor Department of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Email: mkhodadoost@sbm.ac.ir Tel: +98- 21-88773521-5, Fax: +98-21-88795008**ABSTRACT****Background:** Insomnia is a universal health problem that affects the health and quality of life of people worldwide. During the last decade treatment of insomnia with herbal has been introduced to be effective but unfortunately, the safety and efficacy of these medicines are currently uncertain. However, the administration of various herbal medicines for insomnia is increasing mainly due to the diversity of various adverse effects of western medication.**Objective:** The present study is aimed to investigate available herbal medicine options for the treatment of chronic insomnia.**Method:** All demanded data were retrieved from electronic databases, Natural Medicines, TCMID, Natural Medicines Comprehensive Database, MedlinePlus, PubMed, EMBASE, and Google Scholar. Among them, randomized clinical trials were chosen precisely to be investigated more for seeking any additional information related to the treatment of chronic insomnia. All related papers in English and Persian languages included in the study criteria. At first, 261 articles were chosen to be investigated, then after screening all articles based on the PRISMA method, 83 qualified articles remained to be investigated carefully.**Results:** Herbal plants with medical properties as sedative agents are obtaining more and more attention because they contain various types of natural bioactive metabolites with the lowest rate of adverse effects. Moreover, these novel medicines are highly economic, with high efficacy while could be available easily.**Conclusion:** The data from this study demonstrated that medical plants could yield sedative activity and some of them are effective for insomnia, but we must not forget that further clinical trials are demanded to approve this.**Keywords:** Sleep disorders, Chronic insomnia, Herbal medicine, Alternative medication, Treatment.**INTRODUCTION**

Sleep is one of the most important biological processes that are fundamentally needed for improving health and well-being [1]. Insomnia is a sleep disorder in which the person has trouble falling and staying asleep. Insomnia is specified through difficulty in Initiating and maintaining sleep and being unable to get back to sleep [2]. Based on a recent study by Liu [3] it was reported that the prevalence of sleep problems among adults is increasing. As they reported this disease affects people worldwide particularly with higher rates in females, older people, and those with psychiatric or medical illness.

Despite the high prevalence of insomnia, it's not recognized appropriately and remained untreated [4]. Insomnia has a lot of negative effects on the health and well-being of individuals. Moreover, it could cause impairment of the performance, mood, or/and cognition during the day which significantly affects the individual's

life, their families, and also society [5]. Additionally, individuals who experience insomnia more likely to demand to visit hospitals and physicians, the possibility of fatal road accidents among them is higher, are more susceptible to traffic accidents, also with greater absenteeism [6]. In a recent study by Dong et al [7], it was reported that insomnia could be followed by a wide range of diseases such as heart disease, increased risk of mortality, type 2 diabetes, risk of obesity, disorders of memory, concentration, and disturbances in mood.

Based on the clinical studies carried out in the recent decade, a wide range of treatments are available for insomnia that is categorized in the **Table 1**. Using cognitive behavioral therapy has been proved to be effective in the treatment of insomnia in nearly half of patients [8]. Nevertheless, Arnedt et al [9] stated that cognitive-behavioral therapy should not be underutilized as primary therapy for insomnia.

Table 1. Available treatment approaches for insomnia Enrich this reference. Derived per Hassinger et al [10]		
Type of intervention	Include	Usage
Pharmacological	Short-term benzos (triazolam, quazepam, temazepam, flurazepam, and estazolam)	- Impairment of the ability to cope - Severe symptomatic distress
Non-pharmacological	Cognitive-behavioral therapy (CBT)	- Insomnia and sleep hygiene
Complementary and alternative medicines	- Manual therapies (massage, kinesiology) - Ingestive therapies (supplements and herbal medicine)	- Insomnia and sleep hygiene

Various studies have mentioned the effectiveness of herbal medicine in the treatment of sleep disorders mainly due to their low side effects in comparison with other treatment options. The main mechanisms of action of herbal medicines in the treatment of patients with insomnia are related to the synthesis of Novel γ -Aminobutyric Acid (GABA) and GABA-metabolizing enzymes which both affect sleep outcomes. However, herbal remedies cause few side effects as well as nearly higher benefits than benzos. Here we are trying to examine if herbal medicines are effective in the treatment of insomnia as well as collecting the most effective data from available databases in this regard [11].

EMBASE, and Google Scholar were investigated precisely. Databases were searched from 2010 to May 2021 with the most appropriate keywords of Sleep disorders, Chronic insomnia, Herbal medicine, Treatment. Articles were searched in both languages of Persian and English. After searching all the databases, 236 articles were selected for screening with the PRISMA method. Then 31 and 163 articles were deleted due to unrelated and similarity issues respectively. After that, 25 further articles with related subjects were searched and chosen to be included in the main inclusion criteria of this study. Finally, 18 articles were added to this criterion from other available databases and the total number of the articles reached 83. In this study, there was not any limitation of sex, race, age, and general demographic characteristics of participants in included clinical trials. Moreover, it was tried to include all available tested herbal medicines. As could be seen from Figure (1), all the included articles were selected according to the PRISMA standard criteria.

METHOD

Aimed to investigate the effectiveness of herbal medicine for the treatment of chronic insomnia, various databases of Natural Medicines, TCMID, Natural Medicines Comprehensive Database, MedlinePlus, PubMed,

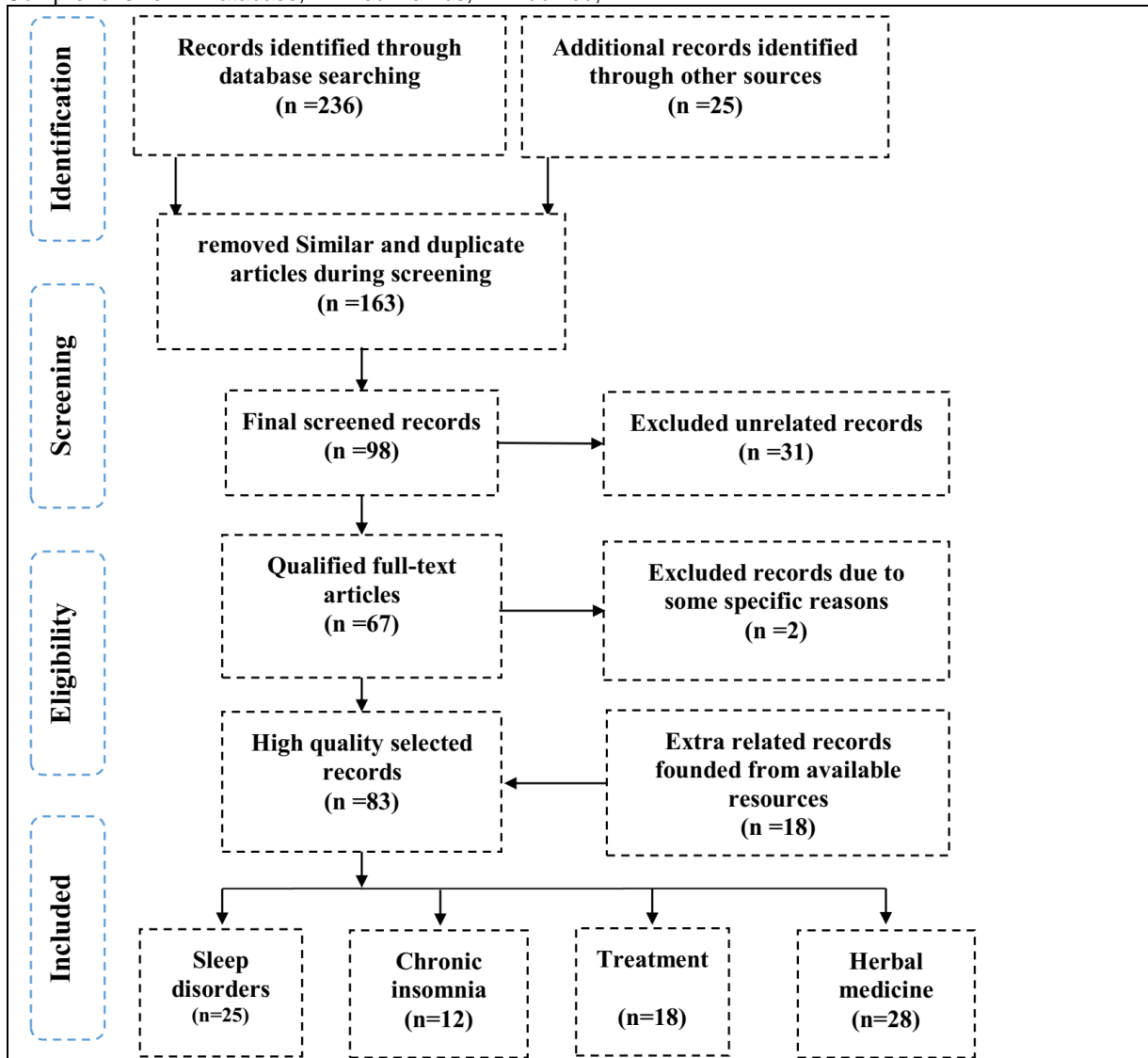


Figure 1. Schematic process of selection of articles in the present study based on the PRISMA method

Epidemiology: Sleep patterns vary with age so that the number of awakenings through the night will be increased, the amount of time spent in deep sleep decreases, and the total time awake increases with age [12]. Anyway, there is not a specific and standardized definition of normal sleep. Additionally, there is also a lack of community-based epidemiologic studies of sleep patterns to investigate the age, mental, and physical health of individuals and its related socioeconomic variables [13]. As defined by Herrero San Martin et al [14] insomnia is a subjective complaint so that individuals with insomnia disorder have more sleep difficulties than normal sleepers. Individuals who have difficulty with sleep are divided into three groups [15]:

- People who get into sleep difficulty and not maintaining sleep
- People who not maintain sleep easily and not getting to sleep
- People who not easily got to sleep and could not maintain sleep.

Some other related studies have reported that the prevalence of insomnia is higher in women, older individuals, widowed women, unemployed individuals,

people belonging to lower socioeconomic groups, and particularly in those with psychiatric and/or medical disorders [16]. Moreover, it has been reported that the association of insomnia with age is lower than its association with dyspnea, nocturia, pain, psychopathology characteristics, and nocturnal myoclonus [17]. Prevalence of anxiety and major depressive disorder (MDD) among individuals suffering from insomnia is documented appropriately and it's proved that insomnia is not a cause of depression or anxiety but is its early symptom [18]. In this regard, without conducting precise longitudinal surveys, any judgment about the prognosis of insomnia could not yield appropriate outcomes.

Unfortunately, there is not much precise information about the differences in the types of insomnia concerning etiology, pathophysiology, and pathogenesis. In their study, Perlis and Gehrman [19], revealed that each of the insomnia types, and potentially the subtypes, occur as a result of different biopsychosocial pathological processes. Various types of insomnia are shown in **Table 2**. Following the studies carried out by Morin et al [20] the etiology and pathophysiology of insomnia are mentioned in **Table 3**.

Table 2. Various types of insomnia. Derived based on Bjorøy et al [21]

Type	Definition	Causes
Primary Sleep Insomnia	Disability to sleep well cause irritability, dozing off, and fatigue	General reasons and not a health problem.
Secondary Sleep Insomnia	When a primary medical illness is responsible for insomnia	It may happen due to some specific health problems such as heartburn, cancer, arthritis, asthma, and depression.
Acute Insomnia	This type of insomnia may last one night to few weeks	<ul style="list-style-type: none"> - Environmental factors such as noise or light. - Changing the place where you sleep - Any physical discomfort include pain, or/and sleeping in an uncomfortable place - Using some medicines - Particular illness - jet lag
Chronic Insomnia	A situation when someone is unable to sleep well at least three nights a week for three months or longer	Long-term medical conditions include; <ul style="list-style-type: none"> - Chronic pain - Restless legs syndrome (RLS) - Fibromyalgia - Hyperthyroidism (overactive thyroid) - Gastroesophageal reflux disease (GERD) - Diabetes - Congestive heart failure (CHF) -Chronic obstructive pulmonary disease (COPD) - Long-term inflammatory disease (asthma)

Table 3. The etiology and pathophysiology of insomnia [19]

Causes	Expression of the disorder
Organic in nature (Physiological Insomnia)	<ul style="list-style-type: none"> - Genetic and/or biological abnormalities -The sleep homeostasis system Underlying neural circuitry of sleep and/or wake control
Lifestyle factors or behaviors (Sleep Hygiene Insomnia Disorder)	-Affect the individual's sleep and/or wake control system

Treatment: The main process of treatment of chronic insomnia starts with an initial quick diagnosis of its signs and then treating its related underlying psychological or/and medical problems. In the treatment process of insomnia, identification, and elimination of those behaviors that may aggravate insomnia signs helps in the treatment of insomnia [22]. After it was diagnosed, a long-term drug may be prescribed for chronic insomnia. U.S. Food and Drug Administration (FDA) has introduced some specific

medications for the treatment of insomnia that could be applied. Anyway, since the side effect of these drugs could not be ignored, some behavioral techniques include reconditioning, sleep restriction therapy, and relaxation therapy has been approved to be useful. Additionally, alternative medicine has attracted a lot of attention in this regard, too. Some recent researches showed that a combination of behavioral interventions with pharmacologic

agents or alternative medicine may be more effective than either approach alone [18].

Pharmacologic treatments: Treatment of insomnia with drugs could be effective just in the alleviation of it in short-time periods and would not be sufficient for long-term management of patients with chronic insomnia. It's while the combination of these agents with behavioral therapy results in a long-lasting recovery in sleep patterns of individuals with insomnia symptoms [23]. Although the efficacy and safety of all available pharmacotherapeutic agents are approved by FDA through clinical trials, it is recommended to follow up five basic principles which

characterize rational pharmacotherapy for the treatment of chronic insomnia [24].

1. Each agent should be administered at its lowest effective dose,
2. Use its appropriate intermittent dosing (2-4 times weekly),
3. The agents should be prescribed only for short-terms of use,
4. The medications should be Discontinued gradually,
5. The patients should remain alert for difficulty initiating or maintaining sleep after discontinuation. Some of the most appropriate therapeutic options for chronic insomnia are summarized in **Table 4**.

Table 4. Appropriate therapeutic options for chronic insomnia				
	Agents	Mechanism of Action	Advantages	Side Effects
First-line pharmacotherapy (These drugs carry the highest level of evidence supporting efficacy and safety)	Benzodiazepines [25,26]	- Improve the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) - Improve the inhibitory action of GABA	- Decrement of the sleep onset - Improving the total duration of sleep - Have sedative, anxiolytic, myorelaxant, and anticonvulsant properties	- Anterograde amnesia - Rebound insomnia - Confusion and cognitive dysfunction in elderly patients - in patients with untreated sleep apnea or chronic pulmonary insufficiency should be used cautiously - Prolonged use may cause emotional blunting, difficulty in new learning abilities, and discontinuation syndrome
	Zopiclone [27]	- Slows down the Rapid eye movement (REM)	- Decreases nocturnal awakenings and sleep latency and improves the total sleep time	- Reported rebound effects are low - With a recommended dosage of 3.75–7.5 mg it has the lowest side effects
	Zolpidem [28]	- Binding with the GABA-A receptor complexes with an alpha-1 subtype.	- Decreases nocturnal awakenings and sleep latency and improves total sleep time - The lowest rebound effects - Minimal anxiolytic, anticonvulsant, and myorelaxant characteristics	- Headache, dizziness, and drowsiness
	Zaleplon [29]	- Binding with the GABA-A receptor complexes with an alpha-1 subtype.	- Improves time to sleep onset	- Has the lowest side-effects at recommended doses (5–10 mg). - Not very effective in decrement of nighttime awakenings
	Eszopiclone [30]	- It acts as an agonist at benzodiazepine (BNZ) receptors.	- Well absorbed orally	- Day-time drowsiness - Headaches - Loss of coordination - Decrement of sexual desire - Severe period pain - Enlargement of breast
	Ramelteon [31]	- It acts by binding to the melatonin receptors in the suprachiasmatic nucleus or nuclei (SCN).	- It is more effective in elderly patients	- Fatigue - Dizziness - Nausea - Insomnia exacerbated
Second-line pharmacotherapy (These drugs have a moderate level of evidence supporting their efficacy and tolerability)	Antidepressants [32]	- Acts as a tricyclic antidepressant (TCAs) - Prevents reuptake of neurotransmitters through selective receptors	- Improve sleep - Appropriate sleep continuity	- Anticholinergic effects (Use it at the lowest effective dose)
	Trazodone [33]	- Acts through both serotonin transporter and serotonin type 2 receptors	- Improves sleep continuity - It is not addictive - Could be used in corporation with stimulating antidepressants (SSRIs) - Sedative properties	- Risk of adrenergic blockade - Orthostatic hypotension (Particularly in elderly patients) - Priapism - Prolonged erection (rare)
	Antihistamines [34]	- Acts through blocking the binding of histamine to its receptors	- Effective for mild insomnia	- Long-term sedative effects - Anticholinergic effects - Psychomotor impairment

Alternative medications: Despite the effectiveness of pharmacologic treatments in the treatment of acute insomnia, some concerns are available regarding the administration of these agents, such as dependency and also their side effects [35]. Therefore, all the individuals who are affected by insomnia at any level and have concerns about the safety and effectiveness of these pharmaceutical agents, are seeking out novel alternative therapies [36]. Due to the holistic healthcare beliefs, the requirement for active healthcare participation, improving the behavior of health-awareness, discontent of patients from Western medicine, motivated insomnia patients to follow up complementary and alternative medicine (CAM) over conventional therapy [37].

In a clinical practice study by Poursaleh et al [38], a case study of treatment of insomnia based on Persian medicine therapy was carried out. Through which a patient with chronic insomnia underwent Persian medicine center during different periods. The patient was advised to follow the principles of Persian medicine therapy including eating and drinking, quality of sleep, appropriate activity. In this regard, all of the phlegmatic eating regimens were deleted, and healthier foods such as honey syrup, and pea soup were recommended instead of water. Based on their studies, some of the best well-known traditional medicines such as almond extract (as brain boosters), rose water syrup, and saffron, and a mixture of apples, rose water, and saffron (as enlivening foods and herbs) were recommended to be used by the patient. They finally, reported that through their traditional therapy a considerable improvement in the quality of sleep was achieved, and also the patient was very satisfied with the outcomes of their therapy [38].

Herbal Medicines and Chronic Insomnia: Since chronic insomnia possibly lasts more than 3 nights per week for 3 months or longer, patients with this disorder are always seeking a novel therapeutic option with lower adverse effects. In this regard, various types of herbal medicines with proven effectiveness on chronic insomnia have been introduced [39]. During the last decade, multiple complex formulas and medicinal herbs have been used for insomnia. The mechanism of chronic insomnia is particularly caused by abnormalities in various pathways, such as glutamate and aspartate amino acids, circadian cycle, cytokines, cortisol level, and Gamma-aminobutyric acid (GABA) receptor [40]. Any disturbances in GABAergic function would cause changes in the expressing level of the GABA receptor. These changes not only cause changes in the mechanism of depression and anxious behavior but causes sleep disorder. All these changes in the GABA receptors are induced by the sedative-hypnotic effects of some drugs [41].

Aiming to eliminate these disorders as a result of consumption of various types of medicines, nowadays herbal medicines are applied as a broad range of complementary/alternative treatments of insomnia. However, there is a question about the fact that which of the introduced herbal medicines are a safer and more effective treatment option for insomnia [42].

They are generally considered safe and effective with very few reported adverse events [39] [50]. Some plants

are often used as sedative agents that are summarized in **Table 5**.

Some systematic reviews have been carried out to collect the available evidence about the effectiveness of herbal medicines in the treatment of insomnia with experimental evidence to support the available traditional evidence about the effectiveness of Valerian, Chamomile, Kava Kava, and Suanzaoren [52].

Valerian: Previous research has reported that the efficiency of Valerian in the treatment of insomnia is quite variable, with various dosages from 200 to 1000 mg. However, there is not a specific study to investigate the most appropriate dosage of valerian in patients who suffer from chronic insomnia. In a study by Zare et al [53], it was reported that valerian is effective in the treatment of chronic insomnia. In a similar study by Shinjo et al [54] it was reported that valerian decreases sleep latency, improves the wake time after sleep, and also improves the total time of sleep. Based on their reports all of these effects could be achieved in a dosage of 900mg in a five-day duration.

Based on the studies carried out by Fernandez-San et al [55], using Valerian at a dose of 300mg per day for two weeks could decrease sleep latency and slow-wave sleep latency. Moreover, Mineo et al [56] reported that administration of valerian at a dose of 200mg per day for two weeks decreases night awakening and improves sleep duration. In their study, Roh et al [57] revealed that using valerian at a dose of 300 mg and 600 mg in comparison with placebo showed that valerian is not effective at improving sleep electroencephalogram (EEG), mood, or psychometric measure. In a similar study, Gammoh et al [58] reported that there are no differences between using valerian at a dosage of 600mg for two weeks and placebo in terms of improving sleep latency, wake after sleep onset, and sleep quality. Tammadon et al [59] demonstrated that valerian produces similar results to oxazepam, with both agents improving sleep quality from baseline. Based on their reports, the levels of satisfaction in patients treated with valerian was over 80%. Similarly, in a study by Taavoni et al [60], it was reported that valerian could be used for improving the quality of sleep particularly in postmenopausal women suffering from insomnia.

Chamomile: Chamomile has been administered traditionally for the treatment of sleep-related disorders. Due to containing Flavonoids and Apigenin, Chamomile is capable of binding to the benzodiazepine receptors in the brain and then promoting a tranquilizing effect which makes it an effective agent for chronic insomnia [61]. Zick et al [62] reported that Chamomile could significantly improve the quality of sleep particularly in older patients with insomnia. It's while they reported that using Chamomile in the dosage of 270mg and for 4 weeks could not improve sleep onset latency, wake after sleep onset time, sleep duration, nocturnal awakening, day time functioning, and sleep quality effectively [62]. However, further clinical trials should be carried out for specifying the most appropriate consumption dosage to end any available doubts about the effectiveness of Chamomile in the treatment of chronic insomnia.

Table 5. Medicinal plants as sedative agents						
Plants	Family	Pharmacological activity	How to be used	Constituents	Usage	Side effects
Rosa damascene [43]	Rosaceae	- antimicrobial -Sedative	flowers	- Volatile oil - Gallic acid - Quercitrin - Tannic acid - Quercitannic acid - Malic acid - Tartaric acid	- Headache - Insomnia - Uterine inflammation - Primary dysmenorrhea	-irritation of the nose and throat
Capparis decidua [44]	Capparaceae	- Sedative - Hypoglycemic -Anticonvulsant - Antidiarrheal - Hypolipidemic -Anti-inflammatory - Anticancer	Barks, roots	- Sitosterol - Capparisidine - Pentacosane - Tricantanol - Stachydrine - Capparisine - Capparisidine	- Diarrhea - Dysentery - Toothache	-Central nervous system depressant activity
Lavandula officinalis [45]	Lamiaceae	- Relaxant - Anodyne - Antidepressant - Nerve tonic - Antimicrobial - Anti-inflammatory - Vulnerary - Digestive -Antiepileptic - Antioxidant	flowers	- Methanol extract	- Hypnotic & sedative	-Constipation -Headache -Increased appetite; -Skin irritation
Anthocephalus chinensis [46]	Madder	- Antioxidant activities	Leaves, bark	- Ethanol extract - Ketamine	Insomnia	-Anaphylactic shock -Pyrogen reaction -Serum sickness
Erythrina Indica Lam [47]	Legumes	Antioxidant	Roots	Extract of E.Indica Lam	Cardiovascular problems	- Earache -Menstrual pain -irregular menstruation -Furunculosis -Dysuria
Kaempferia galangal [48]	Ginger	- Antispasmodic, - Anti-inflammatory, - Anticancer	Rhizome	- Ethyl cinnamate (Sedative) - Ethyl trans-p-methoxycinnamate (Sedative) - N-hexane extract of K. galanga	Rheumatoid Arthritis Anxiety -Depression -Restlessness -Insomnia	- Drop-in energy levels - Lack of appetite, - Excessive urination, - Diarrhea, - Coma, - Even death
Ixora pavetta Vahl [49]	Madder	- Sedative activity - Analgesic - Anti-inflammatory - Antipyretic	Flowers	Amylnitrite	Insomnia	-
Valerian [50]	Honeysuckle	- Sedative - Anxiolytic - Myorelaxant	Roots	- Epoxy-iridoid - Valepotriates	Insomnia	Not safe in pregnancy and young children
Gypsywort [51]	Mints	- provide calm - temperate the excitement - lower the activity of CNS - Improves the duration of sleep - anti-insomnia activity	Aerial parts	- Flavonoids - Terpenes - Saponins - Extract of Lycopos europaeus with diazepam	- Insomnia - Nervousness - Bleeding - Breast pain	Thyroid enlargement

Kava Kava: Kava-kava is extracted from the roots of the Piper methysticum that is used for its sedative, aphrodisiac, and stimulatory effects particularly in the South Pacific [63]. Kava-kava contains a wide range of active compounds the best known amongst which are the kava pyranones such as kavain, desmethoxyyangostin, yangonin, dihydromethysticin, methysticin, and dihydrokavain. But unfortunately, it is not well-known which of them is responsible for any anxiolytic properties [64].

The root of this plant is traditionally used for making beverages with sedative and euphoria effects. Consumption of kava-kava returns to a traditional culture that believed that it could be drunk like alcoholic beverages. Nowadays, many people consume kava-kava

supplements for the treatment of anxiety. Although based on the recommendations of the World Health Organization (WHO) using kava-kava in its traditional form causes the lowest level of health risk, administration of its extracts and supplements it in an inappropriate dosage, may cause liver toxicity [65]. It has been reported that kava-kava interacts with the GABAA receptor, as the main target for hypnotic agents which improves the quality of sleep [66].

Unfortunately, most of the researches related to the administration of kava-kava for the treatment of insomnia is limited to animal studies. It is believed that a particular type of kavalactone may be capable of providing a sedative effect, called Kevain. One of the available researches about the effectiveness of kava-kava for humans reported

that a daily 200mg extract of kava-kava provides significant relief from insomnia after two weeks [67].

Suanzaoren: Suanzaoren is one of the best-known herbal medicines with sedative effects in traditional Chinese medicine. Suanzaoren are dried ripe seeds of Jujube red Chinese date which has been used for the treatment of anxiety, insomnia, and hyperhidrosis among Chinese people [66].

Suanzaoren consisted of a complex mixture of phytochemical compounds such as Spinosin, Jujuboside A, Sanjoinine A, and some other flavonoids with hypnotic and sedative effects which essentially moderated by serotonergic and GABAergic system. In this regard, in another study by Liu et al [68] it was declared that Suanzaoren is capable of being used as an alternative treatment.

Based on a study by Mahmoudi et al [69] it was observed that Suanzaoren has different pharmacological effects that include improving the immune system function, reduce the blood's lipid levels, protecting the functions of cardiovascular systems, and prevention of anxiety. He et al [70] demonstrated that Suanzaoren plus Diazepam creates

better results compared to Diazepam alone. Moreover, they cited that the side effects of using Suanzaoren are fewer than Diazepam.

Persian Medicine: Persian medicine (PM) in Iran comprises valuable information in the field of sleep disorders from decades ago. It is based on essential principles called preventive health measures which consisted of six main steps effective in the prevention and treatment of diseases. All of these six health measures which consisted of drink, food, air, quality of sleep, retention/release, rest/activity, and psychological events are required for keeping a healthier life [71]. In this regard, one of the main aspects of having a good lifestyle is having good sleep which has a critical role in maintaining health. PM texts introduce a low-risk approach toward diagnosis and treatment for sleep disorders that mainly is based on the administration of herbal medicines. Some of these herbs have been reported as sedative agents and potential therapies for insomnia including Saffron, Sweet Viola, Poppy, Almond, and Lettuce that are summarized in **Table 6** [38].

Options	Usage	Effectiveness	Mechanism of action	Instruction	What does it contain	Possible side effects
Saffron [72-74]	- In anxiety and insomnia cases - Prevention and treatment of cardiovascular diseases - Insomnia	- Antidepressants - Anti-apoptotic	Saffron could affect glutaminergic, serotonergic, and γ -aminobutyric acid (GABA)-ergic systems	Decoction of saffron as a syrup	Contains crocin, crocetin, safranal, and kaempferol antioxidants	When used more than 26 weeks as medicine (Xerostomia, drowsiness, agitation, anxiety, nausea or vomiting, flushing, and change in appetite)
Viola odorata [75-77]	- In neurologic disease - cough, fever, common cold, and headache, and insomnia	Hypnotic and sedative effects	Increment of cell membrane permeability and subsequent cellular disruption.	Nasal dropping of violet oil	Vitamin C, mucilage, methyl salicylate, saponins, alkaloid, and glycoside	There isn't enough valid information in this regard
Sweet almond [78]	- Improves the quality of sleep - Improving learning and memory - Treating amnesia and Alzheimer's disease	Sedative effects	Contains inhibitory amino acids that depresses the activity of post-synaptic cells	Eating almond daily (about 10 pieces)	- Vitamin A - Vitamin E - Omega-3 fatty acids - Zinc - Aqueous extract of almond	May cause toxicity in the body (Because it contains hydrocyanic acid)
Papaver somniferum [79,80]	- Headache - Cough - Insomnia - Cardiac asthma - Biliary colic	- Analgesic - Narcotic - Sedative - Stimulant - Nutritive - Antiallodynic activity - Analgesics activity - Antitussive activity - Anti-diarrheal activity - Anti-anxiety activity	Through binding to opioid (μ and δ) receptors in the brain, produces analgesia	Papaver somniferum juice	- Morphine - Codeine - Thebaine - Porphyroxine	- Abuse/addiction - Aberrant drug-taking behavior - Increased risk of mortality
Lettuce [81-83]	In insomnia	- Improves sleep quality - Anticonvulsant activity	- Analgesic, - Anti-inflammatory, antioxidant	Seed oil	- Vitamins A, C, E, K and B group, - Omega-3, and omega-6, - Potassium, calcium, sodium, folic acid, magnesium, iodine, iron, selenium and zinc	- Decrease libido - May cause allergic reactions in some people

CONCLUSION

Insomnia is a sleeping disorder that unfortunately is increasing among individuals mainly due to different sociodemographic and clinical factors. Aiming to manage this health problem various medical strategies are available. Among them, herbal medicines are detected to be useful mainly because of their few side effects in comparison with pharmacotherapeutic agents. Based on the studies evaluated in the present review, Kava Kava, Chamomile, and Valerian are among the best well-known herbal agents that are detected to be effective in the treatment of insomnia even in chronic levels. Additionally, based on PM studies Saffron, Sweet Viola, Poppy, Almond,

and Lettuce are among the most well-known herbs with sedative effects that could be used to treat insomnia. However, it shouldn't be forgotten that some of the investigated trials were of poor methodological quality, so examining these herbal agents in higher-quality randomized controlled trials is an essential demand in this area.

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