Review

Herbal Medications to Manage Insomnia: An Overview of Clinical Trials Using Herbal Treatment for Insomnia

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Abstract

Insomnia is one of the most prevalent sleep disorders worldwide which significantly affects the quality of life. Pharmacological and non-pharmacological approaches have been applied in managing insomnia. The risk of tolerance and dependence on conventional medications and their other side effects leads the surveys to complementary and alternative medicine. This overview aimed to compile the clinical trials on herbal remedies in managing insomnia for facilitating future studies on medicinal plant in this issue. The keywords "Medicinal plant", "Herbal medicine" in combination with "Hypnotic and sedative", "Insomnia" or "Sleep" were searched through PubMed, Google Scholar, and Scopus electronic databases from 1st January 2000 to 31st August 2020. Then, all clinical trials focusing on the efficacy of medicinal plants on insomnia were collected. Based on the inclusion and exclusion criteria, 36 articles were selected, included 16 medicinal plants (23 studies) as a single herb and 13 polyherbal formulations. The most prevalent route of administration among these trials was oral. *Matricaria chamomilla* L., *Valeriana officinalis* L., *Viola odorata* L., and *Passiflora incarnata* L. were among the most prevalent effective herbal medicines on insomnia. Also, the modulation of the GABAergic system was the most common target of these medicinal plants. Herbal remedies can be introduced as safe and effective alternatives for conventional medications in managing insomnia. The popular herbal medicines, such as *M. chamomilla*, *V. officinalis*, *V. odorata*, are suitable for further therapeutic development. Other cited medicinal plants in this review can be more investigated in improvement of sleep.

Keywords: Herbal medicine; Hypnotics; Insomnia; Medicinal plant; Sedative; Sleep

Introduction

Insomnia is a common sleep disorder defined by some characterizations, including problems in falling asleep, keeping asleep, and waking up in the early morning [1,2]. Persistent sleep difficulties (3 nights or more/week) and continued of them for over 3 months are necessary to diagnose this disorder. Insomnia triggers daytime functioning impairment and notably reduced the quality of life by its complications, such as fatigue, reduced energy, mood disturbances, and decreased cognitive functions [3,4]. Insomnia can arise primarily or be comorbid with psychiatric conditions like anxiety and depression in a duplex relationship manner [5,6]. There is a communication between

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insomnia and non-communicable disorders like hypertension as well [7]. Also, insomnia is linked with ethnicity, low-education, unemployment, poor health, and age [8]. The prevalence of insomnia is reported more attention in health care settings.

Treatment of insomniacs is mainly classified as non-pharmacological and pharmacological approaches. Cognitive behavioral therapy for insomnia (CBT-I) is the first line of insomnia treatment. Although CBT-I is safe and effective, its availability is confined to special healthcare settings [9]. γ-aminobutyric acid (GABA), melatonin, histamine, or orexin/hypocretin receptors are the most common receptors involved in the sleep and waking process. Also, various neurotransmitters are associated with promoting sleep or wake properties, such as acetylcholine, dopamine, GABA, glutamate, norepinephrine, serotonin, and orexin/hypocretin. Thus, insomnia medications are categorized into four pharmacodynamics classes, including benzodiazepine receptor agonists, melatonin targeting, a selective antihistamine, and a dual orexin/hypocretin receptor antagonist [5,10]. Estazolam, flurazepam, triazolam, temazepam, and quazepam are FDA indicated benzodiazepine agents for treating short-term insomnia. Also, the immediate-release formulations of zolpidem are FDA approved in treatment of the short-term treatment of this sleep disorder [11]. The risk of tolerance and dependence on medications

and other side effects leads the surveys to complementary and alternative management [12]. Medicinal plants are affordable and possess various bioactive components that hold desirable efficacy in managing insomnia [13]. These medications can be administered on multiple routes, including oral, topical, and intranasal forms [14]. Therefore, the prescription of herbal medicines becomes favorable in the management of insomnia these days.

Many studies investigated the pharmacological mechanism, safety, and effectiveness of these products. This overview aimed to compile the clinical trials on the efficacy of herbal remedies in managing insomnia for facilitating future medicinal plant studies in this issue.

Materials and Methods

Study type
In this narrative study, we reviewed the clinical trials focusing on medicinal plants' efficacy on insomnia.

Search and strategy
The keywords "Medicinal plant" or "Herbal medicine" in combination with "Hypnotic and sedative" or "Insomnia" or "Sleep" were searched through PubMed, Google Scholar, and Scopus electronic databases from 1st January 2000 to 31st August 2020 by three authors (Figure 1).
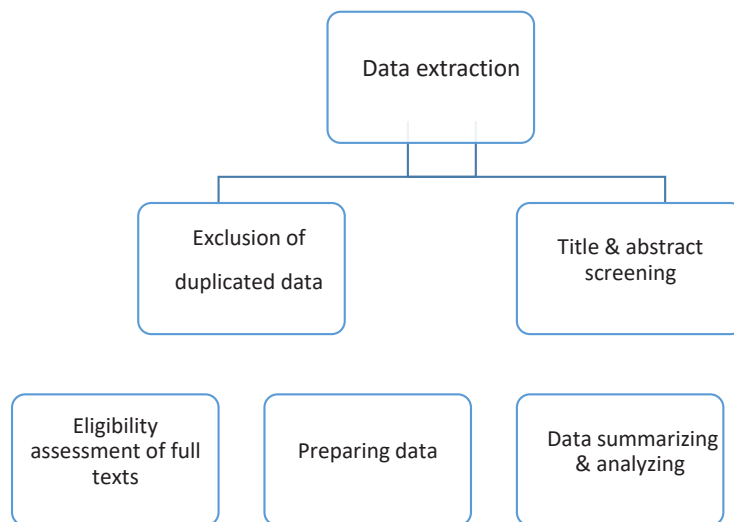
Figure 1. Flowchart of search strategy

Inclusion and exclusion criteria
Inclusion criteria: Clinical trials that evaluated the efficacy of herbal medicines in sleep were included, comprising single-, double-, and triple-blind control

studies, case series, as well as before-after surveys. Experiments covering both polyherbal and straightforward medicines were inclusive. There was no limitation on the subject's age, gender, or ethnicity.

All types of insomnia, whether primary or comorbid with other disorders and the problem with all parts of sleep like sleep onset, maintenance, and duration, were included. Only English papers that we accessed to their full text were collected in this survey.

Exclusion criteria: Laboratory, observational, case reports, review, and cohort surveys were excluded from our investigation. The papers comprising complementary treatments other than herbal medicines such as acupuncture and massage therapy or not mentioning the scientific or common name of herbal medicine in the title or abstract were also omitted.

Data gathering: Three authors extracted data; one of them screened the titles and abstracts of search studies and excluded the duplicated articles from different databases. The others reviewed the full-texts, checking inclusion and exclusion criteria as well as extracting required data.

Finally, the data related to trials evaluating the efficacy of herbal medicines were summarized into two tables. Then, the qualitative analysis was done.

Results

Considering the inclusion and exclusion criteria, 36 articles were selected and classified into two groups, as follow:

Group 1: Efficacy of single herb formulations on insomnia (23 studies, 16 medicinal plants), which have been summarized in table 1.

Group 2: Efficacy of polyherbal formulations on insomnia (13 studies), which have been summarized in table 2.

According to table 1, many researchers have considered and evaluated single medicinal plants' effect on insomnia. Among mentioned herbal medicines in table 1, the effect of *Lactuca sativa* L., *Matricaria chamomilla* L., *Valeriana officinalis* L., and *Viola odorata* L. on insomnia were evaluated in several clinical trials.

The safety and efficacy of L. sativa (seeds) oral administration on insomnia in pregnant women was evaluated and confirmed in a randomized, double-blind placebo-control clinical trial [15]. The seed oil of L. sativa was also influential in topical form for improving childhood sleep disorders [16].

M. chamomilla was utilized orally in three clinical trials, which significantly affected sleep quality and daytime functioning. In a double-blind three-stage clinical trial, 30 drops of *M. chamomilla* was administrated orally in chronic heart failure patients for a week at bedtime, which significantly improved the quality of their life [17]. The daytime functioning in patients with chronic primary insomnia was promot-

ed with oral administration of *M. chamomilla* (6 tablets (540 mg) daily divided into two doses) in a randomized pilot study [18]. Another randomized clinical trial (RCT) on older adults showed the oral administration of the *M. chamomilla* (200 mg twice a day for four weeks in capsule form) is a safe and effective therapeutic agent for enhancing sleep quality [19].

The oral and intranasal administration of *V. odorata* showed desirable effects on improving insomnia symptoms and quality of life in three clinical trials. The intranasal drop of *V. odorata* oil (2 or 3 drops in each nostril every night for a month) showed the hypnotic effect in patients with chronic insomnia [20,21]. In a randomized pilot study, the administration of extracted syrup of *V. odorata* (5 mL BID for four weeks) in patients with depression or obsessive-compulsive disorder improved insomnia symptoms [22].

In nine papers, the herbal products were prescribed topically on the forehead, intranasal, or as inhalation; whereas 27 surveys were ordered oral administration in the form of the teabag, capsule, tablet, and syrup. The target group of surveys varied from healthy, war refugees, and pregnant to having cancer, coronary artery disease, heart failure, diabetes, whether outpatient or hospitalized. Type of investigated insomnia altered from primary to secondary (to prolonged fatigue, stress-induced, and depression or obsessive-compulsive disorder). Their age range differed from childhood to adult and the elderly. Sleep quality and sleep onset were mainly assessed. Considering the severity of insomnia, few studies targeted mild or mild to moderate insomnia. Sample sizes differed from 21 to 442 people. The assessment was mostly subjective using sleep log or diary, Pittsburgh Sleep Quality Index, Mary's Hospital Sleep Quality Questionnaire, insomnia severity index, Epworth sleepiness scale score, Leeds Sleep Evaluation Questionnaire, BEARS" pediatric sleep questionnaire, Pittsburgh Insomnia Rating Scale and sleep dysfunction rating scale. A smaller number of trials covered objective assessment with actigraphy or polysomnography. The most prevalent experimental tools were used to assess the possibility of medicinal plants in the treatment of insomnia are summarized in table 3. In terms of methodology, out of 36 attempts, six were using before-after assessment, 30 were clinical-controlled studies whether comparing with placebo, conventional medicine, or using no intervention. There were 19 double-blind and one triple-blind trial. Considering the results of studies, there were two trials, both including valerian which reported negative effects.

Table 1. Efficacy of single herb formulations on insomniacs

N	Plant name (Common name)	Dose and dosage form (Effective bioactive component or extract), frequency and duration of study	Study type/ Target group	Assessment	Outcomes	Ref.
1	*Aloysia citriodora* Palau (Lemon verbena)	Oral, 10 cc Syrp (total EO: 1.66 mg/10 ml, total flavonoid (quercetin) 3.22 mg/10 ml) 4 W: nightly (1 h before bedtime)	RCT (DB – PC), 100 patients with insomnia	PSQI ISI	Improved sleep quality, ↓ Insomnia severity	[23]
2	*Crocus sativus* L. (Saffron)	Oral, 1 cap (300 mg saffron) 1 W: daily (12 noon till 2 pm)	Quasi-experimental PC study, 50 diabetics	PSQI SAI	↓ Anxiety, Improved sleep quality	[24]
3	*Cucurbita moschata* Duchesne (Pumpkin)	Intranasal (oil in the base of sesame), 2W: 2 drops nightly1 h before sleeping	RCT (DB-PC) ,74 chronic insomniacs	PSQI ISI	Induced sleep, ↑ sleep quantity and quality	[25]
4	*Gardenia jasminoides* J.Ellis	Oral, 2 intervention periods (2 W) with 2 W wash out period: 1 cap (7.5 mg of crocetin) daily (6:00 p.m. till 8:00 p.m.)	RPS (DB-PC, crossover, comparative)/ 21 men (25–59 y), mild insomnia	Actigraphy MHSQ	Improved sleep quality	[26]
5	*Lactuca sativa* L. (Lettuce)	Oral, 2W:1 cap (1000 mg seed) nightly	RCT (DB-PC) ,100 pregnant (20-45y)	PSQI	↓ Insomnia	[15]
		3 W: Topical Seed oil on forehead and temporal + placebo cap (study group) VS topical placebo oil + clonidine cap (control group)	RCT (DB-PC) 67 children (3-6 y) with sleep disorders	"BEARS" pediatric sleep questionnaire	Safe and effective treatment for sleep disorders	[16]
6	*Lavandula angustifolia* Mill. (Lavender)	2 Intervention periods (4 W) with 1 W washout, Inhalation, 3 drops (EO or placebo) smell on a 2 layers' linen fabric for 5 min at bed time	RCT (PC and patients were not blind), 52 diabetic type II, (25-65y)	PIRS-20, WHO-QOL-BREF, BDI scale	Improved sleep quality with short-term use	[27]
7	*Matricaria chamomilla* L. (Chamomile)	1W, Oral:30 drops (whole extract or placebo) before bedtime at 9 p.m.	Clinical trial (DB-PC, 3 stage), 67 CHF patients (40-70 y)	MHSQ	Improved sleep quality	[17]
		4 W: Daily oral:6 tab (total dose:540 mg extract, standardized up to 2.5 mg of (-)-α-bisabolol and up to 2.5 mg of apigenin per tab or placebo) divided into 2 doses	RPS (DB-PC)/ 34 chronic primary insomniac (18-65 y)	Sleep log	Modest benefits of daytime functioning, mixed benefits on sleep log measuements	[18]
		4 W: Oral,1 cap (200 mg chamomile extract or 200 mg wheat flour cap) BD	RCT (SB- PC)/ 195 elderly (>60y)	PSQI	Significantly improved sleep quality	[19]
8	*Melissa officinalis* L.	1 W: Oral,1 cap (500 mg dried leave powder) TDS	RCT (DB-PC)/ 80 coronary artery bypass graft adults (30-70 y)	MHSQ HADS	↓ Anxiety, Improved sleep quality	[28]

9	*Passiflora incarnata* L. or *Passiflora edulis* Sims (Passionflower)	3 W: Oral, Teabag (2 g of dried leaves, stems, seeds and flowers), with boiling water in the full covered cup (equivalent to 250 mL) 10 min	DB-PC/ 41 healthy adult (18-35y)	Sleep log PSG STAI-S	Improved sleep quality and sleep onset latency	[29]
10	*Prunus dulcis* (Mill.) D.A.Webb (Sweet almond)	2W: Oral,10 almonds daily	Before-after study/ 442 students	ISI	Improved the quality of sleep	[30]
11	*Rosa × damascena* Herrm.	2 W: Inhalation,5 drops (EO) on a cotton ball before sleep for 20 min	Before-after study/ Children with sleep disorders	BEARS	Improved sleep quality	[31]
12	*Sesamum indicum* L. (Sesame)	Topical/Shirodhara (unroasted plain sesame oil) by a robotic oil-drip system in seven 30-minute periods (2 W) with either liquid washout period (at least 2 months)	RPS (single blind cross over)/ 22 adults with subjective poor sleep quality in the past month	PSQI ESS WHO-QOL26 sleep monitor instrument (objective sleep measures)	Improved sleep quality and QOL	[32]
13	*Valeriana officinalis* L. (Valerian)	2W: Oral, 1-3 capsules (national brand of valerian "NaturesWay", 470 mg valerian root) nightly 30-60 min prior to retiring	Case study (Before-after)/ 23 Symptomatic (21-75y)	Sleep questionnaire	Effective supplement for treating insomnia	[33]
		Oral, Capsule ("Natures Way", 1600 mg valerian standardized to contain 0.8% valerenic acid), in 2 separate 2–3 h sessions. In each participant were given either valerian or placebo and waited 1 h for absorption	DB-PC (Cross over), 40 healthy adults	SVRT, subjective sleepiness scales, SFST, STI-SIM- DSPP Score	Does not appear to impair driving simulator performance after acute ingestion	[34]
	Valeriana officinalis L. (Valerian) + Acupressure	3 Nights: topical, Bilateral acupoint (穴位 xue w ei) massage with 2 drops of valerian oil (2.5%) for 2 min	3-Group DB clinical trial, 90 ACS adults (>18y) in a coronary intensive care unit	SMHSQ	Improved sleep, ↓ waking during the night	[35]
14	*Valeriana edulis* Nutt.	4 Days (8 h recording each): oral, 3 Cap (450 mg of rhizomes and roots hydroalcoholic extract) 60 min prior to lights out	DB, Cross-over, control study/ 20 outpatients (29-55y)	PSG	Showed hypnotic effect on insomnia	[36]

15	Viola odorata L. (Violet)	1 Month: intranasal, 2 drops (66 mg drops (Violet oil)) in each nostril nightly before sleep	Before-after study (single blind), 50 chronic insomniacs	ISI	Significantly improved sleep and ISI scores after a month	[21]
		1 Month: intranasal, 3 drops (Violet oil, Almond oil or placebo) in each nostril before sleep nightly	DB-PC Study/ 75 patients with chronic insomnia	PSQI ISI	Violet oil was more effective on sleep quality than sleep quantity	[37]
		4W: Oral,5 mL syrp every 12 h	RPS (DB-PC), 83 patients (16–15 y) co-morbid insomnia with mild & moderate depression or OCD	PSQI BDI-II, YBOCS	Significantly improved insomnia symptoms and the scores of depressions and OCD	[22]
16	Withania somnifera (L.) Dunal	10W: Oral, 1 cap (300 mg root extract) BID	RCT (DB-PC)/ 60 patients with insomnia and anxiety	Sleep log PSQI HAMA Sleep actigraphy	Improved sleep quality and sleep onset latency	[38]

EO: essential oil, Syrp: syrups, Tab: tablets, h: hour, W: week(s), RCT: Randomized clinical trial, RPS: Randomized pilot study, DB: Double-blind, PC: placebo-controlled, SB: single-blind, OCD: obsessive compulsive disorder, CHF: chronic heart failure, ACS: acute coronary syndrome, PSQI: Pittsburgh Sleep Quality Index, Cap: capsule BDI: Beck Depression Inventory, HAMA: Hamilton Anxiety Rating Scale, ISI: Insomnia severity index, STAI-S: State-trait anxiety inventory, state version, form-Y, MHSQ: Mary's Hospital Sleep Quality Questionnaire, HADS: Hospital Anxiety Depression Scale, PSG: polysomnography, ESSS: Epworth sleepiness scale score, VAS: Visual analogue scales, LSEQ: Leeds Sleep Evaluation Questionnaire, SVRT: simple visual reaction test, SFST Standardized field sobriety testing, STISIM Depriving simulator performance parameters, SAI: Spielberger Anxiety Inventory, YBOCS: Yale–Brown Obsessive–Compulsive Scale. PIRS-20: Pittsburgh Insomnia Rating Scale, WHOQOL-BREF: WHO Quality of Life-BREF, BFI: Brief Fatigue Inventory, MoCA: Montreal Cognitive Assessment, SDRS: sleep dysfunction rating scale, CGI-I: Clinical Global Impression-Improvement.

Table 2. Efficacy of polyherbal formulations on insomnia

N	Plant name (Common name)	Dose and dosage form (Effective bioactive component or extract), frequency and duration of study	Study type/ Target group	Assessment	Outcomes	Ref.
1	Astragali Radix (1200 mg) + Angelica gigas Nakai (root; 900 mg) + Zizyphi Fructus (fruit; 900 mg)	4W: 3g herbal teabag twice daily	Pilot RCT (control with no intervention), 40 prolonged fatigue adult (35-44 y)	PSQI BDI	↓Fatigue severity, ↑Sleep quality	[39]
2	Melissa officinalis L. (dry powder; 1000 mg) + Nepeta Menthoides Boiss. & Buhse (aqueous extract; 400mg)	2 Cap for 4 W	Triple blind-PC trial, 80 Sleep onset insomniacs (18-60 y)	ISI PSQI Sleep log	Improved sleep onset	[12]

3	Novanuit®/Triple Action: Melatonin + vitamin B6+ extract of (California poppy + passionflower+ lemon balm)	2W: 2 Caps daily (30–60 min before bedtime)	Open label, single arm, pilot study, 40 mild to-moderate insomniacs (20–75y)	Sleep log	Improved sleep quality and daytime function	[40]
4	*Piper methysticum* (Kava, 100 mg of total kavalactones) + *Valeriana officinalis* L. (Valerian, 3.2 mg of valerenic acids)	1 Kava or placebo soft gel cap TID + 2 valerian or placebo soft gel cap (1h before bed time) daily	RCT (DB-PC), 391 participants	ISI, STAI	Not superior efficacy to placebo in relieving anxiety & insomnia	[41]
5	NSF-3: *Valeriana officinalis* L. (valerian; 300 mg) + *Passiflora incarnata* L. (Passion flower; 80 mg) + *Humulus lupulus* L. (hops; 30 mg)	1 Tab for 2 W	RCT (DB- parallel group), controlled study, 91 patients with primary insomnia	Sleep log ISI ESSS	Effective and safe alternative to zolpidem	[42]
6	*Valeriana officinalis* L. (187-mg native extracts; 5–8:1, methanol 45% m/m) + *Humulus lupulus* L. (41.9-mg native extracts; 7–10:1, methanol 45% m/m)	2 Tabs at night for 28 days	RCT (parallel group, multicenter), 184 subjects with mild insomnia	Sleep log and PSG	Improved life and sleep quality, Modest hypnotic effect	[43]
7	*Valeriana officinalis* L. (root; 0.8% of valerenic acid) + *Humulus lupulus* L. (cone dry extract, 0.4% minimum of total flavonoids) + *Ziziphus jujuba* Mill. (seeds dry extract; 2% min. triterpene saponins)	2 Pills, nightly: 30 min before bedtime) for 20 days	RCT (Single blind-PC),120 (>18y) subjects with primary insomnia	Self-assessment questionnaire	Improved all sleep parameters	[44]
8	*Valeriana officinalis* L. (root dry extract; 320 mg) + *Humulus lupulus* L. (Stabile dry extract; 80 mg)	A single dose of valerian-hops or chlorpheniramine (4 mg) or placebo (2 h) before bed time	Comparison trial (Single blind- controlled study), 262 war refugees with insomnia	LSEQ, VAS of anxiety and sedation	Valerian-hops was more effective than antihistamine ↑ sleep quality, ↓Anxiety	[45]
9	*Valeriana officinalis* L. + *Piper methysticum* G.Forst.	3 Intervention periods (6 W) -1st: (Kava, 120 mg) -2nd:(Valerian, 600 mg) -3d: (Kava (120mg) + valerian (600mg)) with 2 W wash out period:	Pilot study (cross over)/ 24 patients with stress-induced insomnia	VAS	Relived stress severity and insomnia by kava or valerian or kava + valerian	[46]
10	*Viola odorata* L.+ *Crocus sativus* L. + *Lactuca sativa* L.	8W: Intranasal, 2 drops (oil) in each nostril (every noon and evening)	RCT (DB-PC)/50 patients with primary chronic insomnia	PSQI ISI	Improved chronic insomnia, ↓ Conventional hypnotic medications dose	[47]

11	Ayurvedic combination: *Valeriana wallichi* (160 mg/tab), *Rosa centifolia* L. + *Nardostachys jatamansi* (D. Don) DC. + *Tinospora cordifolia* (Willd.) Miers + *Withania somnifera* (L.) Dunal + *Piper nigrum* L. + *Zingiber officinale* Roscoe + *Convolvulus pluricalis+ Glycyrrhiza glabra* L.	2 Tabs (1h before sleep) nightly for 3 intervention periods (4-night placebo, 4-night placebo or herbal combination tab, 10-day wash-out period, 4-night placebo or herbal combination tab)	RCT (DB-PC, cross-over), 25 (20–65y) healthy subjects with sleep onset insomnia	MHSQ	↓Sleep latency	[48]
12	THM:*Gamiguibi*-tang: root of *Astragalus* (6.6%) + *Bupleurum* (9.8%)+ *Polygala* (4.9%)+ Japanese Angelica *sinensis* (Oliv.) Diels (6.6%)) + *Ziziphus jujuba* Mill. (9.8%)+ *Atractylodes lancea* (Thunb.) DC. rhizome (9.8%)+ *Panax ginseng* C.A.Mey. (9.8%)+ *Poria sclerotium* (9.8%)+ *Longan aril* (9.8%)+ *Gardenia* fruit (6.6%)+ *Jujube* (4.9%)+Glycyrrhiza (3.3%), *Zingiber officinale* Roscoe (4.9%) + *Saussurea lappa* (Decne.) Sch.Bip. (3.3%)	2W: Oral, 3.75 g of Gamiguibi-tang (spray-dried hot water extracts of plants) with hot water TID	RCT (wait-list-controlled, open-label pilot), 40 patients (>18 y) with cancer and sleep disturbance	ISI, BFI, BDI, MoCA scores	Improved the sleep disturbance, ↓ Fatigue	[49]
13	Huadananshen mistura: *Arachis hypogaea* L. (Peanut) + *Salvia miltiorrhiza* Bunge (Danshen)	2W: Oral, 10 or 20 mL/day, nightly	RCT (DB-PC multi-center), 244 insomniacs (18-65y)	SDRS scores CGI-I scores	Effective hypnotic agent	[50]

THM: Traditional herbal medicine, EO: essential oil, Syrp: syrups, Tab: tablets, h: hour, W: week(s), RCT: Randomized clinical trial, RPS: Randomized pilot study, DB: Double-blind, PC: placebo-controlled, SB: single-blind, OCD: obsessive compulsive disorder, CHF: chronic heart failure, ACS: acute coronary syndrome, PSQI: Pittsburgh Sleep Quality Index, Cap: capsule BDI: Beck Depression Inventory, HAMA: Hamilton Anxiety Rating Scale, ISI: Insomnia severity index, STAI-S: State-trait anxiety inventory, state version, form-Y, MHSQ: Mary's Hospital Sleep Quality Questionnaire, HADS: Hospital Anxiety Depression Scale, PSG: polysomnography, ESSS: Epworth sleepiness scale score, VAS: Visual analogue scales, LSEQ: Leeds Sleep Evaluation Questionnaire, SVRT: simple visual reaction test, SFST Standardized field sobriety testing, STISIM Depriving simulator performance parameters, SAI: Spielberger Anxiety Inventory, YBOCS: Yale–Brown Obsessive–Compulsive Scale. PIRS-20: Pittsburgh Insomnia Rating Scale, WHOQOL-BREF: WHO Quality of Life-BREF, BFI: Brief Fatigue Inventory, MoCA: Montreal Cognitive Assessment, SDRS: sleep dysfunction rating scale, CGI-I: Clinical Global Impression-Improvement

Table 3. Experimental tools

Tools	Description	Ref.
Pittsburgh Sleep Quality Index (PSQI)	19-Criteria questionnaire assessing sleep disturbance and quality over the past month.	[51]
Insomnia Severity Index (ISI)	7-Criteria self-report questionnaire evaluating the nature, severity, and impact of insomnia.	
Pittsburgh insomnia rating scale (PIRS)	65-Criteria scale rating the severity of insomnia in clinical trials	[52]
Leeds Sleep Evaluation Questionnaire (LSEQ)	10 Self-reported criteria evaluating ease of getting to sleep, quality of sleep, ease of awakening from sleep and alertness and behavior following wakefulness	[53]
Visual analog scales (VAS)	Evaluating aspects of sleep and daytime functioning	[54]
Montreal Cognitive Assessment (MoCA)	Assessing cognitive Function	[55]
Sleep log	Tracking sleep patterns over an extended period	[56]

According to table 2, thirteen studies related to the polyherbal formulations on treating insomnia were collected. V. *officinalis*, *Passiflora incarnata* L., *Humulus lupulus*, and *Piper methysticum* were the most common medicinal plants in the effective herbal formulations on insomnia.

Discussion

Insomnia is a widespread psychological health issue that significantly affects quality of life and productivity [57]. The abnormalities in melatonin secretion, GABA receptor, cortisol level, and excitatory amino acid are among the most important causes of sleep disorders [58]. This review compiled the efficacy of herbal medicines to manage insomnia, including 16 medicinal plants and 13 polyherbal formulations. Based on this review's findings, medicinal plants are the preferable alternative treatment in managing insomnia; especially *M. chamomilla*, *V. officinalis*, *V. odorata*, and *P. incarnata* were among the most prevalent effective herbal medicines.

M. chamomilla, commonly named chamomile, is one of the most popular herbal medicines used by humanity. Chamomile was introduced as a safe herbal medicine for treating insomnia via a systematic review and meta-analysis. This paper revealed that the anxiolytic and hypnotic effects of chamomile are related to its flavonoids and apigenin contents, which can bind to benzodiazepine and GABA-A receptors in the brain [59]. Our venture showed that oral administration of chamomile as a single herb or in combination with other medicinal plants could improve sleep quality.

V. officinalis (valerian) belongs to Valerianaceae family, is widely used as a sleep supplement. A systematic review and meta-analysis (published in 2020) suggested that GABAergic and serotonergic signaling pathways are involved in hypnotic and anxiolytic effects of valerian, especially by valerenic acid [60]. Our findings revealed that oral administration of valerian or topical application with acupressure could be a safe therapeutic approach for managing insomnia.

V. odorata (sweet violet) as a member of Violaceae family, traditionally prescribed for treating various diseases such as insomnia [61]. In traditional Persian medicine, intranasal or topical application of violet oil is recommended for neurologic disorders [62]. Linalool was detected via GC/MS from violet oil and melatonin was recognized by enzyme-linked immunosorbent assay (ELISA) in violet flower, are introduced as the main components which are responsible for its hypnotic effects [37]. In our review, the oral and intranasal application of violet was practical and safe in managing insomnia.

P. incarnata (passionflower) from the Passifloraceae family possesses precious documents in treating several psychological disorders such as insom-

nia. According to an in vitro study, a dry extract of *P. incarnata* could inhibit GABA uptake and modulate the GABA system. Hence, various pharmacological effects of passionflower may have related to its modulation effects on the GABA system [63]. A systematic review on P. incarnata (published 2020) revealed that passionflower could be a safe and effective herbal medicine for managing neuropsychiatric disorders, which its neuroprotective effect is linked to chrysin [64]. Based on our findings, the oral administration of passionflower in a teabag form or combination with other herbal medicines can effectively improve insomnia.

It should be considered that medicinal plants can have synergistic or additive effects with conventional drugs, leading to several adverse effects [65]. Hence although medicinal plants can be alternatives for conventional drugs in managing insomnia, conducting clinical study interaction for evaluating the safety of concurrent use of medicinal herbs and conventional medicines is necessary.

As mentioned, several signaling pathways are involved in insomnia. On the other hand, medicinal plants are rich sources of bioactive components. Therefore, clarifying the main components with their target receptors in sleep can be critical in development of future drugs based on herbal compounds. Also, preparing more effective formulations via considering drug targeting systems is suggested for future studies.

Limitations
Some of the trials were missing due to inclusion and exclusion criteria, including those with their full-texts in languages other than English.

Conclusion
Several herbal formulations categorizing into single and polyherbal were mentioned in this study for managing insomnia. The common medicinal plants such as *M. chamomilla*, *V. officinalis*, *V. odorata*, and P. incarnata are suitable candidates for further therapeutic development. Other cited medicinal plants, whether in straightforward or in combination form, can have the potential to be more investigated in treating sleep disorders. Furthermore, various routes of administration and some typical methods of trials as well as their assessment were introduced to assist the conduction of future studies in this area.

Conflict of Interests
The authors affirm that they have no conflict of interest with any organization.

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