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...
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).

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.

Data extraction

Exclusion of duplicated data

Title & abstract screening

Eligibility assessment of full texts

Preparing data

Data summarizing & analyzing

Figure 1. Flowchart of search strategy
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 promoted 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>
<thead>
<tr>
<th>N</th>
<th>Plant name (Common name)</th>
<th>Dose and dosage form (Effective bioactive component or extract), frequency and duration of study</th>
<th>Study type/ Target group</th>
<th>Assessment</th>
<th>Outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Aloysia citriodora</em> Palau (Lemon verbena)</td>
<td>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)</td>
<td>RCT (DB – PC), 100 patients with insomnia</td>
<td>PSQI ISI</td>
<td>Improved sleep quality, ↓ Insomnia severity</td>
<td>[23]</td>
</tr>
<tr>
<td>2</td>
<td><em>Crocus sativus</em> L. (Saffron)</td>
<td>Oral, 1 cap (300 mg saffron) 1 W: daily (12 noon till 2 pm)</td>
<td>Quasi-experimental PC study, 50 diabetics</td>
<td>PSQI SAI</td>
<td>↓ Anxiety, Improved sleep quality</td>
<td>[24]</td>
</tr>
<tr>
<td>3</td>
<td><em>Cucurbita moschata</em> Duchesne (Pumpkin)</td>
<td>Intranasal (oil in the base of sesame), 2W: 2 drops nightly 1 h before sleeping</td>
<td>RCT (DB-PC) .74 chronic insomniacs</td>
<td>PSQI ISI</td>
<td>Induced sleep, ↑ sleep quantity and quality</td>
<td>[25]</td>
</tr>
<tr>
<td>4</td>
<td><em>Gardenia jasminoides</em> J.Ellis</td>
<td>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.)</td>
<td>RPS (DB-PC, crossover, comparative)/ 21 men (25–59 y), mild insomnia</td>
<td>Actigraphy</td>
<td>MHSQ Improved sleep quality</td>
<td>[26]</td>
</tr>
<tr>
<td>5</td>
<td><em>Lactuca sativa</em> L. (Lettuce)</td>
<td>Oral, 2W:1 cap (1000 mg seed) nightly</td>
<td>RCT (DB-PC) ,100 pregnant (20-45y)</td>
<td>PSQI</td>
<td>↓ Insomnia</td>
<td>[15]</td>
</tr>
<tr>
<td>6</td>
<td><em>Lavandula angustifolia</em> Mill. (Lavender)</td>
<td>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</td>
<td>RCT (PC and patients were not blind), 52 diabetic type II, (25-65y)</td>
<td>PIRS-20, WHO-QOL-BREF, BDI scale</td>
<td>“BEARS” pediatric sleep questionnaire Safe and effective treatment for sleep disorders</td>
<td>[16]</td>
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<tr>
<td>7</td>
<td><em>Matricaria chamomilla</em> L. (Chamomile)</td>
<td>1W, Oral:30 drops (whole extract or placebo) before bedtime at 9 p.m.</td>
<td>Clinical trial (DB-PC, 3 stage), 67 CHF patients (40-70 y)</td>
<td>MHSQ</td>
<td>Improved sleep quality</td>
<td>[17]</td>
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<td></td>
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<td>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</td>
<td>RPS (DB-PC)/ 34 chronic primary insomniac (18-65 y)</td>
<td>Sleep log</td>
<td>Modest benefits of daytime functioning, mixed benefits on sleep log measurements</td>
<td>[18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 W: Oral,1 cap (200 mg chamomile extract or 200 mg wheat flour cap) BD</td>
<td>RCT (SB- PC)/ 195 elderly (~60y)</td>
<td>PSQI</td>
<td>Significantly improved sleep quality</td>
<td>[19]</td>
</tr>
<tr>
<td>8</td>
<td><em>Melissa officinalis</em> L.</td>
<td>1 W: Oral,1 cap (500 mg dried leave powder) TDS</td>
<td>RCT (DB-PC)/ 80 coronary artery bypass graft adults (30-70 y)</td>
<td>MHSQ HADS</td>
<td>↓ Anxiety, Improved sleep quality</td>
<td>[28]</td>
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<tr>
<td></td>
<td>Name</td>
<td>Duration and Formulation</td>
<td>Method(s)</td>
<td>End Points</td>
<td>Reference</td>
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<td>9</td>
<td><em>Passiflora incarnata</em> L. or <em>Passiflora edulis</em> Sims (Passionflower)</td>
<td>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</td>
<td>DB-PC/ 41 healthy adult (18-35y)</td>
<td>Improved sleep quality and sleep onset latency</td>
<td>[29]</td>
<td></td>
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<tr>
<td>10</td>
<td><em>Prunus dulcis</em> (Mill.) D.A.Webb (Sweet almond)</td>
<td>2W: Oral,10 almonds daily</td>
<td>Before-after study/ 442 students</td>
<td>Improved the quality of sleep</td>
<td>[30]</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td><em>Rosa × damascena</em> Herrm.</td>
<td>2 W: Inhalation,5 drops (EO) on a cotton ball before sleep for 20 min</td>
<td>Before-after study/ Children with sleep disorders</td>
<td>Improved sleep quality</td>
<td>[31]</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td><em>Sesamum indicum</em> L. (Sesame)</td>
<td>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)</td>
<td>RPS (single blind cross over)/ 22 adults with subjective poor sleep quality in the past month</td>
<td>Improved sleep quality and QOL</td>
<td>[32]</td>
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<td>13</td>
<td><em>Valeriana officinalis</em> L. (Valerian)</td>
<td>2W: Oral, 1-3 capsules (national brand of valerian “NaturesWay”, 470 mg valerian root) nightly 30-60 min prior to retiring</td>
<td>Case study (Before-after)/ 23 Symptomatic (21-75y)</td>
<td>Effective supplement for treating insomnia</td>
<td>[33]</td>
<td></td>
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<td></td>
<td></td>
<td>Oral, Capsule (“Natures Way”, 1600 mg valerian standardize 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</td>
<td>Sleep questionnaire</td>
<td>Does not appear to impair driving simulator performance after acute ingestion</td>
<td>[34]</td>
<td></td>
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<tr>
<td>14</td>
<td><em>Valeriana edulis</em> Nutt.</td>
<td>3 Nights: topical, Bilateral acupoint (穴位 xue w ei) massage with 2 drops of valerian oil (2.5%) for 2 min</td>
<td>3-Group DB clinical trial, 90 ACS adults (&gt;18y) in a coronary intensive care unit</td>
<td>Improved sleep, ↓ waking during the night</td>
<td>[35]</td>
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<td>4 Days (8 h recording each): oral, 3 Cap (450 mg of rhizomes and roots hydroalcoholic extract) 60 min prior to lights out</td>
<td>DB, Cross-over, control study/ 20 outpatients (29-55y)</td>
<td>Showed hypnotic effect on insomnia</td>
<td>[36]</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Plant name (Common name)</td>
<td>Dose and dosage form (Effective bioactive component or extract), frequency and duration of study</td>
<td>Study type/Target group</td>
<td>Assessment</td>
<td>Outcomes</td>
<td>Ref.</td>
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<tr>
<td>1</td>
<td>Astragali Radix (1200 mg) + Angelica gigas Nakai (root; 900 mg) + Zizyphi Fructus (fruit; 900 mg)</td>
<td>4W: 3g herbal teabag twice daily</td>
<td>Pilot RCT (control with no intervention), 40 prolonged fatigue adult (35-44 y)</td>
<td>PSQI BDI</td>
<td>↓Fatigue severity, ↑Sleep quality</td>
<td>[39]</td>
</tr>
<tr>
<td>2</td>
<td>Melissa officinalis L. (dry powder; 1000 mg) + Nepeta Menthoides Boiss. &amp; Buhse (aqueous extract; 400mg)</td>
<td>2 Cap for 4 W</td>
<td>Triple blind-PC trial, 80 Sleep onset insomniacs (18-60 y)</td>
<td>ISI PSQI Sleep log</td>
<td>Improved sleep onset</td>
<td>[12]</td>
</tr>
</tbody>
</table>

Table 2. Efficacy of polyherbal formulations on insomnia

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Description</th>
<th>Administration</th>
<th>Study Design</th>
<th>Outcome Measures</th>
<th>Results/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Novanuit®/Triple Action: Melatonin + vitamin B6 + extract of (California poppy + passionflower + lemon balm)</td>
<td>2W: 2 Caps daily (30–60 min before bedtime)</td>
<td>Open label, single arm, pilot study, 40 mild to-moderate insomniacs (20–75y)</td>
<td>Sleep log</td>
<td>Improved sleep quality and daytime function</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Piper methysticum (Kava, 100 mg of total kavalactones) + Valeriana officinalis L. (Valerian, 3.2 mg of valerenic acids)</td>
<td>1 Kava or placebo soft gel cap TID + 2 valerian or placebo soft gel cap (1h before bed time) daily</td>
<td>RCT (DB-PC), 391 participants</td>
<td>ISI, STAI</td>
<td>Not superior efficacy to placebo in relieving anxiety &amp; insomnia</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NSF-3: Valeriana officinalis L. (Valerian; 300 mg) + Passiflora incarnata L. (Passion flower; 80 mg) + Humulus lupulus L. (hops; 30 mg)</td>
<td>1 Tab for 2 W</td>
<td>RCT (DB-parallel group), controlled study, 91 patients with primary insomnia</td>
<td>Sleep log</td>
<td>Effective and safe alternative to zolpidem</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Valeriana officinalis L. (187-mg native extracts; 5–8:1, methanol 45% m/m) + Humulus lupulus L. (hops; 30 mg)</td>
<td>2 Tabs at night for 28 days</td>
<td>RCT (parallel group, multicenter), 184 subjects with mild insomnia</td>
<td>Sleep log and PSG</td>
<td>Improved life and sleep quality, Modest hypnotic effect</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>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)</td>
<td>2 Pills, nightly: 30 min before bedtime) for 20 days</td>
<td>RCT (Single blind-PC),120 (&gt;18y) subjects with primary insomnia</td>
<td>Self-assessment questionnaire</td>
<td>Improved all sleep parameters</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Valeriana officinalis L. (root dry extract; 320 mg) + Humulus lupulus L. (Stable dry extract; 80 mg)</td>
<td>A single dose of valerian-hops or chlorpheniramine (4 mg) or placebo (2 h) before bed time</td>
<td>Comparison trial (Single blind- controlled study), 262 war refugees with insomnia</td>
<td>LSEQ, VAS of anxiety and sedation</td>
<td>Valerian-hops was more effective than antihistamine ↑ sleep quality, ↓ Anxiety</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Valeriana officinalis L. + Piper methysticum G.Forst.</td>
<td>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</td>
<td>VAS</td>
<td>Relieved stress severity and insomnia by kava or valerian or kava + valerian</td>
<td></td>
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<tr>
<td>10</td>
<td>Viola odorata L. + Crocus sativus L. + Lactuca sativa L.</td>
<td>8W: Intranasal, 2 drops (oil) in each nostril (every noon and evening)</td>
<td>RCT (DB-PC)/50 patients with primary chronic insomnia</td>
<td>PSQI ISI</td>
<td>Improved chronic insomnia, ↓ Conventional hypnotic medications dose</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Ayurvedic combination: <em>Valeriana wallichii</em> (160 mg/tab), <em>Rosa centifolia</em> L. + <em>Nardostachys jatamansi</em> (D. Don) DC. + <em>Tinospora cordifolia</em> (Willd.) Miers + <em>Withania somnifera</em> (L.) Dunal + <em>Piper nigrum</em> L. + <em>Zingiber officinale</em> Roscoe + <em>Convolvulus pluricalis</em> + <em>Glycyrrhiza glabra</em> 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)</td>
<td>RCT (DB-PC, cross-over), 25 (20–65y) healthy subjects with sleep onset insomnia</td>
<td>MHSQ</td>
<td>↓Sleep latency</td>
<td>[48]</td>
<td></td>
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<tr>
<td>12</td>
<td>THM: Gamiguibi-tang: root of <em>Astragalus</em> (6.6%) + <em>Bupleurum</em> (9.8%) + <em>Polygonum</em> (4.9%) + Japanese Angelica <em>sinensis</em> (Oliv.) Diels (6.6%) + <em>Ziziphus jujuba</em> Mill. (9.8%) + <em>Atractylodes lancea</em> (Thunb.) DC. rhizome (9.8%) + <em>Panax ginseng</em> C.A.Mey. (9.8%) + <em>Poria sclerotium</em> (9.8%) + <em>Longan aril</em> (9.8%) + <em>Gardenia</em> fruit (6.6%) + <em>Jujube</em> (4.9%) + <em>Glycyrrhiza</em> (3.3%), <em>Zingiber officinale</em> Roscoe (4.9%) + <em>Saussurea lappa</em> (Decne.) Sch.Bip. (3.3%) 2W: Oral, 3.75 g of Gamiguibi-tang (spray-dried hot water extracts of plants) with hot water TID</td>
<td>RCT (wait-list-controlled, open-label pilot), 40 patients (&gt;18 y) with cancer and sleep disturbance</td>
<td>ISI, BFI, BDI, MoCA scores</td>
<td>Improved the sleep disturbance, ↓Fatigue</td>
<td>[49]</td>
<td></td>
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<tr>
<td>13</td>
<td>Huadananshen mistura: <em>Arachis hypogaea</em> L. (Peanut) + <em>Salvia miltiorrhiza</em> Bunge (Danshen) 2W: Oral, 10 or 20 mL/day, nightly</td>
<td>RCT (DB-PC multi-center), 244 insomniacs (18-65y)</td>
<td>SDRS scores CGI-I scores</td>
<td>Effective hypnotic agent</td>
<td>[50]</td>
<td></td>
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</tbody>
</table>

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 insomnia.

### Table 3. Experimental tools

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

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http://jtim.tums.ac.ir
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 modulatory 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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