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Herbal Insomnia Medications that Target GABAergic Systems: A Review of the Psychopharmacological Evidence

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Abstract: Insomnia is a common sleep disorder which is prevalent in women and the elderly. Current insomnia drugs mainly target the γ-aminobutyric acid (GABA) receptor, melatonin receptor, histamine receptor, orexin, and serotonin receptor. $GABA_A$ receptor modulators are ordinarily used to manage insomnia, but they are known to affect sleep maintenance, including residual effects, tolerance, and dependence. In an effort to discover new drugs that relieve insomnia symptoms while avoiding side effects, numerous studies focusing on the neurotransmitter GABA and herbal medicines have been conducted. Traditional herbal medicines, such as *Piper methysticum* and the seed of *Zizyphus jujuba* Mill var. *spinosa*, have been widely reported to improve sleep and other mental disorders. These herbal medicines have been applied for many years in folk medicine, and extracts of these medicines have been used to study their pharmacological actions and mechanisms. Although effective and relatively safe, natural plant products have some side effects, such as hepatotoxicity and skin reactions effects of *Piper methysticum*. In addition, there are insufficient evidences to certify the safety of most traditional herbal medicine. In this review, we provide an overview of the current state of knowledge regarding a variety of natural plant products that are commonly used to treat insomnia to facilitate future studies.

Keywords: Hypnotic, insomnia, natural products, sedatives, γ-aminobutyric acid.

1. INTRODUCTION

Sleep is a crucially important process in the animal kingdom. Sleep disorders affect a large portion of the general population worldwide, and insomnia is the most commonly reported sleep disorder. More than half of the American population suffers from sleep disorders [1]. Because the prevalence of insomnia increases with age, this problem is potentially more serious in countries, such as China, that contain an increasing elderly population. Insomnia is characterized by difficulty in initiating sleep and/or maintaining sleep, non-restorative sleep or poor-quality sleep [1, 2]. Sleep disturbances cause people to suffer from mental dysfunction and daytime sleepiness and can lead to various health and socioeconomic issues. People who suffer from insomnia for long time periods may also suffer from depression and experience a decreased quality of life [3].

Sleep remains one of the most poorly understood biological processes. The function and molecular processes underlying sleep remain elusive but are becoming clearer after decades of research [4]. Mammalian sleep states are characterized by altered brain activity during the rapid eye movement (REM) stage and several non-rapid eye movement (NREM) stages that follow a clearly defined cyclical pattern [5, 6]. Several signaling molecules that play a role in sleep have been identified. Various neurotransmitters, including noradrenaline, acetylcholine, histamine, dopamine, serotonin, and the neuropeptides orexin A and B (also referred to as hypocretins), promote wakefulness. By contrast, GABA and adenosine promote sleep [5]. GABA is the major neurotransmitter that exerts inhibitory activity in the central nervous system (CNS), and more than 20% of all brain neurons are GABAergic. Three pharmacologically distinct classes of GABA receptors have been identified: $GABA_A$ receptors, $GABA_B$ receptors, and $GABA_C$ receptors. The $GABA_A$ receptor, which was the first to be identified, has a pentameric transmembrane structure that includes 19 subunits (α1-6, β1-3, γ1-3, δ, ε, π, θ, and ρ1-3). Different subunit combinations produce subtypes with varying locations and physiologies [7, 8]. $GABA_A$ receptors are ligand-gated chloride ion channels that are activated by GABA and the agonist muscimol, blocked by bicuculline, and coupled to the GABA, barbiturate, benzodiazepine, and picrotoxin binding sites [9]. $GABA_A$ receptors are important therapeutic targets for the treatment of insomnia because they rapidly inhibit neurotransmission and participate in tonic inhibition [10]. $GABA_B$, the second identified receptor, is a G-protein-coupled heterodimer composed of the subunits $GABA_B$ R1 and $GABA_B$ R2, and it plays a critical role in synaptic transmission through the regulation of a meta-botropic second messenger pathway that regulates Ca^{2+} or K^+

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channels [11, 12]. The third receptor identified, $GABA_C$, is a Cl ionophore comprising three subunits (ρ1, ρ2, ρ3). It is more sensitive to GABA than the $GABA_A$ and $GABA_B$ receptors [13]. $GABA_C$ receptor antagonists decrease total slow-wave sleep and paradoxical sleep [14].

Sleep is regulated by the circadian rhythm and homeostatic mechanisms, which are dominated by the CNS. GABA is the primary inhibitory neurotransmitter in the CNS, and the GABA receptor is a target of the majority of sleep medications, including non-benzodiazepine "Z drugs" (zaleplon, zolpidem, zopiclone, and eszopiclone) and benzodiazepines (BZDs), both of which target GABAergic signaling pathways [5, 15, 16]. Three generations of hypnotics have been developed based on $GABA_A$ receptor-mediated inhibitory processes. First- and second-generation hypnotics include barbiturates and BZDs, respectively, third-generation hypnotics include imidazopyridines and cyclopyrrolones. All decrease waking, increase slow-wave sleep, and enhance the intermediate stage of sleep, which is situated between slow-wave sleep and paradoxical sleep, at the expense of the last sleep stage. Third-generation hypnotics are distinguished from other drugs by a slight decrease in paradoxical sleep that occurs in the absence of increases in the intermediate stage of sleep during the first few hours after treatment [13, 15, 16].

Pharmacological treatments for insomnia that are currently approved by the Food and Drug Administration (FDA) include GABA response modulators, melatonin receptor agonists, and histamine receptor antagonists. Benzodiazepine receptor agonists (BZRAs), including BZD and non-BZD hypnotics, modulate GABA responses by activating the $GABA_A$ receptor and inducing an inward chloride ion flux finally hyperpolarizes the membrane and reduces its action potential [8]. Barbiturates are effective but are associated with several safety concerns include low lethal doses, residual sedation, tolerance, and dependence [17]. BZRAs have essentially replaced barbiturates due to their sufficient pharmacokinetic variability and substantially improved therapeutic effects. However, BZDs have addictive properties and are associated with abuse liability, physical dependence, and tolerance, limiting their long-term use [18]. Melatonin receptor agonists improve sleep onset with better safety, but the onset of efficacy occurs slowly [19]. The first FDA-approved melatonin receptor agonist, Ramelteon, is well tolerated, but it also has several adverse effects, including headache, somnolence, nausea, and fatigue [20]. The only selective H_1 histamine receptor antagonist is low-dose doxepin, which is used to treat insomnia with difficulty in sleep maintenance. Doxepin was proven safe and effective in clinical trials, with no abuse potential, but it is associated with adverse events, including somnolence, nausea, and upper respiratory tract infection [8]. Furthermore, the efficacy and safety data for other drugs used to treat insomnia are inadequate. Because the previously mentioned drugs cannot fulfill the needs of all insomnia patients, additional safe and effective drugs are needed to treat insomnia.

Herbal medicine has been used to treat insomnia in worldwide countries for centuries. The anxiolytic and sedative properties of these medicinal plants were described in plant records during ancient times; one such example is the Compendium of Materia Medica [2, 21]. Herbal medications have been used both separately and in combination. More than 29,000 prescriptions for herbal medications were received in Taiwan in 2002 [2]. Over the last two centuries, the scientific understanding of herbal plants has advanced significantly. Traditional pharmacognosy research is often based on single active compounds that have been isolated from plant material [22].

Herbal medicines typically contain complex mixtures of compounds, and their mechanisms of action often remain unclear. However, recent studies have shown that central GABAergic neurotransmission changes when people or animals ingest the extracts of most herbal plants that are reported to possess anxiolytic and sedative properties. The results of studies involving herbal plants published between 2000 and 2013 are addressed in this review.

2. MATERIALS AND METHODS

The authors conducted a computer-based search using SCI Finder (Chemical Abstracts Service, CAS). An initial search was performed using the terms "natural product", "herbal product", and "sleep" in combination with the term "GABA". Following an examination of the retrieved literature, additional searches were conducted using the terms "insomnia", "sedative", and "hypnotic" in combination with "GABA", "natural products", "herbal", and "extract". All papers that did not meet these criteria were excluded.

3. RESULTS

3.1. *Piper methysticum* L.f. (Family: Piperaceae)

Piper methysticum originates in the Pacific Polynesian Islands, and its extract, kava-kava, has been traditionally used as an herbal medicine to treat insomnia and anxiety in the South Pacific since the 18th century. Its historic use, combined with modern scientific data demonstrating its safety and efficacy, led the German Commission E (expert committee of the German Federal Institute for Drugs and Medical Devices) to approve the use of kava-kava preparations as nonprescription drugs for the treatment of anxiety disorders, stress, and restlessness in 1990 (Table **1**). There are eighteen kavalactones isolated from kava-kava root extract, four chiral and two achiral enantiomers of them perform most of the activaties including yangonin, desmethoxyyangonin (5,6-dehydrokawain), methysticin, 7,8-dihydromethysticin, kawain, and 7,8-dihydrokawain. It also have been reported that administration of the lactones alone did not exert the same pharmacologic activity as whole kava-kava extract, some researchers suggested that this may due to the modulation of transport and/or metabolism [24].

Nevertheless, several cases of kava-kava-induced fulminant hepatic failure and acute hepatitis were reported in the year 2001 and 2002 [48-50], including which 11 hepatic failure required liver transplants and eventually resulted in four deaths [50], liver biopsy and histologic examination showed hepatocellular necrosis, inflammatory infiltration

Table 1. Herbal hypnotics: mechanisms of action and clinical applications.

Herbal Medicine	Common Names	Medicinal Parts	Mechanisms of Action	Type of Evidence*	Major Sedative Constituents	
					Compound Names	Type of Compound
Piper methysticum L.f. (Piperaceae)	Kava, Kava Kava, Kava Pepper, Kava Shrub, Kava-Kava, Kawa Pepper, Yangona Pepper	Root	Modifies the $GABA_A$ receptor [23]	1, 2, 3	Kawain, Dihydrokawain, Methysticin, Dihydromethysticin, Yangonin, and Desmethoxyyangonin [24]	Lactones
Zizyphus jujuba Mill var. *spinosa* (Rhamnaceae)	Plants, Chinese Date, Common Jujube	Seed	Modifies the $GABA_A$ receptor; Activates the $GABA_A$ receptor; Increases GABA synthesis by GAD activation [25]	1, 2, 3	Sanjoinine A [25]	Alkaloids
Valeriana officinalis L. (Caprifoliaceae)	All Heal, Common Valerian, Garden Heliotrope, Garden Valerian, Garden-Heliotrope, Valerian	Root	Modifies the $GABA_A$ receptor [26]	1, 2	Valerenic acid [26]	Sesquiterpenoids
Hypericum montbretii Spach (Hypericaceae)	—	—	Modifies the $GABA_A$ -benzodiazepine receptors [27]	1	Rutin and Quercitrin [27]	Flavonids
Pinus massoniana Lamb. (Pinaceae)	Pine Needles	Acicular leaf	Increases GABA levels [28]	1	Volatile oil [29]	Volatile oils
Scutellaria baicalensis Georgi (Lamiaceae)	Baikal Skullcap, Chinese Skullcap, Golden Root, Helmet Flower	Root	Modifies the $GABA_A$ receptor [30]	1	Baicalein and Baicalin [30, 31]	Flavonoids
Atractylodes macrocephala Koidz. (Compositae)	—	Rhizome	Modifies the $GABA_A$ receptor [32]	1, 3	Atractylenolide II and III [32]	Sesquiterpene lactones
Ipomoea orizabensis (Pelletan) Ledeb. ex Steud. (Convolvulaceae)	Mexican scammony root	Root	Increases GABA release in the cortices of the brains of mice [33]	1	Convolvulin [33]	Resin glycosides
Ternstroemia lineata DC. (Pentaphylacaceae)	—	Calyx and Fruit	Influences GABA release [34]	1	Jacaranone [34]	Quinones
Rhus parviflora Roxb. (Anacardiaceae)	Tintidikah	Fruit	Modifies $GABA_A$-benzodiazepine receptors [35]	1	Mesuaferrone B, Rhusflavone, and Agathisflavone [35]	Biflavonoids
Dimocarpus longan Lour. (Sapindaceae)	Longanae Arillus	Fruit	Modifies GABAergic systems [36]	1, 3	Methanol extract [36]	Unknown
Crassocephalum bauchiense (Hutch.) Milne-Redh. (Compositae)	—	Leaf	Blocks dopamine D-2 receptors and active GABAergic systems [37]	1	Alkaloid fraction [37]	Alkaloids

Table 1. contd….

Herbal Medicine	Common Names	Medicinal Parts	Mechanisms of Action	Type of Evidence*	Major Sedative Constituents	
					Compound Names	Type of Compound
Chrysanthemum morifolium Ramat. (Compositae)	Florist`s Chrysanthemum, Florist's Chrysanthemum, Florist's Daisy, Florists' Chrysanthemum, Mum	Flower	Increases expression levels of GAD [38]	1	Ethanol extract [38]	Unknown
Dorstenia arifolia Lam. (Moraceae)	—	Rhizome	Mediates GABAergic pathways [39]	1	Methanol extract [39]	Unknown
Magnolia officinalis Rehder & E.H.Wilson (Magnoliaceae)	Medicinal Magnolia	Bark of the root and stem	Modifies the $GABA_A$ receptor [40]	1, 2	Honokiol and Magnolol [40, 41]	Lignans
Glycyrrhiza glabra L. (Leguminosae)	Common Licorice, Black Sugar, Common Licorice, Cultivated Licorice, Kahles S, Kahles S ssholz, Licorice, Licorice-Root, Licorice, Russian Licorice, Spanish Juice, Spanish Licorice, Sweet Licorice, Sweet Wood, True Licorice	Root	Modifies $GABA_A$-BZD receptors [42]	1	Glabrol [42]	Flavonoids
Ecklonia cava Kjellman (Lessoniaceae)	Paddle Weed	—	Modifies $GABA_A$-BZD receptors [43]	1	Eckol, Eckstolonol, Dieckol, and Triphlorethol-A [43]	Phlorotannins
Melissa officinalis L. (Lamiaceae)	Balm, Lemon Balm	Whole herb	Decreases the level of GABA-T, thereby increasing GABA levels [44]	1	*Melissa officinalis* oil [45, 46] (citral a, citral b and citronellal [47])	Monoterpenaldehydes

*1: Experimental evidence of sedative activity, 2: Human clinical data, 3: Traditional medical systems and pharmacopoeia-endorsed use.

and bile duct proliferation consistent with chemical hepatitis [48]. Kava-kava were banned throughout the European Union and Canada by January 2003, and the use of these extracts was subject to caution and advisories by the FDA [48].

Kava-kava extract toxicity appears to be idiosyncratic. While the hepatotoxic features of commonly used herbal products, including kava-kava, have been studied [51], the underlying mechanisms remain uncharacterized. Possible mechanisms for kavalactone hepatotoxicity include inhibition of cytochrome P450, reduction in liver glutathione content and, more remotely, inhibition of cyclooxygenase enzyme activity. In particular, no clear evidence supports a causative role for the kavalactone and non-kavalactone constituents isolated from kava-kava, including pipermethystine and flavokavain B, in hepatotoxicity. Thus the possibility of direct toxicity of kava-kava extracts is precious little under any analysis, yet the potential for drug interactions and/or the potentiation of the toxicity of other compounds may play the main role [52]. Presently, kava-kava toxicity appears to be "idiosyncratic". The risk-to-benefit ratio of kava-kava extracts, nevertheless, remains high in comparison with that of other drugs used to treat anxiety. Therefore, novel enzymatic, analytical, toxicological, ethnobotanical, and clinical studies are needed.

A double-blind, randomized, placebo-controlled study of kava-kava for the treatment of generalized anxiety disorder was performed in April 2013. Importantly, GABA was analyzed as a potential pharmacogenetic marker of response in this trial, specific GABA transporter polymorphisms appear to potentially modify anxiolytic response to kava-kava, a significant reduction in anxiety was observed in the kava-kava group. What's remarkable important is that standardized kava-kava was well tolerated and showed no obvious hepatotoxicity. In this study, no significant adverse effects or liver function impairment were observed [53, 54]. This is consistent to the point that the risk-to-benefit ratio of kava-kava extracts is superior to that of other drugs that are used to treat anxiety. According to a previous analysis, the rate of incidence is 0.3 cases per one million daily doses of kava-kava, which is quite favorable with the benzodiazopenes, including which hepatic adverse effects rate per million daily doses is 0.90 for bromazepam, 1.23 for oxazepam, and 2.12 for diazepam. Similarly, the hepatotoxicity rate of nonsteroidal

anti-inflammatory drugs was 3%–5% (acetylsalicylic acid), of which 3% again are potentially life-threatening [24]. Acetaminophen-containing products also brought 258 cases of acute liver failure in the period 1998–2000 in US [55]. A recent pharmacologic study measured the electro-encephalograms (EEGs) and electromyograms (EMGs) of rats with electrodes implanted in their frontal cortices and dorsal neck. When kava-kava extract was administered at a dose of 300 mg/kg, the sleep latency of sleep-disturbed rats was remarkably shortened; no effects were observed on the total duration of wakefulness and NREM sleep [23]. Besides, J. Sarris *et al*. found that the aqueous kava-kava preparation produced significant anxiolytic and antidepressant effects while take no safety concerns, which implied that aqueous rootstock extracts of kava-kava may be a new break point for the management of anxiety [48].

These latest studies demonstrate that kava-kava is an effective and safety-promising anti-anxiety therapy and GABA may be the active target of kava-kava. In general, kava-kava continues to have potential value for the treatment of sleep disorders. It should be stressed again that even the safest of the preferred prescription drugs appear to exhibit a hepatic adverse event rate at least three times that of the kavalactones, thus research on the toxicity of kava-kava would be of significant interest and impact. Further studies should focus on the identification of additional hepatotoxic constituents, with particular consideration given to possible adulterants and impurities, such as ochratoxin A- and aflatoxin (AF)-producing varieties of *Aspergillus* [56].

3.2. *Zizyphus jujuba* Mill var. *spinosa* (Family: Rhamnaceae)

Zizyphi spinosi semen (ZSS), the maturate seed of *Zizyphus jujuba* Mill var. *spinosa*, is a historic classic herbal medication widely used in treating insomnia in Asian countries. There are three main types of ingredients in ZSS that also display lipid oxidation resistance properties: saponins, alkaloids, and flavonoids [57]. The underlying mechanism of ZSS remains unclear although numerous studies have been conducted over the past years. One of the major alkaloid compounds, sanjoinine A, enhances pentobarbital-induced sleeping behaviors, which are more commonly referred to as hypnotic effects. As Ma Yuan *et al*. reported, sanjoinine A behaves similarly to other $GABA_A$ receptor agonists in a dose-dependent manner and increases chloride influx in primary cultured cerebellar granule cells, thereby modifying GABAergic systems [25]. In another study by Ma Yuan *et al*., over-expression of the α- and γ-subunits of the $GABA_A$ receptor and glutamic acid decarboxylase (GAD65/67) in cultured cerebellar granule cells was observed after sanjoinine A (5.0 μM) treatment [58]. Furthermore, ZSS is one of the ingredients in Suan Zao Ren Tang, which exhibits binding affinity for the serotonin (5-hydroxytryptamine, 5-HT) $5\text{-}HT_{1A}$ and $5\text{-}HT_2$ receptors and GABA receptors. Serotonergic activation was reported following treatment with Suan Zao Ren Tang [59], but the exact chemical constituents responsible are unclear. Research regarding the effects of Sansohnin-to on sodium pentobarbital-induced sleep duration revealed that the underlying mechanism of action of Sansohnin-to is related to stress-induced functional changes in the CNS [60]. ZSS is widely reported to be an effective treatment for insomnia, but it is often present as Suan Zao Ren Tang or as a component of some listed drugs. Single-component drugs have not yet been developed.

3.3. *Valeriana officinalis* L. (Family: Caprifoliaceae)

Valerian (*Valeriana officinalis*) is widely used as a sedative and an anti-anxiety drug in folk medicine. Valerian root is most commonly used for its sedative and hypnotic properties in patients with insomnia. It is native to Europe and Asia and has been naturalized in eastern North America. Valerian contains over 150 chemical constituents, many of which are physiologically active, including alkaloids (e.g., actinidine, which affects GABAergic metabolism), terpenes, organic acids and their derivatives (e.g., valeric acid and valerenic acid; both affect the CNS), valepotriates (e.g., valepotriates and valeranone, which affect smooth muscle), and flavones [61]. In an effort to reveal the underlying mechanism of action of valerian, another study investigated the modulation of $GABA_A$ receptors using valerian extracts of different polarities and sesquiterpenic acid contents in *Xenopus laevis* oocytes expressing $GABA_A$ receptors composed of the α1, β2, and γ2S subunits. The results of this study revealed that the extent of $GABA_A$ receptor modulation by valerian extracts is related to the valerenic acid content, and one possible mechanism for the sedative and sleep-inducing effects of *V. officinalis* L. is stimulation of the $GABA_A$ receptor [26]. Moreover, another study sought to identify the mechanism underlying the effects of valerian extracts on postsynaptic potentials (PSPs) in cortical neurons. Treatment with an extract of macerated valerian roots in ethyl acetate (EA-E) at a concentration of 10 mg/mL increased PSPs. PSP induction was completely blocked by treatment with the $GABA_A$ receptor antagonist picrotoxin (100 μm) [62]. However, the general mechanism of action of valerian (and particularly the mechanism underlying its mild sedative effects) remains unknown.

Ziegler G *et al*. reported that 600 mg/die valerian extract LI 156 was at least as efficacious as a treatment with 10 mg/die oxazepam in the treatment of non-organic insomnia [63]. Many other studies also demonstrated that valerian is efficient in treating mild psychophysiological insomnia [63, 64]. But the clinical studies of valerian on improving sleep quality reported have been turned out to be more negative than positive [65]. Also in a meta-analysis of 18 reported randomized clinical trials, analysis had been done to describe the effectiveness of valerian on insomnia, the results showed that there are only 0.70 min difference in LT between the valerian and placebo groups [66]. Therefore, it seems difficult to develop valerian into a specific medicine for insomnia, in our concern mild psychophysiological insomnia may be the most suitable indication for valerian clinical applications.

3.4. *Hypericum montbretii* Spach (Family: Hypericaceae)

Hypericum grows in temperate and subtropical regions of the Northern Hemisphere; and the family Hypericaceae comprises over 400 species. In the past few years, various *Hypericum* species have been widely studied for their pharmacological activity in the CNS. Moreover, *Hypericum*

is used as a treatment for alcohol, nicotine, and caffeine addiction, and it is accepted as an anxiolytic, antidepressant [67] and sedative [68]. The main chemical components of *H. montbretii* extracts are chlorogenic acid and flavonoids, including rutin, hyperoside, apigenin-7-O-glucoside, quercitrin, quercetin, and vitexin [69]. Özgür Devrim Can *et al*. used different behavioral methods, including the activity cage test and Hxb-induced sleep, to investigate the sedative activity of a methanol extract of *H. montbretii* containing rutin (1519 ppm) and quercitrin (784 ppm). This *H. montbretii* extract possessed sedative and anticonvulsant activities mediated *via* the $GABA_A$-benzodiazepine ($GABA_A$-BZD) receptor complex in the CNS of mice [27]. E. Ernst *et al*. evaluated the adverse drug reactions (ARDs) of *Hypericum perforatum* only to find that the most common adverse effects were gastrointestinal symptoms, *Hypericum perforatum* showed an excellent tolerance with an incidence of adverse reactions similar to the placebo. A potential serious adverse effect may be photosensitivity which appears to occur extremely rarely [70]. *Hypericum perforatum* may present pharmacokinetic interactions with anticancer drugs in the findings of Sparreboom A *et al*. [71] and may confound cancer care. However, studies are far more needed of *Hypericum* for its general clinical use, current studies are limited and more researches concerned on the active ingredient and mechanistic are needed.

3.5. *Pinus massoniana* Lamb. (Family: Pinaceae)

Pine needles are needle-like leaves of *Pinus massoniana* Lamb. Pine needles are traditionally used as insecticides, antipruritics, and anxiolytics, and they are also used as tea in China, where a majority of the research on compounds from this plant has been performed. Chinese researchers Zhao G Z *et al*. studied the effects of different pine needle extracts on neurotransmitters and determined the levels of GABA and glutamic acid in hippocampal slices of treated mice by HPLC. They observed significant increases in sodium pentobarbital-induced sleep duration and levels of GABA, indicating that pine needle extracts confer sedative and hypnotic effects [28]. *The Chinese Materia Medica* states that the volatile oil of pine needles could improve sleep quality in mice when administered with pentobarbital sodium. Deng Y *et al*. observed sedation after treatment with volatile oil in the shaking cage test and dynamic time test , however components of pine needles are extremely complex and diversiform than other herbal medications that increased the difficulty in studying its underlying mechanism. Moreover, the volatile oil has a significant synergistic effect with pentobarbital sodium [29]. The main chemical components of pine needles are volatile componentsincluding α-ocimene (29.3%), sabinene (10.9%), β-myrcene (9.6%), β-caryophyllene (8.0%), β-cadinene (7.3%), α-terpinolene (4.9%), 2-hexanal (4.5%), and β-pinene (4.3%), of which had antibacterial effects *in vitro* [72]. Latest research taken by LI Hong- yu *et al*. in the year 2012 isolated 6 aroma chemical components of pine needles including vanillin, dihydroactinidiolide, 2-isopropyl-5-methyl-2- hexenal, α-curcumene, oleanitrile and (Z)-13-docosenamide including which vanillin and dihydroactinidiolide were the main components, and were isolated from the *P.massoniana* for the first time. Vanillin has been used in epilepsy treatment and was demonstrated to have certain effects on nervous system [73]. However, studies so far only concerned on the extraction and analyzed the volatile component of pine needles with a limited number of studies in China, sedative and hypnotic effects of the volatile oils and the mechanisms are unclear, which may lead to the breakthrough point for further study if we can separate a active volatile component responsible for the sedative and hypnotic effect. As a widely distributed and easily achieved herbal medication with mild nature, we believe there is a huge potential for pine needles in insomnia treatment, or as a supplement of prescription medicine, to say the least. Therefore, for the sake of prospective use in clinical, further research may focus on the sedative effects and side effects of pine needles.

3.6. *Scutellaria baicalensis* Georgi (Family: Lamiaceae)

Scutellaria baicalensis is a traditional Chinese medicinal herb, especially its dried roots, Scutellariae Radix, which has been documented to possess therapeutic effects for hundreds of years. Its main active components of anti-inflammatory are baicalin, baicalein, and wogonin [74]. It has been widely used in China and other Asian countries for its anti-inflammatory, anti-pyretic, anti-bacterial, anti-hypertensive, anti-allergic and sedating effects [30]. Recently, several studies have demonstrated the effectiveness of Scutellariae Radix in insomnia treatment, nevertheless, the clinical practice focus on the CNS regulation function of *Scutellaria baicalensis* is limited [30].

Baicalein (BA) is one of the primary flavonoids in *S. baicalensis*. One report demonstrated that the baicalin, the glycoside of the aglycone baicalein, decreased slow wave sleep (SWS) during the first 2 h of the light period but did not affect rapid eye movement sleep (REMS) after intracerebroventricular administration. Baicalin-mediated blockade of IL-1β enhanced SWS, suggesting that IL-1 receptor antagonism is involved in the ability of baicalin to reduce SWS during the light period. However, IL-1β concentrations during the light period were not altered following baicalin administration. By contrast, baicalin increased both SWS and REMS during 8–10 hours of the dark (active) period when baicalin was administered at the beginning of the dark period, and this effect can be blocked by the $GABA_A$ receptor antagonist bicuculline. Taken together, these results demonstrated that baicalin exhibits biphasic effects on sleep-wake regulation (decreases in SWS during the light period and increases in SWS and REMS during the dark period) and the inhibition of IL-1 action together with enhancement of $GABA_A$ receptor activity may mediate the effects of baicalin during the light and dark periods, respectively [30]. Besides baicalein, wogonin (monoflavonoid, 5,7-dihydroxy-8-methoxyflavone), a benzodiazepine receptor ligand isolated from *Scutellaria baicalensis* Georgi had been tested by Kwok Min Hui *et al*. as an alternative for BZDs, their study showed wogonin can exert GABA activation effect include enhancing the GABA-activated current in rat dorsal root ganglion neurons and expressing recombinant rat $GABA_A$ receptors in Xenopus laevis oocytes, and these enhancement can partially be reversed by benzodiazepine site antagonist anexate (Ro15-1788) [75]. Wogonin was also proved to initiate little side-effects compared with BZDs although the underlying mechanisms are still unclear.

Previous studies suggest us the sedative and hypnotic effects of *Scutellaria baicalensis* may apply to activation GABA system, whereas the elucidation of the active ingredients awaits further research. Later studies should also be focus on verifying the effect and mechanism of baicalein and baicalin.

3.7. *Atractylodes macrocephala* Koidz. (Family: Compositae)

Atractylodes macrocephala is an essential ingredient in the common Chinese herbal formula Jia-Wey-Shiau-Yau-San. LC Chen *et al*. performed a 4-year-long clinical observation survey on outpatients with primary insomnia from January 2003 to December 2006, in which 6860 patients were treated by Chinese herbal medicines, and Jia-Wey-Shiau-Yau-San turned out to be the second most widely used herbal formula in the treatment of insomnia meanwhile *Atractylodes macrocephala* is the second widely used herb items. But due to the constitute of herbal formulae is of great complexity, it is difficult to identify the active ingredient clearly [76]. In addition, it has long been used as a digestive agent and may stimulate immune responses [77]. Atractylol, atractylon, and butenolide A, B are the active ingredients of *Atractylodes macrocephala* [78]. In 2012, Singhuber *et al*. reported that positive allosteric modulation of GABA-induced chloride currents (I_{GABA}) might be partially responsible for the traditional ethnopharmacological use of *A. macrocephala* herbal drug as a sedative. In this study, two microelectrode voltage clamps were placed on recombinant $\alpha_1\beta_2\gamma_{2S}$ $GABA_A$ receptors expressed in *X. laevis* oocytes, and the ability to modulate I_{GABA} was measured. The petroleum ether extract of *A. macrocephala* rhizomes displayed strong I_{GABA} potentiation, and atractylenolide II and III, the primary components isolated from *A. macrocephala*, were apparently responsible for the observed positive modulation of I_{GABA} (166 ± 12%, n = 3 and 155 ± 12%, n = 3) *in vitro*, And these effects were independent of the benzodiazepine binding site [32].

Despite the vitro and clinical observation studies showed great efficiency of *A. macrocephala* on insomnia and GABA modulation, further studies are still needed to clarify the therapeutic potential of *A. macrocephala* in human and its molecular mechanism. For clinical application, clinical trials concerning adverse effects and drug interactions are also needed.

3.8. *Ipomoea tyrianthina* (Pelletan) Ledeb. ex Steud (Family: Convolvulaceae)

Ipomoea tyrianthina has been used as a mild purgative in traditional Mexican medicine to treat nervous disorders and as an anti-tumor agent due to its characteristic resin glycosides. In the year 2008, I León-Rivera *et al*. found four new partially acylated tetrasaccharides of 11-hydroxyhexadecanoic acid (1−4) which were isolated from a methanolic extract of *Ipomoea tyrianthina* showed antimycobacterial activity and exerted the potentiation of hypnosis induced by pentobarbital, protected against seizures induced by pentylenetetrazole, and released GABA and glutamic acid [79]. In 2011, León-Rivera *et al*. reported that convolvulin (IT-EM), an ether-insoluble resin glycoside isolated from the root of *I. tyrianthina* can increase the hypnotic effect induced by pentobarbital and the release of GABA in the mouse brain cortex. IT-EM (20, 40, or 80 mg/kg, i.p.) prolonged the duration of loss of righting reflex induced by pentobarbital sodium (30 mg/kg) compared to the control group ($P < 0.05$). IT-EM (2.5 μg/mL) induced a time-dependent increase in GABA content in mouse brain cortex slices [33]. Taken together, these pharmacological results demonstrate that IT-EM produces sedative effect. Because IT-EM does not affect the release of glutamic acid, this sedative effect might be specifically mediated by increased GABA levels [33]. However, there is insufficient evidence to link IT-EM activity to GABA, which represents an area of future research. IT-EM also displays vasodilatory and toxic effects toward tumor cells, and thus the balance between treating insomnia and inducing toxicity must be considered when determining the dosage. If further research findings can convince us with a safe dosage of treatment without causing cytotoxicity, *Ipomoea tyrianthina* may turn to be a promising herbal medication to treat insomnia without serve side effects.

3.9. *Ternstroemia lineata* DC. (Family: Pentaphylacaceae)

Ternstroemia pringlei (a synonym of *Ternstroemia lineata* DC.), which is traditionally used as a tranquilizer and to diminish insomnia and fear in Mexico, is widely employed and commercially exploited [34]. In 2010, Lozada *et al*. reported that i.p. administration of organic and aqueous extracts of *T. pringlei* calyx and fruits, in which the active ingredient was established as jacaranone (1), resulted in dose-dependent decreases in the number of rearings in the exploratory cylinder model in mice and GABA release at ratios of 217 and 179 pmol/g protein in GABA release experiments using mouse brain slices *in vitro*. Moreover, the sedative effects of these extracts were as follows (ED_{50}): aqueous (77.58 mg/kg) > methanol (232.80 mg/kg) > dichloromethane (345.93 mg/kg) > hexane (446.68 mg/kg). The sedative compound jacaranone was isolated from the MeOH crude extract, and its efficacy was clearly demonstrated in a dose-dependent response analysis (ED_{50} = 25 mg/kg mouse weight). However, none of the extracts derived from *Ternstroemia pringlei* displayed anxiolytic activity when tested in the elevated plus-maze model [34]. In 2008, Balderas *et al*. tested the sedative effect of an aqueous extract of the dried fruits of *Ternstroemia pringlei* (rose) in synergy with 6 CNS depressant drugs and found that the aqueous extract can induce a sedative effect in a dose-dependent manner and potentiate the sedative effect of buspirone, diazepam, diphenhydramine, haloperidol or pentobarbital and produce an attenuation of the sedative effect of ethanol. They believe that this plant has hard non-predictive interactions with CNS depressant drugs; thereafter the combination of this plant with CNS depressant drugs should be avoided [80]. However, other researchers have reported different issues, such as super-additive interactions, which imply us further studies are still needed to confirm the drug interactions and other side effects of *Ternstroemia pringlei* before it becomes an recommended treatment for insomnia.

3.10. *Rhus parviflora* Roxb. (Family: Anacardiaceae)

In southern Asia (Ayurveda), *Rhus parviflora* is used to treat Vāta vikāra, which causes neurological complications.

R. parviflora is an important part of the traditional medicinal system in these countries and is referred to as Tintidikah. *R. parviflora* is also used to treat stomach disorders. In the past year, the methanol extract of *R. parviflora* fruit (RPME) was shown to exhibit significant $GABA_A$-BZD receptor binding capacity by Shrestha *et al*. in a search for natural products that enhance sleep quality. There was a dose-dependent decrease in sleep latency and an increase in sleep duration in mice treated with pentobarbital and RPME (125, 250, 500, and 1000 mg/kg) orally. Moreover, the hypnotic effect of RPME was completely inhibited by ^{3}H-Ro15-1788 flumazenil. In addition, the biflavonoids mesuaferrone B, rhusflavone, and agathisflavone, which were isolated from the ethyl acetate fraction, competitively blocked flumazenil binding with Ki values of 0.280, 0.045, and 0.091 μM. It was proposed that the conjugated ketone and C6-C8 biflavonoid linkage in rhusflavone decreased sleep latency and increased sleep duration by activating the BZD-site of $GABA_A$ [35]. However, these finding were only clinical manifestations without theory supporting, this hypothesis awaits confirmation in molecular biology studies to identify the target of rhusflavone. Also drug interactions and side effects need to be tested before it become a candidate for further preclinical studies of herbal medicine aimed at the treatment of insomnia since most of the patients may take more than only one species of hypnotics.

3.11. *Dimocarpus longan* Lour. (Family: Sapindaceae)

Dimocarpus longan is a popular fruit in many subtropical countries due to its delicious taste, particularly in China and South Asia. Moreover, its pulp and fresh Longanae Arillus have been consumed in Asia for many years to treat anxiety and insomnia. Yuan Ma *et al*. investigated the sedative/ hypnotic effects of a standardized methanol extract of Longanae Arillus (MELA) on pentobarbital-induced sleep behavior and whether the underlying mechanisms involve GABAergic systems. They reported that MELA prolonged pentobarbital-induced sleep duration and reduced pentobarbital-induced sleep latency in a similar fashion as muscimol, a $GABA_A$ receptor agonist. MELA increased both the rate of sleep and sleep duration when administered with pentobarbital at a sub-hypnotic dosage, and it displayed synergic effects with muscimol in potentiating pentobarbital-induced sleep onset and enhancing pentobarbital-induced sleep duration. However, treatment with MELA alone did not induce sleep at the higher doses used in this experiment. In addition, both MELA and pentobarbital increased chloride influx in primary cultured cerebellar granule cells. MELA increased the expression of the $GABA_A$ receptor γ-subunit but did not affect the expression of the α- and β-subunits and glutamic acid decarboxylase in primary cultured cerebellar granule cells, thus differing from the effects induced by pentobarbital. In conclusion, although MELA itself does not induce sleep, its synergistic effect with pentobarbital enhances the sleep behaviors induced by pentobarbital by modifying GABAergic systems [36]. Further evidence is needed to confirm how MELA affects GABAergic systems and find the answer why MELA alone did not induce sleep at the higher doses. In addition, the difference between the active ingredients of *Dimocarpus longan* with other hypnotics should be revealed. The underlying mechanism and its advantages may lead to a novel therapy pathway for insomnia and bring us with new thoughts.

3.12. *Crassocephalum bauchiense* (Hutch.) Milne-Redh. (Family: Compositae)

Crassocephalum bauchiense (Hutch.) Milne-Redh (Compositae) is a medicinal herb that has been reported to confer beneficial effects such as analgesia and antibacterial in the Cameroonian traditional system of medicine. It contains alkaloids and is consumed to treat insomnia, dementia, and psychotic disorders [81]. The aqueous extract (20, 40, 80 and 160 mg/kg, p.o.) and the alkaloid fraction (5, 10, 20 and 40 mg/kg, p.o.) of *C. bauchiense* inhibit novelty-induced rearing behavior in a dose-dependent manner, decrease apomorphine-induced stereotypy and fighting, and significantly decrease body temperature. Sodium pentobarbital-induced sleep duration was prolonged by the aqueous extract, and this effect was blocked by *N*-methyl-*β*-carboline-3-carboxamide, a partial inverse agonist of the benzodiazepine site of the $GABA_A$ receptor complex, and flumazenil, a specific antagonist of the benzodiazepine site of the $GABA_A$ receptor complex. However, bicuculline, which is a light-sensitive competitive antagonist of the $GABA_A$ receptor complex, was unable to inhibit the activity of the aqueous extract of *C. bauchiense*. In biochemical experiments, the concentration of inhibitory GABA was significantly increased in the brains of animals treated with the aqueous extract of *C. bauchiense* and sodium valproate. These results suggest that the aqueous extract and alkaloid fraction prepared from *C. bauchiense* leaves possess antipsychotic and sedative properties in rodents, which are mediated by the blockade of dopamine D-2 receptors and GABAergic activation [37]. The results of another study seeking to determine the toxicity of *C. bauchiense* extracts demonstrated that it is safe for the treatment of bacterial infection [82]. However, all these studies lacked the analysis of composition, so the specific composition of the *C. bauchiense* extract is eager to be estimated for future research. Thus, safety and composition studies represent the next phase of *C. bauchiense* research.

3.13. *Chrysanthemum morifolium* Ramat. (Family: Compositae)

The flowers of *Chrysanthemum morifolium* Ramat (FC) have been used in Asian countries for hundreds of years as a medicinal herbal tea. Its main components are volatile oils (e.g., borneol, camphor, and Chrysanthenone), flavonoids (e.g., diosmetin and luteolin), and amino acids (e.g., aspartic acid and glutamic acid) [83]. In China and some other Asia countries like Korea, dried FC in herbal tea has traditionally been used to treat insomnia. Some other studies have also been described additional biological features of FC include antioxidant, cardiovascular-protective, anti-tumorigenic, and anti-inflammatory properties. As Kim J W *et al*. reported in 2011, administration of an ethanol extract of *Chrysanthemum morifolium* flowers (EFC) prolonged pentobarbital-induced sleep duration at doses of 50 and 100 mg/kg without affecting sleep latency. However, treatment with EFC increased the rate of sleep onset and sleep duration induced by a subhypnotic dose of pentobarbital (28 mg/kg, i.p.), and the effects of 100 mg/kg EFC were similar to those of

muscimol. Furthermore, EFC treatment (100 mg/kg) increased the expression of GAD without influence the levels of the α1-, β2-, and γ2-subunits of $GABA_A$ receptor. The treatment of granule cells with EFC (1–4 μg/mL) significantly increased chloride ion influx. These results suggest that EFC may induce Cl^- channel opening in $GABA_A$ receptors [38]. It would be economically advantageous if this ornamental plant could be used in medicine, but further studies are needed to confirm that there is no difference between EFC and currently available drugs. Besides, how to make the extraction of the active ingredients efficient enough to become a medication may be the most important hurdle for FC before applying in pharmaceutical industry.

3.14. *Dorstenia arifolia* Lam. (Family: Moraceae)

Dorstenia arifolia has been used for years as a folk medicine to produce hypnotic, sedative, and anxiolytic effects; however, its pharmacological properties have not been studied. The smoke of its rhizome can induce a lethargic sensation. *D. arifolia* extracts have been reported to contain triterpenes esterified by fatty acids, unesterified triterpenes, triterpenes esterified by acetic acid, and furanocoumarin [84]. Gisele Z S *et al*. reported a significant decrease in the locomotor activity of mice after i.p. administration of a methanol extract (ME) of the *D. arifolia* rhizome (10 and 50 mg/kg). and this ME-induced sedation can be blocked by flumazenil (10 mg/kg), an antagonist of $GABA_A$ receptor. In addition, pentobarbital-induced sleep duration significantly increased after treatment with ME (50 mg/kg). Furthermore, ME promoted pentylenetetrazol-induced seizure protection and decreased mortality in a dose-dependent manner compared to the control groups. To sum up, it is likely that the sedative activity of ME is mediated by the GABAergic pathway, as GABAergic transmission produces profound sedation in mice [39]. Studies of *D. arifolia* have been limited, and further exploration is warranted.

3.15. *Magnolia officinalis* Rehder & E.H.Wilson (Family: Magnoliaceae)

Decoctions of *Magnolia officinalis* bark are prescribed as a drug in Hangekouboku-to, Saiboku-to and other traditional Chinese medicine. They are primarily used to treat clinical depression and anxiety-related disorders, such as anxiety neurosis and anxiety hysteria. *M. officinalis* bark extracts and several of its active constituents, such as honokiol and magnonol, have been studied in various mouse models. Their activities were compared with diazepam (a classic benzodiazepine anxiolytic that has been used to treat anxiety disorders since the 1960s) [85]. A proprietary patented blend of the extract from the bark of *Magnolia officinalis* Rehder & Wilson [Magnoliaceae] together with the extract of the bark of *Phellodendron amurense* Rupr [Rutaceae] has been produced and named Relora® (US Patent Nos. 6,582,735 and 6,814,987) to help alleviate symptoms associated with stress, such as nervous tension, irritability, concentration difficulties, and occasional sleeplessness [85].

Honokiol and magnolol (6, 6′, 7, 12-tetramethoxy-2, 2′-dimethyl-1-β-berbaman, $C_{18}H_{18}O_2$) are two major bioactive constituents of *M. officinalis* bark which proved to be efficient in sedative and hypnotic. Honokiol increased pentobarbital-induced sleep duration in a dose-dependent manner, and treatment with honokiol (20 or 50 μM) increased the $[Cl^-]$ concentration to 36.9 or 43.9 mM in primary cultured cerebellar neurons. Additional treatment of primary cultured cerebellar granule cells showed selective $GABA_A$ receptor α-subunit expression increase, on the other hand, chronic honokiol treatment did not affect GAD abundance. These results suggest that honokiol potentiates pentobarbital-induced sleep through $GABA_A$ receptor Cl^- channel activation [40]. In 2012, Wei-Min Qu *et al*. reported that i.p. honokiol (10 or 20 mg/kg) significantly shortened the sleep latency to NREM sleep and promoted NREM sleep by modulating the benzodiazepine site on the $GABA_A$ receptor in mice. Unlike other commonly used sedative-hypnotic drugs, honokiol did not affect the amount of REM sleep or the electroencephalogram power density of either NREM or REM sleep. Moreover, honokiol induced a type of NREM sleep similar to physiological NREM sleep and may be suitable for the treatment of insomnia [86]. Magnolol significantly shortened sleep latency and increased the amount of NREM and REM sleep after 3 h following its administration, and it also increased the number of NREM and REM sleep episodes. Immunohistochemical analyses revealed that magnolol increased c-Fos expression in the neurons of the ventrolateral preoptic nucleus (VLPO), a group of neurons in the hypothalamus that release the inhibitory neurotransmitter GABA during sleep, and decreased c-Fos expression in the arousal tuberomammillary nucleus, which is a dominant arousal regulation area located in the caudolateral hypothalamus. Magnolol-induced sleep-promoting effects and changes in c-Fos expression were reversed by flumazenil, an antagonist of the benzodiazepine site on the $GABA_A$ receptor. These results indicate that magnolol increases NREM and REM sleep *via* the $GABA_A$ receptor [41].

Several *M. officinalis* bark extracts have been approved for use, and their efficacy for the treatment of insomnia has been confirmed; especially honokiol and magnolol as we mentioned, it seems to have a great future for *M. officinalis* in insomnia treatment. Further studies may focus on isolation of other active ingredients and reveal its sedative-hypnotic mechanism more deeply. In addition, adverse reactions and drug interactions should also be evaluated.

3.16. *Glycyrrhiza glabra* L. (Family: Leguminosae)

Licorice root (*Glycyrrhiza glabra*, GG) is one of the most frequently used natural medicines in the world and has been described as “the grandfather of herbs”. Licorice root has been used medicinally in both Western and Eastern countries for more than 4,000 years. GG extract is extensively used in the US, and it is considered generally safe for use in foods by the FDA [42]. GG is also used as an ingredient in Suan Zao Ren Tang, which is a well-known traditional Chinese remedy for insomnia [76]. In addition, a root component (glycyrrhizin) is generally regarded as the major biologically active component of GG [87].

Cho S *et al*. reported dose-dependent pentobarbital-induced sleep potentiation and an increase in the amount of NREM sleep in mice, without a decrease in delta activity, after GG ethanol extract (GGE) administration. The

$GABA_A$-BZD receptor antagonist flumazenil inhibited the hypnotic effect of GGE. Moreover, the ability of glabrol, which was isolated from the flavonoid-rich fraction of GGE, to inhibit [^{3}H]-flumazenil binding to the $GABA_A$-BZD receptors in rat cerebral cortical membranes with a binding affinity (Ki) of 1.63 μM suggests a possible mechanism of action. The molecular structures and pharmacophore models of glabrol also indicate that the isoprenyl groups of glabrol are critical for binding to $GABA_A$-BZD receptors. Glabrol increases sleep duration and decreases sleep latency in a dose-dependent manner (5, 10, 25, and 50 mg/kg). In addition, its hypnotic effect can be blocked by flumazenil. These results imply that allosteric modulation of $GABA_A$-BZD receptors may be responsible for the sleep-inducing activity of GGE and its flavonoid glabrol [42].

In consideration of its safety and abundance using experience, it's reasonable to identify Licorice root has an ambitious application prospect. However, there are still several problems need to be solved besides the drug safety: the $GABA_A$ agonist-like effect of GGE remains unclear, and its elucidation awaits further study. Furthermore, how to draw the largest biological activity of Licorice root is also a challenge for researchers.

3.17. *Ecklonia cava* Kjellman (Family: Lessoniaceae)

Ecklonia cava Kjellman, an edible brown seaweed, is found in the coastal areas of Japan and Korea. The main active chemical components of *E. cava* are phlorotannins (e.g., eckol and phloroglucinol [88]). Cho *et al*. reported that treatment with an ethanol extract of *E. cava* Kjellman (ECK-E) significantly potentiated pentobarbital-induced sleep in mice. In the four solvent fractions that were isolated from ECK-E, the hypnotic activity was proportional to the total content of phenols and phlorotannins, which are known as seaweed polyphenols. The major phlorotannins of the ethyl acetate (EtOAc) fraction that demonstrated the highest activity were eckol, eckstolonol, dieckol, and triphlorethol-A, and their Ki (binding affinity, l M) values for [^{3}H]-flumazenil binding were 1.070, 1.491, 3.072, and 4.419 respectively. The hypnotic effects of the ECK-E and the EtOAc fractions were fully inhibited by flumazenil, a specific $GABA_A$–BZD receptor antagonist [43]. Furthermore, the ECK enzymatic extract displayed significant sleep-inducing (> 500 mg/kg) effects on pentobarbital-induced sleep in mice [89]. These results suggest that ECK-derived phlorotannins induces sleep through positive allosteric modulation of the $GABA_A$–BZD receptor.

3.18. *Melissa officinalis* L. (Family: Lamiaceae)

Lemon balm (*Melissa officinalis* L.), which belongs to the family Lamiaceae, is planted widely in central and southern Europe, Asia, and tropical countries, such as Brazil [45]. *M. officinalis* regulates a number of behavioral measures, such as disturbed sleep and reduced excitability and anxiety. *M. officinalis* oil can also be used to treat herpetic infections, spasms, and antimicrobial infections due to its antitumor and antioxidant properties [45, 46]. *M. officinalis* can greatly influence GABA metabolism by decreasing the level of GABA-T thereby increasing GABA levels, which indicate that *M. officinalis* could acts as a sedative in a way [44]. But a huge number of researches including animal model analysis and molecular biology studies are still need to be done to certitude its sedative effect before reality use.

4. DISCUSSION

Sedative-hypnotic drugs are the most common treatments for insomnia, of which the most commonly used are BZDs and non-benzodiazepines. However, adverse effects such as dependence, impairment of memory or movement, and residual effects have limited the prescription of these drugs [90]. Herbal medications have been widely used to treat insomnia worldwide for thousands of years. Increasing preclinical and clinical studies indicate the complex mechanisms by which herbal medicines treat sleep disorders and anxiety, such as that *Humulus lupulus* prolonged pentobarbital induced sleeping time and valerian improved sleep latency and quality in patients with sleep disorders. The mechanisms of herbal insomnia medications that target GABAergic systems include: (1) modifying $GABA_A$ receptors, the most common sites of action of the discussed herbal medications, as shown for kava-kava; (2) increasing GABA synthesis by activating GAD, as shown for *Zizyphus jujuba*; and (3) influencing GABA release, such as *Ternstroemia lineata*.

Although herbal medications show their effectiveness to some extent, several aspects of the psychopharmacology of herbal medicines must be resolved, including poor *in vivo* evidence of pharmacodynamics of human studies, lack of bioequivalence between plant extracts, difficulty in evaluating efficacy in clinical trials, and the production of standardized extracts, as various factors contribute to the composition of herbal preparations [91]. Herbal medications are also associated with a certain of adverse reactions and drug interactions such as allergic reactions of *Humulus lupulus* and the withdrawal symptoms at large doses of valerian [61, 92], the scaly skin rash called "kava dermopathy" and hepatic damage after long-term use of kava-kava were also reported [24]. The most serious hepatotoxicity might be concerned with pharmacogenomics effects and bile duct inflammation [52]. Honokiol has central depressant and muscle relaxant effects which may lead to behavioral side effects at high concentrate, but this is nearly impossible because it's unlikely to reach the purity required to initiate the side effects *via* inartificial magnolia bark [93]. The hypnotic effects of *Zizyphus jujuba* involve the activation of $GABA_A$ receptors, serotonin receptor binding, and increased GAD expression levels, which yield positive results, making *Zizyphus jujuba* a promising herbal medication to treat insomnia without serious adverse effects [94]. Also, a research concerned on anticancer agents reported that kava-kava and *Hypericum perforatum* may participate in potential pharmacokinetic interactions with anticancer drugs because of their potential to significantly modulate the activity of drug-metabolizing enzymes (notably cytochrome P450 isozymes) and/or the drug transporter P-glycoprotein [71]. But to our point of view, cancer patients may not pay so much attention to herbal insomnia medication even they are troubled by sleeplessness.

The effects of hypnotic plant-derived compounds on the GABAergic system should be meticulously investigated to facilitate the eventual discovery of new, more potent and more effective chemical entities that confer fewer adverse effects. However, due to the small total sample sizes of clinical trials and the high clinical heterogeneity, substantial effort may be required to obtain additional data from experimental studies and clinical trials to ensure the safe use of over-the-counter sleeping aids to prevent the occurrence of adverse reactions. Further, the effects of hypnotic plant-derived compounds on the GABAergic system should be meticulously investigated because the results of such studies may lead to the eventual discovery of new, more potent and effective chemical entities that confer fewer adverse effects.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

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