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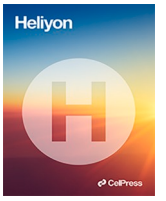

Review article

Research progress on the effect of medicine and food homology resources for sleep improvement

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ABSTRACT

Insomnia can have a negative impact on people's life or even cause mental or physical diseases. In China, the usage of medicine food homology herbal resources to treat insomnia has a long history. This review, which is based on the theory of traditional Chinese medicine (TCM), summarizes the research progress of medicine and food homology (MFH) resources in treating insomnia. Through literature search from the last 8 years, we compared the understanding of insomnia between TCM and modern pharmacology, found 21 kinds of MFH plants and 15 kinds of prescriptions containing MFH plants that have the effect of improving sleep and summarized the mechanism of their treatment of insomnia. Our study will provide theoretical support for the development and utilization of MFH plant resources with sleep-enhancing properties and provide positive insights and direction references for more effective treatment of insomnia disease.

1. Introduction

Adequate sleep is an indispensable and essential factor in maintaining good health, as it accounts for one-third of a person's life. However, according to the World Health Organization survey, about 16.4–25.0 % of individuals globally suffer from sleep problems [1]. Sleep disorders have emerged as a modern chronic epidemic disease, including insomnia, circadian rhythm disorders, sleep-disordered breathing, hypersomnia, parasomnias, and restless legs syndrome [2], and insomnia is the most prevalent one. The cause contribute to insomnia is mainly related to mental disorders and organ diseases [3], however, more and more modern people are developing bad sleep conditions as a result of different stress-related factors and societal changes [4]. The lack of sleep is harmful both physically and psychologically [5,6], not only affecting life quality, but also causing anxiety, depression, and even increasing the risk of suicide [7]. Benzodiazepines, benzodiazepine receptor agonists, and certain antidepressants are now the most often prescribed medications for the treatment of insomnia [8]. However, the treatment of these drugs is often dependent and tolerant, and certain side effects will be brought by long-term administration [9].

Traditional Chinese medicine (TCM) is a treasure of Chinese culture, which has long been embraced by the general public and is said to have precise curative effects, safe pharmaceutical formulations, and sound theoretical underpinnings for the prevention and treatment of illness. At present, a large number of studies have explored the Chinese medicinal herbs, especially the medicinal and edible homologous plants, that have the function of improving sleep. Without causing any undesirable side effects, medicine and food homology (MFH) plants are widely used in the folk. These plants can be utilized not only to make food for human use but also to treat illnesses and offer medical care [10,11]. MFH plants are favored by researchers and medical professionals due to their high nutritional

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Abbreviations

5-HT	5-hydroxytryptamine
5-HT1A	5-hydroxytryptamine receptor 1A
5-HT2A	5-hydroxytryptamine receptor 2A
A2AR	Adenosine Receptor A2a
ACH	Acetyl choline
ADMA	Asymmetric dimethylarginine
BCL-2	B-cell lymphoma gene2
CCK-8	Cholecystokinin-8
CKD	Chronic kidneys disease
DA	Dopamine
DDAH	Dimethylarginine dimethylaminohydrolase
DPR	Prostaglandin DP receptor
ERK	Extracellular regulated protein kinase
GABA	Gamma-aminobutyric acid
GABA(A)	γ-aminobutyric acid type A
GABA(B)	γ-aminobutyric acid type B
Glu	Glutamic acid
H1R	Histamine H1 receptors
HBA	P-hydroxybenzyl alcohol
HPA	Hypothalamic-pituitary-adrenal
IL	Interleukin
IFN	Interferon
MFH	Medicine and food homology
MT	Melatonin
NE	Norepinephrine
NF-κB	Nuclear factor kappa-B
NLRP3	Nucleotide-binding oligomerization domain -like receptor-pyrin-containing protein 3
NO	Nitric oxide
NREMS	Nonrapid eye movement sleep
OX2R	Orexin Receptor 2
PCPA	p-chlorophenylalanine
p-ERK	Phosphorylated extracellular regulated protein kinase
PGD2	Prostaglandin D2
PTSD	post-traumatic stress disorder
REMS	Rapid eye movement sleep
SCFA	Short-chain fatty acids
SD	Sleep deprived
SZS	Semen Ziziphi Spinosae
TCM	Traditional Chinese medicine
VLPO	Ventrolateral preoptic nucleus

value, high safety, abundance of functional components, and rich pharmacological effects [12]. It has been determined that the underlying mechanisms of MFH plants treating insomnia primarily involve regulating central neurotransmitters, affecting the level of inflammatory factors, and improving intestinal flora [13,14]. As the concept of diet therapy gradually came to the public consciousness [15], the exploration of MFH plants in the treatment of insomnia has become deepened.

Based on the holistic view of TCM, this paper carries out a comprehensive literature search by searching the latest progress through the retrieval of keywords such as 'insomnia', 'sleep-promoting', 'the Latin Name of herbs', 'the type of ingredients', and so on from Web of Science, PubMed, CNKI, Google Scholar and other literature databases. Firstly, the understanding of modern pharmacology and TCM on insomnia is described. Then, the TCM materials that can treat insomnia in MFH were screened, and the effect, experimental model and mechanism of action of these plant materials in the treatment of insomnia were summarized from the perspective of TCM syndrome differentiation and classification, as well as the sleep aid mechanism of related prescriptions. We hope that by sorting out and discussing these research results, we can provide theoretical support for the in-depth development of MFH materials and the exploration of TCM treatment ideas for insomnia.

2. Insomnia pathogenesis

2.1. The idea of modern pharmacology

Insomnia is one of the most common sleep disorders and is characterized by difficulty falling asleep, sleep maintenance, and/or poor sleep quality [16]. The mechanism of insomnia has been extensively studied in modern pathology and is mainly thought to be the problem of neurotransmitter secretion. However, with great importance attached to insomnia in recent years, more and more studies have found a variety of factors affecting its pathogenesis.

2.1.1. The disorders of neurotransmitter

It is generally believed that insomnia is related to the abnormal level of neurotransmitters caused by overexcitation of cerebral cortex nerves. The balance of neurotransmitters, which are mostly produced in the hypothalamus, determines whether a person is awake or asleep. It mainly includes gamma-aminobutyric acid (GABA) [17], melatonin (MT), 5-hydroxytryptamine (5-HT) [18], acetyl choline (ACH), dopamine (DA), norepinephrine (NE), glutamic acid (Glu), histamine [19] etc. In addition, the hypothalamus secretin/orexin system and the hypothalamic-pituitary-adrenal (HPA) axis are also involved in sleep-wake regulation [16].

2.1.2. The imbalance of intestinal flora

A growing body of evidence contends that the imbalance of intestinal flora can induce insomnia [14]. We are all aware that a diverse gut flora helps safeguard human health [20]. People with insomnia have lower levels of anaerobic bacteria and bacteria that produce short-chain fatty acids (SCFA), lower levels of intestinal microorganism diversity and richness, and altered microorganism composition [21]. The brain-gut-microbiota axis is a bidirectional communication system linking the gut and the brain, which results in the dysregulation of gut microbiota leading to insomnia by affecting neurotransmitter levels [22].

2.1.3. Inflammation and immune reaction

Chronic insomnia is an inflammatory disease that also has a pathological basis for a variety of diseases, and nucleotide-binding oligomerization domain-like receptor-pyrin-containing protein 3 (NLRP3)/caspase-1/interleukin (IL)-1β may be a potential therapeutic target for controlling inflammation and improving symptoms of chronic insomnia [23]. The imbalance between the circulating pro-inflammatory mediators IL-12, interferon (IFN)-γ and intercellular cell adhesion molecule-1 and the anti-inflammatory cytokine IL-1ra is also one of the key causes of chronic insomnia [24].

2.1.4. Traumatic event or illness

Severe anxiety, depression, and metabolic disorders can lead to the onset of insomnia [25], and other factors such as asthma and intake of stimulant substances can also play a role in worsening insomnia [26]. Traumatic events refer to brain tissue damage or dysfunction caused by accidents. Traumatic insomnia can occur without fully-fledged post-traumatic stress disorder (PTSD), or it can be a precursor to the subsequent development of PTSD [27].

2.2. The understanding of insomnia in TCM

In the ancient theory of TCM, insomnia belongs to the category of “Bu Mei”, characterized by the inability to get normal sleep frequently. MFH herbs belong to a class of TCM, and they have some similarities in their understanding of insomnia. As time goes by, the general understanding of insomnia has developed into a whole system in TCM. Based on the thinking of syndrome differentiation and holistic therapy, TCM points out the complicated etiology and pathogenesis of insomnia from a different perspective through collected medical practice experience by inspection, auscultation, olfaction, interrogation, and pulse palpation [28,29].

TCM regards the human body as a whole and believes that insomnia is highly related to constitution bias, Qi deficiency, Yang deficiency, blood stasis, and Qi stagnation [30]. It also highlights the significance of maintaining the equilibrium of the human body environment and the control of the zang-fu organs, as weakening and malfunctioning of the heart, liver, spleen, kidneys, and other organs can cause insomnia. TCM often categorizes the symptoms that appear at a certain stage in the course of a disease. Different syndrome types represent certain pathological properties in the course of disease development, the elements of symptom patterns in insomnia were identified as fire-heat and phlegm-heat [31]. It may be broadly classified into the following 9 kinds of syndrome types [32]: depressed liver transforming into fire, yin deficiency with overexuberant fire, phlegm-heat attacking internally, disharmony between heart and kidneys, heart-spleen deficiency, qi deficiency of both heart and gallbladder, stomach qi disharmony, exuberance of heart fire, and internal blockade of static blood.

3. The treatment of insomnia by MFH resources

China has a long history of using MFH resources, combining concepts like diet therapy, herbal cuisine and health preservation. Numerous plants with dual uses as food and medicine have steadily gained attention in the evolution of both traditional food culture and contemporary Chinese medicine. Among them, several plants possess sleep-improving effects [33]. The effectiveness of plants was assessed by the ancients based on their many qualities, which allowed them to ascertain the medicinal properties of various materials via experience and practice.

The evaluation of medicine efficacy comes from the nature, flavor and scent of the medicinal ingredients. Nature is the period that

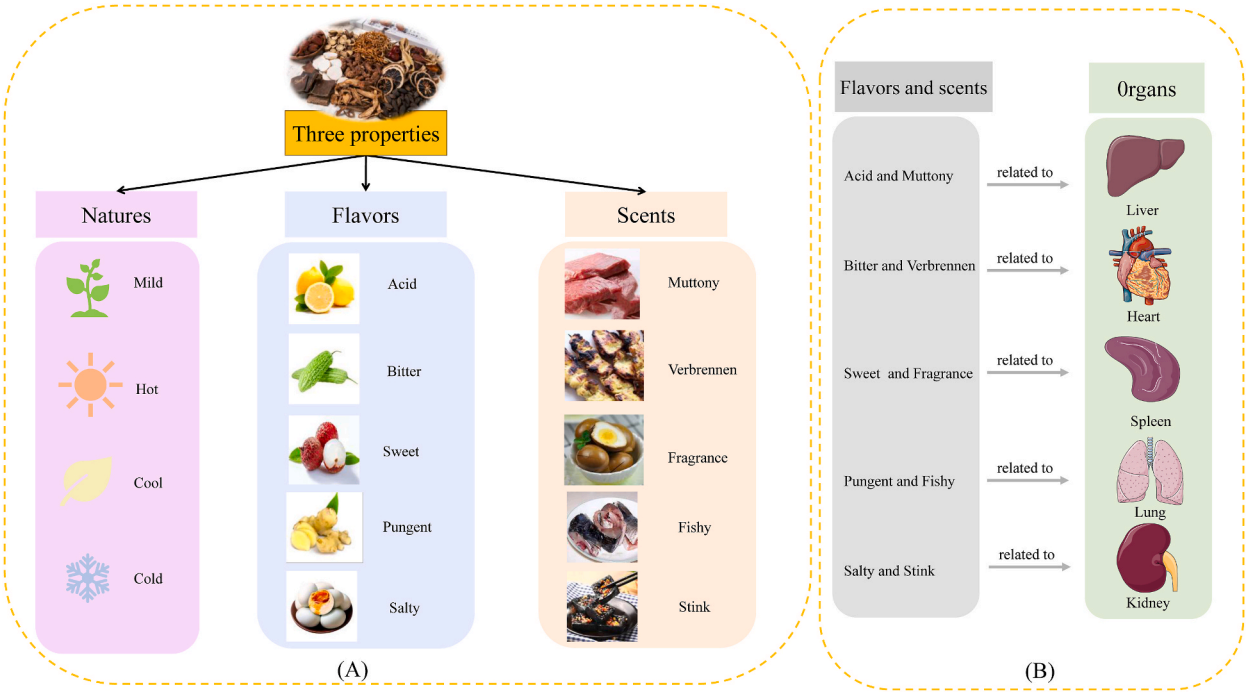

Fig. 1. The three properties of TCM according to the theory of Chinese medicine (A) and the relationship between its properties and target organs of drug effect (B) (Pictures sources: Baidu website and Servier Medical Art, Icons source: Powerpoint).

Table 1
The characteristics of 21 kinds of MFH plants that have the effect of improving sleep in TCM.

Herbs Latin name	Chinese name	Medicinal parts	Channel tropism	Classification	Properties	Function
Gastrodia elata Bl.	Tian Ma	Dried tubers	Liver	Liver pacifying and wind extinguishing medicine	Sweet	Calming liver yang. Dispelling wind and unblocking collaterals.
Prunella vulgaris L.	Xia Ku Cao	Dried ears	Liver Gallbladder	Antipyretic medicine	Pungent Bitter Cold	Clearing liver fire. Dispersing nodules and reducing swelling.
Nelumbo nucifera Gaertn	Lian Zi	Dried ripe seeds	Spleen Kidneys Heart	/	Sweet Astringent	Tonifying spleen and kidneys. Nourishing heart and tranquilizing mind.
Schisandra chinensis (Turcz.) Baill.	Wu Wei Zi	Dried ripe fruits	Lung Heart Kidneys	Astringent medicine	Acid Sweet Mild	Convergence of astringency. Nourishing qi and generating saliva. Tonifying kidneys and calming heart.
Cinnamomum cassia (L.) D. Don	Rou Gui	Dried barks	Kidneys Spleen Heart Liver	Interior-warming medicine	Pungent Sweet Hot	Warming middle energizer and dispelling cold. Regulating qi and relieving pain.
Polygala tenuifolia Willd.	Yuan Zhi	Dried roots	Heart Kidneys Lung	Sedative medicine	Bitter Pungent Mild	Tranquilizing mind. Communicating heart with kidneys
Poria cocos (Schw.) Wolf	Fu Ling	Dried sclerotium	Heart Lung Spleen Kidneys	Clearing damp and promoting diuresis medicine	Sweet Light	Diuretic. Invigorating spleen. Calming heart and tranquilizing mind.
Eleutherococcus senticosus (Rupr. & Maxim.) Maxim.	Ci Wu Jia	Dried roots and rhizomes or stems	Spleen Kidneys Heart	Tonifying deficiency medicine	Pungent Slightly bitter Mild	Nourishing qi and invigorating spleen. Tonifying kidneys and tranquilizing mind.
Ziziphus jujuba var. *spinosa* (Bunge) Hu ex H. F. Chow	Suan Zao Ren	Dried ripe seeds	Liver Gallbladder Heart	Sedative medicine	Sweet Acid	Nourishing heart and tonifying liver. Calming heart and tranquilizing mind. Reducing sweating and generating saliva.
Polygonatum sibiricum Delar. ex Redoute	HuangJing	Dried rhizomes	Spleen Lung Kidneys	yin tonic medicine	Sweet	Nourishing qi and yin. Strengthening spleen. Moisturizing lung. Benefiting kidneys.
Panax ginseng C. A. Mey.	RenShen	Dried roots and rhizomes	Spleen Lung Heart Kidneys	qi-invigorating medicine	Sweet Slightly bitter Slightly mild	Invigorating vital energy. Tonifying spleen and lung. Generating saliva and nourishing blood. Tranquilizing mind.
Ganoderma lucidum	Ling Zhi	Dried fruiting bodies	Heart Lung Liver Kidneys	Sedative medicine	Sweet	Invigorating qi and tranquilizing mind. Relieving cough and asthma
Perilla frutescens (L.) Britt.	Zi Su	Dries leaves	Lung Spleen	/	Pungent Mild	Eliminating cold pathogenic factors. Promoting qi circulation and stomach function.
Lilium brownii var. *viridulum* Baker	Bai He	Dried fleshy scaly leaves	Heart Lung	Tonifying deficiency medicine	Sweet Slightly cold	Nourishing yin and moisturizing lung. Clearing heart and tranquilizing mind.
Nelumbo nucifera Gaertn	He Ye	Leaves	Liver Spleen Stomach	/	Bitter	Clearing heat and eliminating dampness. Emanating energy upwards. Cooling blood for hemostasis.
Liriope spicata Lour.	Mai Dong	Dried roots and tubers	Heart Lung Stomach	Nourishing-Yin medicine	Sweet Slightly	Moisturizing lung and nourishing yin. Benefiting stomach and

(*continued on next page*)

Table 1 (*continued*)

Herbs Latin name	Chinese name	Medicinal parts	Channel tropism	Classification	Properties	Function
					bitter Slightly cold	generating saliva. Clearing heart and eliminating restlessness.
Amygdalus communis L.	Xing Ren	Seeds	Lung Stomach	/	Sweet	Moisturizing lung and regulating stomach. Dispelling phlegm and relieving cough.
Rhodiola rosea L.	Hong Jing Tian	Dry roots and rhizomes	Lung Heart	Tonifying deficiency medicine	Sweet Bitter	Nourishing qi and promoting blood circulation. Eliminating wheezing.
Curcuma longa L.	Jiang Huang	Dried rhizomes	Spleen Liver	Blood activating and stasis resolving medicine	Pungent Bitter Mild	Promoting blood and qi circulation. Unblocking meridians and relieving pain.
Panax notoginseng (Burk.)F. H.Chen	San Qi	Dried roots and rhizomes	Liver Stomach	Hemostatic medicine	Sweet Slightly bitter Mild	Dispelling blood stasis and hemostasis. Reducing swelling and relieving pain.
Gynostemma pentaphyllum (Thunb.) Makino	Jiao Gu Lan	Whole grasses	Lung Spleen Kidneys	Tonifying deficiency medicine	Bitter Slightly sweet Cool	Nourishing qi and invigorating spleen. Resolving phlegm and relieving cough. Nourishing heart and tranquilizing mind.

medicinal materials grow; it corresponds to the four seasons—spring, summer, fall, and winter—which are classified as mild, hot, cool, and cold. *Salvia miltiorrhiza Bunge*, for instance, thrives during the winter, suggesting that the medicine has a cold character and a heat-clearing action. Flavor, the taste of the tongue, is related to the five organs: the liver, heart, spleen, lung, and kidneys are represented by the categories of acid, bitter, sweet, pungent, and salty. Scent refers to the smell of the nose, also corresponds to the five viscera, and can be further divided into muttony, verbrennen, fragrance, fishy and stink. The four natures, five flavors and five scents are the most basic characteristics to determine the medicinal properties of ancient people (Fig. 1).

The treatment of MFH herbs based on calming the heart, nourishing the blood, tranquilizing the mind, tonifying the body, and lowering fire, which has therapeutic effects on insomnia by regulating mental agitation and improving blood circulation. Following the TCM theory and the medicinal properties of MFH herbs, a total of 21 kinds of plants were retrieved (Table 1), they have been demonstrated to effectively relieve sleeplessness under different syndrome types.

3.1. The type of depressed liver qi transforming into fire

This type describes how stress affects the liver's normal function, leading to symptoms such as depression and irritability. *Gastrodia elata* and *Prunella vulgaris* are two treatments for this ailment that can be utilized in the MFH plants. *Gastrodia elata*, is a medicinal plant whose dried tuber is typically used for soothing the liver and clearing collaterals [34], while, *Prunella vulgaris* is known as a self-healing plant, traditionally used for clearing the liver and expelling fire [35].

3.1.1. Gastrodia elata Bl

Significant therapeutic effects on insomnia have been observed for two phenolic compounds isolated from *Gastrodia elata*: gastrodin and p-hydroxybenzyl alcohol (HBA) [36]. Long et al. [37] measured the content of 5-HT, the ratio of phosphorylated extracellular regulated protein kinase (p-ERK) to extracellular regulated protein kinase (ERK), and the protein expression of B-cell lymphoma gene2 (BCL-2), IL-1β, and IL-6 in the cerebral cortex of experimental mice confirmed the sleep aid effect of gastrodin. Furthermore, an adenosine analogue isolated from *Gastrodia elata*, N6-(4-hydroxybenzyl) adenine riboside, elicited somnogenic effects by activating GABAergic neurons in the ventrolateral preoptic nucleus (VLPO), that is mediated by adenosine Receptor A2a (A2AR) and effectively ameliorated acute stress-induced insomnia [38].

3.1.2. Prunella vulgaris L

For the first time, Lin et al. [39] investigated the plant's active components that are crucial to its ability to prevent insomnia. In a 70 % ethanol-eluted fragment of *Prunella vulgaris*, they discovered three potential bioactive ingredients, namely mangiferin, rosmarinic acid and salviaflaside. Their ability to promote sleep has been demonstrated in mice, but the potential mechanisms and pathways haven't been well elucidated.

3.2. The type of disharmony between heart and kidneys

Being a prevalent form of condition in TCM, the goal of treatment is to communicate kidneys with the heart by nourishing their Yin and Yang and relieving their fire. Four MFH herbs are retrieved. As a food material, multiple functional components contained in the seed of *Nelumbo nucifera* make it have anti-inflammatory, anti-cancer, anti-anxiety effects, and also have therapeutic use in protecting kidneys and heart [40]. In addition to being a substantial preventive measure against colitis, the fruit of *Schisandra chinensis* is a promising resource for the treatment of neurological illnesses [41,42]. The bark of the warm-tonifying herb *Cinnamomum cassia* has been employed in medicinal dishes to help dredge meridians and tonify kidney Yang [43]. A type of natural herb called *Polygala tenuifolia* can preserve the brain, enhance memory, prevent dementia, calm hypnosis, clear phlegm, and ease coughing [44].

3.2.1. Nelumbo nucifera Gaertn

The mature, dried seed of the nymphaeaceae plant *Nelumbo nucifera* is known as the lotus seed. Researchers conducted an experiment on fruit flies fed with caffeine and found that 10 mg/ml of lotus seed extract decreased nocturnal activity and overall sleep duration [45]. According to a recent study by Jo et al. [46], the water extract from lotus seeds, which has a GABA content of about 2.33 mg/g, can lengthen sleep duration and shorten wake times in rats with caffeine-induced insomnia by interacting with GABA (A) receptors [46].

3.2.2. Schisandra chinensis (Turcz.) Baill

Schisandrin B, a lignin compound, is one of the primary active ingredients in the dried, ripe fruit of *Schisandra chinensis* that we employ for therapeutic purposes [47]. It can statistically shorten the sleep latency and lengthen the sleep period in rats. This result is attained by controlling the amounts of GABA and 5-HT in the hypothalamus [48]. Zhu et al. [49] also demonstrated that the supercritical carbon dioxide fluid extraction of *Schisandra chinensis*, which contains more than 58 % of lignans can effectively reverse the negative effects of caffeine and *p*-chlorophenylalanine (PCPA). Although the underlying mechanism might be relevant to the serotonergic and GABAergic systems, further investigation is needed to verify.

3.2.3. Cinnamomum cassia (L.) D. Don

It has been demonstrated that cinnamon extract reduces PCPA-stimulated rat insomnia by increasing serotonin and melatonin levels and decreasing norepinephrine levels to enhance the HPA axis and modify brain neurotransmitter systems [50].

3.2.4. Polygala tenuifolia Willd

Polygala tenuifolia has been proved to have an effective sleep-aid effect in elderly rats with insomnia [51]. The *Polygala tenuifolia* saponins fraction has been shown to have therapeutic potential in various neurological diseases [52], as evidenced by improving the levels of neurotransmitters and hormones associated with the serotonergic system and GABAergic system and regulating the levels of inflammatory cytokines [53]. Meanwhile, another study shown that when tenuifolin, the primary constituent of the saponins fraction, is administered orally in doses ranging from 40 to 80 mg/kg, it dramatically improves mouse model sleep quality and ability to fall asleep. The mechanism attributed to its sleep-aid function is increasing the proportion of c-Fos in cholinergic wake-promoting neurons, reducing the level of NE, and up-regulating the levels of GABA and ACH [54]. The sleep-inducing effects of tenuifolin have also been demonstrated in zebrafish models [55].

3.3. The type of heart-spleen deficiency

The typical clinical manifestations of heart-spleen deficiency syndrome are palpitation, insomnia, fatigue, poor appetite and loose stool, and the main treatment is to tonify the spleen and heart, nourishing blood and calming. The MFH plants that can be used to treat this disease are *Poria cocos*, *Eleutherococcus senticosus*, *Semen Ziziphi Spinosae* (SZS), *Polygonatum sibiricum* and so on. *Poria cocos* is a member of the poraceae family, whose active components are found in the tissues of the heart, liver, spleen, lung and kidneys [56,57]. *Eleutherococcus senticosus* is a medicinal plant with neuroprotective effects, and its root is its medicinal site [58]. Concentrated in the four channels of the heart, spleen, liver, and kidneys, SZS is the seed of *Ziziphus jujuba* in the rhamnus family, mostly used to treat qi deficiency syndrome [59]. *Polygonatum sibiricum* has an impact on nourishing the heart and spleen, tonifying qi and blood, which is beneficial in treating mild insomnia [60,61].

3.3.1. Poria cocos (Schw.) Wolf

The sleep-aid effect of the dried sclerotium of *Poria cocos* has been elucidated in clinical trials [62]. Oral administration of *Poria cocos* 75 % ethanol extract possesses an alleviating insomnia role in mice with endocrine disorders via promoting inhibitory neurotransmission via the γ-aminobutyric acid type A (GABA(A)) receptors [63].

3.3.2. Eleutherococcus senticosus (Rupr. & Maxim.) Maxim

Ciwujia Tablets, made from the extract of the dried rhizome of *Eleutherococcus senticosus* were elucidated to have the ability to alleviate the insomnia symptoms of rats by increasing the content of 5-HT and GABA in the brain and suppressing the synthesis of DA and NE [64]. Furthermore, the molecular mechanism of its effect is associated with the regulation of tryptophan metabolism, folate biosynthesis, phenylalanine metabolism, and other metabolic levels in the body [65], which are involved in 5-HT synthesis.

3.3.3. *Ziziphus jujuba var. spinosa (Bunge) Hu ex H. F. Chow*

As the most frequently cited herb in insomnia [66], the anti-insomnia activity of SZS has been extensively studied for many years [67], which has recently been found that can ameliorate the symptoms of insomnia by bolstering liver and brain function [68]. In a rat model, the therapeutic effects of SZS 70 % ethanol extract on insomnia were confirmed to be related to the serotonergic and GABAergic systems [69]. Numerous metabolic pathways are involved in this process, including hydrogenation, hydrolysis and glycolaldehyde acidification, phenylalanine, tyrosine and tryptophan biosynthesis, phenylalanine metabolism, niacin and niacinamide metabolism, etc [70,71]. SZS water extracts also have the ability to alleviate insomnia symptoms by controlling the amounts of monoamines and amino acid neurotransmitters in the brain [72], in which spinosin, 6" -feruloylspinosin, Jujuboside A, and Jujuboside B are responsible to the sleep-inducing effects [73]. Additionally, SZS extract could reverse the imbalance of intestinal flora brought on by sleeplessness and increase the contents of SCFAs in feces [74].

The effective components of sleep aid in SZS and its target are also continuously being unearthed. The saponin of SZS is the main component of its sedative and hypnotic effect, which can remarkably alter the concentrations of 5-HT, DA, NE, Glu, IL-6, IL-1β, nitric oxide (NO), prostaglandin D2 (PGD2) and prostaglandin DP receptor (DPR) [75]. A recent experiment conducted by Xiao et al. [76] confirmed that two saponins, jujuboside B and jujuboside A, show the best binding capacity with GABA-specific receptors GABA(A) Rα1 and GABA(A)Rγ2 in the hypothalamus [76]. Jujuboside A mainly accumulates in the hippocampus region of the brain [77] and produces a mechanism of action similar to melatonin by regulating the expression of GABA receptor mRNAs and affecting the intercellular cytokine network that connects the brain's nerve cells [78]. The jujubosides of SZS will also have an impact on the generation of cerebral asymmetric dimethylarginine (ADMA) level and dimethylarginine dimethylaminohydrolase (DDAH) in sleep-deprived rats [79]. Moreover, vitexin and nuciferine in SZS showed DA antagonistic activity and 5-HT2A antagonistic activity, respectively [80].

3.3.4. *Polygonatum sibiricum Delar. ex Redoute*

In a PCPA-induced insomnia test, researchers found that GABA(A)Rα2 and 5-HT1A could both dramatically rise in protein and mRNA levels in response to the aqueous extracts of *Polygonatum sibiricum* rhizome. Additionally, glyceryl monolinoleate and oleamide, two fatty acids, had better binding activity in the competitive binding assays than did the extract [81]. In a follow-up study, they found that one of the isomers of glyceryl monolinoleate, glyceryl-1-monolinoleate, is the major active substance through binding to GABA (A)- benzodiazepines receptors [82].

3.4. *The type of deficiency of heart qi*

In TCM, the term "heart qi disharmony" refers to a state of weak or dysfunctional heart, primarily caused by insufficient heart energy. Both *Panax ginseng* and *Ganoderma lucidum* are frequently used medications that are intended to calm nerves and stimulate qi. As a popular herbal remedy for several pathological disorders and diseases, *Panax ginseng* root has been shown to increase life energy [83,84]. *Ganoderma lucidum* is a tranquilizing drug that has cardiovascular protective effects and is often used to treat insomnia [85,86].

3.4.1. *Panax ginseng C. A. Mey*

Rats lacking sleep benefit from the preventive properties of *Panax ginseng*'s main active constituent, total ginsenosides [87]. Shao et al. [88] demonstrated that ginseng extract ginsenoside Rg5 and Rk1 have a sleep-promoting effect. By raising the GABA/Glu ratio, it may be possible to up-regulate the expression of GABA (A) and GABA (B). In the meantime, 5-HT1A expression may also be up-regulated Protopanaxatriol ginsenoside Rg1 shows its sleep-promoting effect via the modulation of noradrenergic and serotonergic systems [89]. The sedative and hypnotic effects of ginseng glycoproteins are linked to regulating 4 metabolic pathways including arginine and proline metabolism, purine metabolism, alanine, aspartate and glutamate metabolism, and steroid hormone biosynthesis [90].

3.4.2. *Ganoderma lucidum*

After 28 days of administrating the acidic portion of *Ganoderma lucidum* mycelium alcohol extract, PCPA-induced sleep in mice was improved. The extract therapy resulted in higher levels of 5-HT and Tph2, Iptr3 and Gng13 transcripts, decreased serum lipopolysaccharide and elevated peptidoglycan levels. Its ability to induce sleep is also affected by metabolites and gut flora [22].

3.5. *The type of stomach qi disharmony*

Originating in China, *Perilla frutescens* (L.) Britt. has the function of regulating qi and resolving damage in the stomach [91]. The inhalation administration of *Perilla frutescens* essential oil can ameliorate the symptoms of insomnia by modulating the level of GABA (A)α1 and GABA(A)α2 in the hypothalamus and cerebral cortex [92]. Rosmarinic Acid, one of the major constituents of *Perilla frutescens*, has been reported to have the potential to treat insomnia also through GABA(A)ergic transmission in rodents [93].

3.6. *The type of exuberance of heart fire*

Eating foods with a fire-clearing effect, such as *Lilium brownii*, Lotus Leaf, and *Liriope spicata*, which have anti-inflammatory and protective effects on cardiomyocytes, can help reduce symptoms of exuberance of heart fire, which include upset, chest tightness, and

dreaming [94,95].

3.6.1. *Lilium brownii var. viridulum Baker*

A series of studies conducted by Si et al. [96] provides the evidence that *Lilium* possesses the potential to be an agent for treating insomnia. First, they discovered that *Lilium* extract may help reduce insomnia by enhancing levels of 5-HT, NE, MT, and other neurotransmitters in the hypothalamus, as well as HPA axis serum hormones. They subsequently verified that *Lilium* can reverse the imbalance of intestinal flora diversity and abundance and faecal metabolic phenotype and that it can also alleviate insomnia by influencing the metabolism of arachidonic acid, tryptophan [97,98]. In a different investigation, scientists extracted a novel chemical called liliumtides A from lily bulbs and shown through the pentobarbital-induced sleep duration experiment that it decreased sleep latency and considerably increased sleep duration [99]. The primary metabolic pathway utilized by liliumtides A may resemble *Lilium*'s, albeit not having been fully characterized.

3.6.2. *Lotus leaf (Nelumbo nucifera)*

Researchers observed that Lotus Leaf extract can successfully treat sleep disturbances brought on by caffeine by extending sleep duration, improving sleep quality, and acting as a hypnotic agent. Concurrently, the results of the ligand binding studies using [H-3] -flumazenil indicated that the ingredient in lotus leaf extract known as quercetin-3-glucuronic acid ester can improve sleep via binding to GABA(A) receptors [100].

3.6.3. *Liriope spicata Lour*

Liriope spicata is a common medicinal and dietary supplement whose saponins are important in promoting sleep. It has been traditionally used to treat insomnia. Both the extraction of total saponins and the purification of saponins from L. spicata have been shown in the study by Li et al. [101] to be efficient in reducing mice's sleep latency. The full saponins portion, which contained more Lilium saponins, showed a stronger capacity to increase the expression of neurotransmitter receptors, whereas the purified saponins component showed a more evident impact in lowering the levels of inflammatory markers.

3.7. *The type of internal blockade of static blood*

Individuals who have an internal static blood blockage frequently experience sleeplessness, manic episodes, nightmares, etc. The major goals of treatment are to relax the spirit, control qi, and increase blood flow by eliminating blood stasis. In this regard, *Amygdalus communis*, *Rhodiola rosea*, *Curcuma longa*, *Panax notoginseng* and *Gynostemma pentaphyllum* have more prominent therapeutic advantages [83,102–105].

3.7.1. *Amygdalus communis L*

Amygdalus communis aqueous extract affects pentobarbital-induced sleep by increasing the frequency of falls asleep and lengthening the duration of sleep, which results in considerable sedative and hypnotic effects [106].

3.7.2. *Rhodiola rosea L*

Rhodiola is a Chinese herbal medicine commonly used to intervene in insomnia. When evaluating the saponin fraction's capacity to reduce insomnia symptoms, researchers found that the saponin-rich fraction generated following additional purification had a greater effect on improving sleep than the entire saponin fraction. The saponin contents of the two fractions were 28.92 % and 65.69 %, respectively. Both of them could remarkably raise the plasma concentrations of GABA, 5-HT, NE, PGD2 and IL-1β, while simultaneously decreasing the levels of IL-6 [107].

3.7.3. *Curcuma longa L*

Curcuma longa is one of the most common plants used to treat disorders of the central nervous system [108]. The powder form of *Curcuma longa* root becomes Turmeric. Turmeric extract has been shown to have a pro-sleep impact by inhibiting histamine H1 receptors (H1R), which reduces sleep latency and improves nonrapid eye movement sleep (NREMS) [109]. Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are polyphenolic compounds produced from turmeric known as curcuminoids. In a study, researchers used molecular docking assays, H1R binding assays and knockout animal assays found that curcuminoids and its constituents shorten sleep latency and boost the amount of NREMS in mice induced by pentobarbital by strongly binding to the H1R, functioning as H1R modulators, indicating that they may be useful in the treatment of insomnia [110].

3.7.4. *Panax notoginseng (Burk.) F.H.Chen*

Recent research by Shao et al. [111] has demonstrated that although the saponins derived from the leaves of *Panax notoginseng* by methanol or water are quite different in diversity and richness, they will yield comparable compounds, such as ginsenoside Rd and ginsenoside F-2, upon intestinal flora metabolism. Therefore, it is proved that *notoginsenoside* can alleviate insomnia symptoms by transformed in intestinal flora.

3.7.5. *Gynostemma pentaphyllum (Thunb.) Makino*

G. pentaphyllum has a wide range of pharmaceutical uses. In a study, two sections rich in saponins have the effect of shortening sleep latency and extending sleep time, however, the portion containing 40.7 % saponin content was more effective in stimulating the

expression of 5-HT1A, 5-HT2A and TNF-α, while the part with 67.5 % saponin content was more significant in increasing the expression of GABA(A)Rα2, GABA(A)Rα3, GAD 65/67 and IL-1β [112].

4. The prescription of MFH for insomnia treatment

Chinese herbal medicines have the advantage of multi-component, multi-target and multi-pathway treatment. To further their benefits, these medications frequently employ precise ratios of various plants to build formulae. Many formulas consisting of MFH resources have been proved to have advantages in alleviating insomnia symptoms by regulating the function of multiple parts of the body.

One of the most commonly used TCM formulas is Suanzaoren Decoction, with SZS as the main ingredient, is said to help calm the mind, ease liver discomfort, treat depression, and enhance sleep [113]. It may influence to ameliorate insomnia by affecting several metabolic pathways, including the biosynthesis of valine, leucine and isoleucine, the metabolism of triglycerides, the metabolism of alanine, aspartate and glutamate, the metabolism of phenylalanine, cysteine and methionine, and the metabolism of tryptophan [114,115]. In rats given PCPA to produce sleeplessness, Suanzaoren Decoction can ameliorate the pathological alterations in the liver and brain tissues [116]. Its active ingredients can be detected in the blood plasma and brain of rats [117]. The protective effect of Suanzaoren Decoction on the liver was related to the restoration of bile acid content [118]. It can also play a role in improving insomnia by regulating the structure of the bacterial community [119]. In a study of modified Suanzoren Decoction (MSZRD), which is supplemented with *Dendrobium officinalis* to SZRD, researchers found that MSZRD could help improve gastrointestinal discomfort related insomnia, by regulating the expression of Orexin-A, cholecystokinin-8(CCK-8) and Orexin receptor 2(OX2R), the release of related neurotransmitters and the homeostasis of HPA axis in insomnia mice were affected [120,121].

Clinical trials have proved the efficaciousness of Jiaotai Pill, including *Rhizome Coptidis and Cinnamomum cassia*, in treating cardio-renal incompatibility insomnia [122], it can increase GABA levels in the brain and serum [123], and also causes the changes of neurotransmitters in the heart, liver, adrenal gland and other tissues [124], so that neurotransmitters can function as messengers to communicate between heart and kidneys. Li et al. [125] found that Jiaotai pills can improve insomniac behaviors in rats by regulating the levels of monoamine neurotransmitters and inhibiting the expression of organic cationic transporters in multiple organs. In addition, its effect on improving the level of insomnia inflammation has also been confirmed, which is achieved by inhibiting the transfer of inflammatory molecules along the gut-brain axis [126].

Chaihu Longgu Muli Decoction originated from the Treatise on Febrile Cold written by Zhang Zhongjing, a physician of the Eastern Han Dynasty [127], with the potential to improve sleep better than conventional medications [128]. Chaihu Longgu Muli Decoction has a sedative and hypnotic effect on insomniac mice, and can play a protective role in the hypothalamic and control the activation of NLRP3 inflammasome [129]. Adenine-induced chronic kidney disease (CKD) model mice can greatly benefit from Chaihu Longgu Muli Decoction in terms of their circadian rhythm and sleep disturbance. This may be due to the up-regulation of Orexin-A and CaMK-K2/AMPK phosphorylation, as well as the inhibition of the nuclear factor kappa-B (NF-κB) signaling pathway, which reduces inflammation in the nervous system [130].

Sun et al. [131] verified that Shuangxia Decoction water extract, which modulates the immunological system and serotonergic system, had more sedative and hypnotic effects on mice than ethanol extract in the PCPA-induced insomnia model. In another study, 10 compounds in Shuangxia Decoction were found to enter the blood and 9 compounds into the brain. It was further found that rosmarinic acid was mainly distributed in the hypothalamus and striatum, and caffeic acid was primarily detected in the hypothalamus, striatum and hippocampus. The results of molecular docking showed that danshensu and HMLA had strong binding properties to GABA (A) receptor and DA2 receptor [132]. Moreover, the impact of Shuangxia Decoction lyophilized powder on the sleep model of drosophila melanogaster stripped by light has also been confirmed [133].

Huoxue Anshen Decoction has protective effects on a sleep deprived (SD)-induced myocardial injury, mainly in improving hormone, inflammation, and endothelial function, reducing infarct size, improving the pathologic state of the heart, restoring heart function, improving cardiomyocyte apoptosis [134]. Hewei Anshen Decoction lowered the expression of orexin A and enhanced the expression of CCK-8 in the hypothalamus of insomnia rats [135]. In addition, common sleep aid prescriptions include Nyctinastic herbs decoction [136], Zhumian Granules [137], Shumian Capsule [138], Songyu Anshen Fang [139], *Foshouningshen* decoction [140], Banxia Houpo decoction [141]. The specific effects are shown in Table 2.

5. The development and innovation of MFH research method

5.1. The wide application of network pharmacology

With the ongoing advancements in research methods, the fusion of TCM and modern biotechnology has become a new trend in this field. Based on the idea of systems biology, network pharmacology is a method of network analysis that is crucial to the investigation of TCM disease mechanisms [142]. Its process includes the determination of drug components, the prediction of drug targets, the prediction of disease targets, the establishment of the network diagram between drug-component-target-disease, the establishment of the protein interaction network, and the further exploration of the mechanism of action through GO and KEGG analysis. By the combination with herbal remedies, TCM syndromes, complex illnesses, and other conditions, to investigate how Chinese medicine extracts or prescriptions work [143]. For instance, Gong et al. [144] discovered 48 key targets between the ingredients in SZS and sleeplessness using network pharmacology. According to GO and KEGG pathway analyses, the primary pathways implicated in its sleep-inducing effect were seven different kinds, with the brain ligand receptor route being the most significant. In another study, a Sishen

Table 2
The specific function of TCM formulas used to treat insomnia.

Pharmaceutical name	Composition (Medicinal materials belonging to MFH)	Experimental model, object	Dosage	Biological sample collection	Pharmacological effects	Refs.
Nyctinastic herbs decoction	*Albizia julibrissin* Durazz. Polygonum multiflorum Thunb Lilium brownie F. E. Brown var. viridulum Baker *Nelumbo nucifera Gaertn*	PCPA, male Wistar rats	3,6,12 g/kg	Hypothalamus	Nyctinastic herbs decoction reduced the proportions of NE, DA and ACh in PCPA induced insomnia rats, suggesting that it could effectively inhibit the excitability of the central nervous system.	[136]
Zhumian Granules	*Ziziphi Spinosae* Semen *Schisandrae Chinensis* Fructus *Caulis Polygoni* Multiflori *Angelicae Sinensis* Radix *Corydalis* Rhizoma *Anemarrhenae* Rhizoma	PCPA, male KM mice	1.8,3.6,7.2 g/kg	Brain	Zhumian Granules maintain the production of 5-HT,5-HTIAA, NE, DA, GABA and decrease the cell death of nerve	[137]
HuoxueAnshen Recipe	*Salvia miltiorrhiza* Bunge *Panax pseudoginseng* Wall. *Astragalus mongholicus* Bunge *Ziziphus jujuba* var. *spinosa* (Bunge) Hu ex H. F. Chow	the modified multiple platform method, male Wistar rats	1.4 g/kg	Heart	HuoxueAnshen Recipe could not only improve hormone disorders, inflammation, endothelial dysfunction, and mental state after SD, but also ameliorate SD-induced myocardial apoptosis and I/R injury.	[134]
Heweianshen Decoction	*Pinellia ternate* (Thunb.) Breit *Coix lacryma-jobi L. var.mayuen* (Roman.) Stapf *Citrus reticulata* Blanco *Poria cocos* (Schw.) Wolf *Acorus gramineus Cortex albiziae Caulis Polygoni* Multiflori	PCPA, male Wistar rats	5.25,10.5,21 g/kg	Hypothalamus	Heweianshen Decoction decreased orexin A content and increased CCK-8 content in hypothalamus of insomnia rats in a dose-dependent manner	[135]
Shuangxia decoction	*Pinellia ternate* (Thunb.) Breit *Prunella vulgaris* L.	PCPA, male Wistar rats	2.5,5and10 g/kg	Cerebral cortex, hypothalamus	Shuangxia decoction alleviate PCPA induced insomnia by increasing the content of 5-HT in cortex, decreasing the content of DA and NE, enhanced the expression of 5-HT1A and 5-HT2A receptors in hypothalamic and reduced serum levels of IL-1, TNF-α	[131]
Chaihu-Longgu-Muli Decoction	*Bupleurum chinense* DC. *Fossilia Ossia Mastodi Scutellaria baicalensis* Georgi *Zingiber officinale* Roscoe	PCPA, male ICR mice	5,10 mg/kg	Brain, Hypothalamus	Chaihu-Longgu-Muli Decoction has regulatory effect on DA, 5-HT, NE, and 5-HTR1A, can ameliorate the histopathological changes in the hypothalamic of sleepless mice and deactivation the NLRP3 inflammasome.	[129]
	Panax ginseng C. A. Mey. *Cinnamomum cassia* (L.) J.Presl *Poria cocos* (Schw.) Wolf	a 0.2 % adenine diet, C57/BL6 mice	2.36,4.725and9.45 g/kg	Hypothalamus, hippocampus	Chaihu-Longgu-Muli Decoction can improve sleep disturbances and reduce neuron loss in CKD mice. The mechanism may be related to the up-regulation of orexin-A and increases in the phosphorylation level of	[130]

(*continued on next page*)

Table 2 (*continued*)

Pharmaceutical name	Composition (Medicinal materials belonging to MFH)	Experimental model, object	Dosage	Biological sample collection	Pharmacological effects	Refs.
	Pinellia ternata (Thunb.) Makino *Rheum palmatum* L. *Ostrea gigas* Thunberg *Ziziphus jujuba* Mill.				CaMKK2/AMPK, which further inhibit NF-κB downstream signaling pathways without affecting renal function.	
Jiaotai pill	*Rhizome Coptidis Cinnamomum cassia* (L.) J.Presl	PCPA, male SD rats	2.2 mg/kg	Brain stem, hippocampus, prefrontallobe and hypothalamus, r serum	Jiaotai pill increased the level of GABA in brain stem, prefrontal lobe and serum	[123]
		PCPA, male SD rats	6 ml/kg	Brain, heart, liver, kidneys, adrenal gland, serum, urine	The levels of 5-HT, epinephrine, DA, Glu, ACH, NE, GABA, 5-HIAA and vanillaldehyde (HVA) in the blood and tissues of insomnia rats were all changed. Jiaotai Pill reduced the levels of neurotransmitters in different tissues, especially in brain and adrenal gland. It is suggested that one of the mechanisms of Jiaotai pill in treating cardio-renal incompatibility insomnia may be through regulating the content of neurotransmitters in blood and tissue, thereby connecting the heart and kidneys and restoring the relationship between normal information exchange and physiological function of the body.	[124]
		PCPA, male SD rats		Hypothalamus, blood, heart, liver, kidneys	It can down-regulate the activity of organic cation transporters and norepinephrine in peripheral organs by down-regulating the activity of serotonin transporter and dopamine transporter in hypothalamus and various organs transporter expression is upregulated in the hypothalamus. The underlying molecular mechanism involves the regulation of monoamine transporters and organic cation transporters.	[125]
		Exposed to 80–100 dB of noise, obesity-resistant rats	1.1,2.2 g/kg	Blood, intestine and brain tissues	Jiaotai pill can reduce the increased levels of Aβ42, caspase3, IL-6 and TNF-α in rat brain tissue caused by sleep deprivation, improve the activation of intestinal TLR4/NF-κB pathway, and reduce the expression of IL-6 and TNF-α. It also has beneficial effects on tight junction protein and intestinal permeability in intestinal tissue. The possible underlying mechanism is by preventing an inflammation trigger being transferred through the gut-brain-axis.	[126]
Suanzaoren decoction	*Ziziphi Spinosae Semen* *Poria cocos* (Schw.)	PCPA, Male Wistar rats	31.2 g/kg	serum and brain	Suanzaoren decoction can regulate various phenotypes of host metabolism in insomnia	[115]

(*continued on next page*)

Table 2 (*continued*)

Pharmaceutical name	Composition (Medicinal materials belonging to MFH)	Experimental model, object	Dosage	Biological sample collection	Pharmacological effects	Refs.
					rats, so as to play an anti-insomnia role.	
	Wolf *Anemarrhena asphodeloides* Bunge. *Ligusticum chuanxiong* Hort. *Glycyrrhiza uralensis* Fisch	PCPA, male SD rats	8.0 g/kg	Serum, hippocampus, liver, brain	It can improve the liver and brain lesions caused by insomnia, and regulate the levels of neurotransmitters in the hippocampus (5-HT, DA, Glu, GABA, NE) and inflammatory cytokines in the serum (PGD2, TNF-α, IL-1β, IL-6). This therapeutic effect is closely related to amino acid metabolism and other pathways	[116]
		A sleep deprivation device, Male kunming mice	13 g/kg	Serum, liver, ileum	With the determination of AST, ALT, TBA in serum and liver index, Suanzaoren Decoction was proved had liver protection effect on insomnia mice. It can also improve the pathological changes of liver tissue and ileum tissue and restore bile acid levels in each tissue, which shows that Suanzaoren Decoction can repair the disorder of bile acid hepatoenteric circulatory system caused by insomnia.	[118]
		PCPA, male SD rats	8.0 g/kg	Hippocampus, intestinal contents	Suanzaoren Decoction regulates the structure of intestinal flora and promotes the production of short-chain fatty acids by influencing metabolic pathways such as amino acids, thus indirectly playing a role in improving sleep.	[119]
Modified Suanzaoren decoction	*Ziziphus jujuba* Mill. var.*spinosa* (Bunge) Hu ex H.F.Chou *Dendrobium officinale* Kimura et Migo *Ligusticum chuanxiong* Hort. *Poria cocos* (Schw.) Wolf *Glycyrrhiza uralensis* Fisch	chronic unpredictable mild stress combined with PCPA, ICR male mice	3.6,7.2,14.4 g/kg	Serum、hypothalamus、hippocampus	Three doses of modified Suanzoren decoction can increase the production of 5-HT in hypothalamus, and affect the content of NE and DA. GABA and Glu in the blood of the insomniac mice were also affected. The modified Suanzoren decoction significantly improved the pathological damage of the hippocampus of mice, regulated the amount of CRH, ACTH, COTR, and decreased the expression of OX2R protein. Therefore, it is concluded that the hypnotic effect of this innovative health food is related to the regulation of neurotransmitter levels to restore the homeostasis of the HPA axis.	[120]
		Modified water-filled multiple platforms, Male SD rats	1.55,3.72,7.44 g/kg	Serum, brain, stomach	By regulating CCK-8 and orexin A, modified Suanzoren decoction increased the expression of GABA and decreased the secretion of GAS, MTL, gastric acid and pepsin, thus producing hypnotic and gastric protective effects on insomnia rats with gastrointestinal discomfort.	[121]

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Table 2 (*continued*)

Pharmaceutical name	Composition (Medicinal materials belonging to MFH)	Experimental model, object	Dosage	Biological sample collection	Pharmacological effects	Refs.
Shumian Capsule	*Ziziphi Spinosae Semen* *Bupleuri Radix* *Paeoniae Radix Alba* *Albiziae Flos* *Albiziae Cortex* *Bombyx batryticatus* *Cicadae Periostracu* *Junci Medulla.*	sleep deprivation box, Male C57BL/6 mice	0.25,0.5,1 g/kg	Hypothalamus	Shumian Capsule treatment restored the alterations in the expression levels of OX1R and OX2R. Meanwhile, the results indicated that the regulation of OX1R by Shumian Capsule treatment is through MT receptors,	[138]
Songyu Anshen Fang	*Nardostachys chinensis Batal* *Curcuma petiolate* *Rosa rugosa* *Fossilia Ossis Mastodi* *Concha Margaritifera Usta* *Cauls Polygoni Multiflori* *Salviae Miltiorrhizae Semen Ziziphi Spinosae* *Cortex Albiziae*	PCPA, male SD rats	8.5and17 g/kg	Hypothalamus	Songyu Anshen Fang can significantly normalized the level of GABA, Glu and adjusted the expression of GABA(B) mRNA and GABA(B) protein of PCPA-induced insomnia rats. The mechanism may be related to the modulation of neurotransmitter levels and the expression of GABA(B) receptor in the hypothalamus	[139]
Foshouningshen decoction	*Citrus medica* 'Fingered' *Lilium brownii* var. *viridulum* Baker *Semen Ziziphi Spinosae* *Poria cocos* (Schw.) Wolf *Nelumbo nucifera* Gaertn	PCPA, male SD rats	6,12,24 g/kg	Hippocampus	Foshouningshen decoction can up-regulate the content of 5-HT in hippocampus and increase the expression level of 5-HT1AR protein and mRNA in hippocampus.	[140]
Banxia Houpo decoction	*Pinellia ternate* (Thunb.) Breit. *Magnolia officinalis Rehd.et Wils.* *Poria cocos* (Schw.) Wolf *Perilla frutescens* (L.) Britt. *Zingiber officinale Roscoe*	Pentobarbital sodium induces sleep,male SD rats	500 mg/kg	Serum and urine	Banxia Houpu Decoction can induce sleep in rats by regulating the content of glutamine, creatine phosphate and 2-ketoglutaric acid to reduce nerve excitability in brain.	[141]
Polygala tenuifolia granule	*Polygala tenuifolia*	PCPA + D-gal, male SD rats	0.0875,0.175,0.35 g/kg	Hippocampus	The level of 5-HT and GABA are upregulated in Aged Insomnia Rats, while the level of Glu is downregulated. The sedative effect of the granule in aged insomnia rats may be related to neuro, metabolism pathways, especially GABAergic signaling pathway.	[51]
Ciwujia Tablets	*Eleutherococcus senticosus*	PCPA, male SD rats	600,300,150 mg/kg	Brain	The treatment of insomnia by Ciwujia Tablets is involved in the regulation of 5-HT, GABA, DA, NE and several pathways discovered by network pharmacology	[64]

pills-herb-compound-target-insomnia network was established to confirm the relationship between Sishen pills and insomnia, and the key targets were verified by silicon and animal experiments [145].

5.2. In-depth utilization of molecular docking

Molecular docking has been extensively employed in investigating the sleep-promoting properties of MFH materials, exploring the binding ability of effective components and receptors, and serving as a guide for the mining of effective components. Huang et al. [146]'s research uses molecular docking and bioinformatics analysis, and through the study of small drug molecules, it is found that they can regulate the insomnia-related protein, providing a basis for the clinical treatment of insomnia. Zheng et al. [147] used bioinformatics tools such as similarity integration docking, homologous modeling, and bioinformatics to find that the lignan extract of *Kadsura longipedunculata* can target the 5-HT1AR receptor.

5.3. The emergence of other new technologies

Furthermore, there exist other situations that offer fresh perspectives for the comprehensive investigation of MFH resources. Some researchers have confirmed that by integrating TCM syndrome images with modern medical text data, the therapeutic effect can be enhanced [148]. Various possibilities of herbs as raw materials for functional food were explored recently by means of fermentation and other technological measures [149,150]. It is also possible to create novel compounds through structural modifications, for example, HBA synthesized with carboxylic acids form a derivative, 4-hydroxybenzyl alcohol 3-furancarboxylic acid diester, which exhibited the strongest sedative-hypnotic activity compared with HBA and other derivatives [151]. In certain studies, the identification of five zang-fu syndromes by machine learning is used to investigate the fundamental principles of diagnosis and treatment [152,153]. These cases of applying multiple new methods to develop and innovate in the field of TCM increase its practicality and popularity.

6. The limitations on using MFH plants to treat insomnia

Insomnia has the characteristics of high incidence, complex pathogenesis and wide prevalence, although the treatment by MFH plants has a solid research base, there are still several issues in this area of research, including the definition of pathological indicators, the safety of administration and the optimization of the model.

6.1. Lack of key pathological indicators

The experience of ancient people provides the theoretical foundation for the MFH therapy of insomnia, which is mostly based on subjective feelings and a lack of objective reaction to the key indicators of efficacy. Additionally, the etiology, pathophysiology, syndrome distinction, and classification of insomnia are not unified or systematically introduced. Although MFH herbs has long been used to treat insomnia, there is a dearth of studies on the pathophysiology of this combination of modern medicine and TCM therapy (Deng et al., 2022).

6.2. Concerns of toxicological safety

TCM is believed to come from natural herbs and have no toxic side effects on the body, but safety problems in Chinese medicine also occur from time to time [154]. This may be due to extrinsic factors such as the residues of endocrine disrupting chemicals from planting to processing [155], or it can be intrinsic. For example, the saponins of *Polygala tenuifolia* are toxic ingredients, excessive or prolonged raw consumption of it can have toxic effects on the gastrointestinal tract [156]. Excessive intake of *Panax ginseng* saponin also caused acute toxicity in young zebrafish [157]. Cyanide-containing compounds in *Rhodiola rosea* can release cyanide ions, long-term use should also pay attention to its potential toxicity [158]. The etiology of insomnia is complicated and has a protracted duration, only a small number of studies have addressed the safety of TCM decoction, and the majority of clinical trials have not taken this into consideration (Jun et al., 2020). Small sample sizes and unknown diseases have an impact on clinical trial dependability. Therefore, well-designed, larger randomized controlled trials are needed in the future to improve the safety and accuracy of studies.

6.3. Model imperfection

A disease-fitting animal model can aid in translational medicine by providing insights into the pathophysiology [159]. The most commonly used model of insomnia is a rodent model induced with PCPA, which can significantly shorten the sleep time and prolong the sleep latency of experimental animals [160]. In addition, there are insomnia models established for animals such as fruit flies and zebrafish [45,55], as well as cases of insomnia induced by caffeine, ACTH as a chemical factor [46,161]. Since insomnia is a subjective representation, it is not possible to reproduce it in vitro. To evaluate the effects of sleep assistance in vitro, the researchers employed cells that are important in controlling circadian cycles or suppressing neural activity, such as HT22 cell [76], PC12 cell [162] and hypothalamic cell [93]. However, the clinical manifestations of insomnia are intricate, frequently coexisting with other illnesses, and result in the malfunction of several bodily functions. As a result, the single component construction method is unable to accurately replicate the symptoms of sleeplessness; instead, the multi-factor modeling approach more closely aligns with TCM [163]. Few in vivo

Table 3
The underlying mechanism involved in the effect of the treatment of insomnia by MFH resources.

The name of TCM	Extraction methods	Types	Animal types	Sampling parts	Caused pharmacological changes	Related molecular mechanism	Refs
Nelumbo nucifera	Water	Extract	Rat	Cerebral cortex	GABA(A)-R2↑ 00GABA(B)-R1↑ 5-HT1A↑	Played a GABAergic and serotonergic action	[46]
Cinnamomum cassia (L.) D. Don	70 % ethanol	Extract	Rat	Serum	CRH↓ ACTH↓ CORT↓	Improving the HPA axis and regulating neurotransmitter levels in the brain	[50]
				Hypothalamus	5-HT↑ NE↓ MT↑		
Poria cocos(Schw.) Wolf	75 % ethanol	Extract	Rat	Superior Cervical Ganglion	Cl^- Influx↑ GABA-induced Cl^- current↑	Promoting inhibitory neurotransmission via the GABA(A) receptors	[63]
Semen Ziziphi Spinosae	Water	Extract	Rat	Hippocampus	5-HT↑ GABA↑ Glu↓ DA↑ Gln↓ Aspartate↓	Improves brain and liver function	[68]
				Serum	PGD2↑ Glu↓ phenylalanine ↓ 2-phenylacetamide↓		
				Liver	phenylalanine↓ tyrosine↓ tryptophan↓		
Semen Ziziphi Spinosae	70 % ethanol	Extract	Rat	Hypothalamus	5-HT↑ GABA↑ HTR1A↑ HTR2A↓ GABRA1↑ GABRG2↑	Regulate 5-serotonergic synapses (important related targets: HTR1A and HTR2A) and GABAergic synapses	[69]
Semen Ziziphi Spinosae	Water	Extract	Rat	Brain	5-HT↑ GABA↑ Glu↓ NE↓ DA↑	Modulating the levels of monoamines and amino acid neurotransmitters in the brain.	[72]
Semen Ziziphi Spinosae	70 % ethanol and petroleum ether	Extract and oil	Rat	Feces	SCFAs↑	Regulate metabolic profiles and improve the composition of intestinal flora	[74]
Polygonatum sibiricum Delar. ex Redoute	Water	Extract	Rat	Cerebral cortex	GABA(A)-R2↑ 5-HT1A↑	Mediated by the regulation of GABAergic and serotonergic signaling	[81]
Ganoderma lucidum	Alcohol	Extract	Mice	Hypothalamus	5-HT↑	Related to serotonergic synapse signaling in the hypothalamus and the gut microbiota of mice	[22]
				Serum	Lipopolysaccharide (LPS)↓ Peptidoglycan (PG)↑		
				Gut	alters gut metabolites changes the composition of the gut microbiota		
Lilium brownii var. *viridulum* Baker	60 % acetone	Extract	Rat	Serum	CRH↓ ACTH↓ CORT↓	Regulate the hypothalamic related neurotransmitters, melatonin, and homeostasis of HPA axis,	[96]
				Hypothalamus	5-HT↑ NE↓ MT↑ GABA(A)-R↑ 5-HT1A↑		
Perilla frutescens (L.) Britt.	Steam distillation	essential oil	Mice	Hypothalamus	5-HT↑ GABA↑ GABA(A)α1 ↑ GABA(A)γ2↑	Through the GABAergic pathway	[92]
				Cerebral cortex	5-HT↑ GABA↑		

(*continued on next page*)

Table 3 (*continued*)

The name of TCM	Extraction methods	Types	Animal types	Sampling parts	Caused pharmacological changes	Related molecular mechanism	Refs
					GABA(A)α1 ↑ GABA(A)γ2↑		
Panax ginseng C. A. Mey.	/	Total ginsenosides	Rat	Plasma	ACTH↓ TSH↓ CA↓ CORT↓ Testosterone↓ serotonin ↓	Regulating the dysfunction of energy metabolism, BCAA metabolism, adenosine metabolism, and oxidative stress.	[87]
				Hippocampal	NO↓		
Rhodiola rosea L.	70 % ethanol→petroleum ether、ethyl acetate、butanol→50 % ethanol	Two saponin extracts	Rat	Plasma	IL-1β↑ IL-6↓ NE ↑ GABA↑, 5-HT↑ DA↓ PGD_2↑	Modification of the serotonergic, GABAergic, and immune systems.	[107]
				Hypothalamus Hippocampus	$5\text{-}HT_{1A}$↑ $5\text{-}HT_{2A}$↓ GABA(A)Rα2 ↑ GABA(A)Rα3↑ DPR↑ PGD2↑ IL-1β↑		
Gynostemma pentaphyllum (Thunb.) Makino	75 % ethanol→petroleum ether、ethyl acetate、n-butanol→50 % ethanol	Two saponin extracts	Mice	Plasma	5-HT↑ DA↑ NE↑ Glu↓ IL-6↓ TNF-α↑ IL-1β↑ PGD_2↑	Modification of the serotonergic, GABAergic, and immune systems	[75]
				Hypothalamus Hippocampus	DPR↑ PGD2↑ $5\text{-}HT_{1A}$↑ $5\text{-}HT_{2A}$↓ GABA(A)Rα2 ↑ GABA(A)Rα3↑ IL-1β↑ IL-6↓ TNF-α↑		
Polygala tenuifolia Willd.	85 % ethanol→petroleum ether、ethyl acetate、n-butanol→70 % methanol	Two saponin extracts	Mice	Plasma	5-HT↑ DA↓ NE↓ PGD2↑ TNF-α↑ IL-1β↑	Altered serotonergic, GABAergic and immune systems	[53]
				Hypothalamus Hippocampus	5-HT1A↑ 5-HT2A↓ GABA(A)Rα2↑ GABA(A)Rα3↑ DPR↑ PGD2↑ iNOS↑ TNF-α↑		
Semen Ziziphi Spinosae	Petroleum ether→70 % ethanol→ethyl acetate、n-butanol→50 % ethanol	Two Saponin Extracts	Mice	Plasma	5-HT↑ DA↑ NE↑ Glu↓ IL-6↓ IL-1β↑ NO↑ PGD2↑	Modulation of some neurotransmitters, cytokines and hormones.	[75]
				Hypothalamus Hippocampus	5-HT1A↑ 5-HT2A↓ GABA(A)Rα2↑ GABA(A)Rα3↑ GAD65/67↑ IL-6↓		

(*continued on next page*)

Table 3 (*continued*)

The name of TCM	Extraction methods	Types	Animal types	Sampling parts	Caused pharmacological changes	Related molecular mechanism	Refs
Liriope spicata Lour.	85 % ethanol →petroleum ether、ethyl acetate、n-butanol→70 % ethanol	Two Saponin Extracts	Mice	Plasma	IL-1β↑ PGD2↑ DPR↑ 5-HT↑ DA↑ NE↑ NO↑ PGD2↑ IL-6↓ TNF-α↑	regulating the expression inflammatory cytokines and neurotransmitters in plasma, along with influencing receptor levels in the hypothalamus and hippocampus	[101]
				Hypothalamus Hippocampus	5-HT1A↑ 5-HT2A↓ GABA(A)α2↑ GABA(A)α3↑ GABA(A)α5↑ IL-6↓ PGD2↑ DPR↑		

models are able to replicate the pathological damage associated with insomnia, and even fewer have been examined to be consistent with TCM symptoms.

7. Discussion and conclusions

Insomnia is a common sleep disorder characterized by insufficient sleep time or poor sleep quality that interferes with normal daytime activities. Based on the theory of TCM, MFH plants has unique advantages in alleviating the symptoms of insomnia, enhancing daily nutrition, and improving the quality of life. Even if Chinese and Western medicine have distinct understandings of the pathophysiology of insomnia, it is nevertheless possible to refer to insomnia clinically in a comprehensive manner.

In this paper, a total of 21 kinds of MFH plants were retrieved to play a role in the corresponding TCM syndrome type of insomnia, including deficiency tonic drugs, qi tonic drugs, sedative drugs, etc., with sweet taste and mild nature as the main features. They can act on the heart, liver, spleen, kidneys and other organs, producing a variety of different beneficial effects in the TCM concept. The effects of the isolated monomers and extracts by different methods are shown in Tables 3 and 4. The primary mechanism for promoting sleep is controlling the brain's neurotransmitter levels, mainly involving GABAergic [164]and serotonergic systems [165], which is compatible with the TCM concept of "An Shen" for treating insomnia. In Chinese, "Shen" refers to the nervous system, hence tranquility is defined as soothing the nerves or reducing the excitability of the cerebral cortex to reduce excessive arousal. Moreover, the inflammatory response is also intimately linked to fire and qi depression. It has been reported that ginseng water extract can reduce the myocardial inflammatory response of the TLR4/NF-κB pathway induced by qi-deficiency [166]. Additionally, controlling body metabolism, treating abnormalities of the intestinal flora, and enhancing intestinal health are all associated with numerous organs, including the heart, liver and intestines [167]. It has been proved that the main idea of regulating the body's homeostasis, which plays a role in assisting sleep, can also be confirmed by the theory of modern pharmacology.

After the aforementioned 21 plants were examined, we discovered that saponins, the most prevalent components in Chinese herbal medicines and potential contributors to the nine syndrome types, were the essential element in most MFH plants. Fig. 2 depicts the structure of the saponins that are mentioned in this paper. Whether exist as monomers or compounds, saponins can play a sedative and hypnotic role by affecting the levels of neurotransmitters, inflammatory factors and hormones in the serum, hippocampus, hypothalamus and cerebral cortex, as well as improving the imbalance of intestinal flora. Furthermore, studies have shown that ginsenosides can improve heart function and lessen the damage caused by myocardial infarction [168]; Anemarrhena saponins can improve liver injury induced by insulin resistance [169]; saponins can also improve the pathological alterations and antioxidant capacity of kidneys and spleen [170,171]. These studies enlighten us that perhaps the pathological damage of internal organs brought on by insomnia can also be improved by saponins or MFH plants, which is consistent with the improvement of body function and repair of internal organ damage of TCM, and it may also reinforce the meridian-reducing effect of Chinese herbal medicine to help sleep.

Chinese culture is rich and profound. Throughout its lengthy history, TCM has created several MFH remedies to enhance sleep, which have broad development prospects and have been widely used in the clinical treatment of insomnia for thousands of years. Merely relying on simplistic ideas to elucidate the process is insufficient, since several factors collaborate through different channels to enhance sleep's ability to modulate the functioning of various organs. However, the amount of research on prescription drugs is still limited and insufficient, only fifteen kinds of agents were identified in all from the literature search conducted between 2016 and 2024. Compared with medicinal extracts and monomer components, the formulation of sleep aids has more distinctive effects involving the regulation of various organs damage in the entire body, such as the heart, liver and kidneys [121,124,125,134]. Especially, according to O'Brien and Weber [172], the heart is a major organ implicated in insomnia. Meanwhile, other compounds including

Table 4
Functional component of MFH plants for the treatment of insomnia.

Component	Classifications	TCM	Animal types	Sampling parts	Caused pharmacological changes	Related molecular mechanism	Refs
Gastrodin	Phenolics	*Gastrodia elata Bl.*	Mice	cerebral cortex	5-HT ↑ p-ERK/ERK↓ BCL-2↑ IL-1β↑ IL-6↓	Inhibit ERK molecular phosphorylation and improve inflammatory response	[37]
Rosmarinic Acid	Polyphenols	*Perilla frutescens* (L.) Britt.	Rat	hypothalamus	GAD65/67 ↑	through GABA(A)-ergic transmission	[93]
N6-(4-hydroxybenzyl) adenine riboside	Adenosine	*Gastrodia elata Bl.*	Rat	VLPO	c-fos of GABA↑	Mediated by the A2ARs to activate GABAergic neurons in the VLPO	[38]
schisandrin B	Lignans	*Schisandra chinensis* (Turcz.) Baill.	Rat	hypothalamus	5-HT↑ 5-HIAA ↑ HTRlA↑ GABA↑ Glu↓ GAD↑ GABA-T↓ GABA(A) Rα1↑ GABA(A) Rγ2↑	Regulate GABAergic and serotonergic action	[48]
Tenuifolin	Saponins	*Polygala tenuifolia* Willd.	Mice	VLPO、LC、Pef、LDT PPT PPT、LDT	NE↓ GABA↑ Ach↑	Mediated the activation of endogenous GABAergic and/or by inhibition of no-radrenergic systems	[54]
			Zebrafish	Whole larvae	gad1 ↑ gabra1↑ gat1↑	Regulate GABAergic systems	[55]
Jujuboside B	Saponins	*Semen Ziziphi Spinosae*	Rat	Hippocampus	GABA↑ Glu↓ Glu/GABA↓ 5-HT↑ DA↓ 5-HT/DA ↑ GABA(A)Rα1 and γ2↑	Activate the GABA nervous system	[76]
Jujuboside A	Saponins	*Semen Ziziphi Spinosae*	Rat	intestinal tissues	IL-1α↓ MIP-1α↓ IL-1β↓ IL-2↓	Downregulate the synthesis and secretion of pro-inflammatory cytokines in intestinal mucosal system and be transmitted to the brain through the blood circulatory system	[78]
				brain tissues	IL-1α↓ IFN-γ↓ IP-10↓ TNF-α↓		
			Rat	Cerebral	8-isoprostane↓ DDAHI↑ DDAHII↑ ADMA↓ NE↓ Glu↓ 5-HT↑ GABA↑	Decreasing the level of ADMA and improving the production of DDAH	[79]

(*continued on next page*)

Table 4 (*continued*)

Component	Classifications	TCM	Animal types	Sampling parts	Caused pharmacological changes	Related molecular mechanism	Refs
Rg5/Rk1	Saponins	*Panax ginseng* C. A. Mey.	Mice	Serum	GABA↑ Glu↓	Affecting the GABA nervous system and the serotonin nervous system	[88]
				CECUM	GABA↑ 5-HT↑		
			Rat	Serum, hippocampus, hypothalamus, and cortical	GABA↑ Glu↓		
				Brain	GABA(A) receptor↑ GABA(B) receptor ↑ 5-HT1A ↑		
Rg1			Rat	locus coeruleus (LC), dorsal raphe nucleus (DRN), laterodorsal pontine tegmentum (LDT), VLPO	NE↓	Related to the regulation of norepinephrine and serotonergic systems	[89]
				DRN	Fos + ratio of serotonergic neurons↑		
				LC	Fos + ratio of noradrenergic neurons↓		

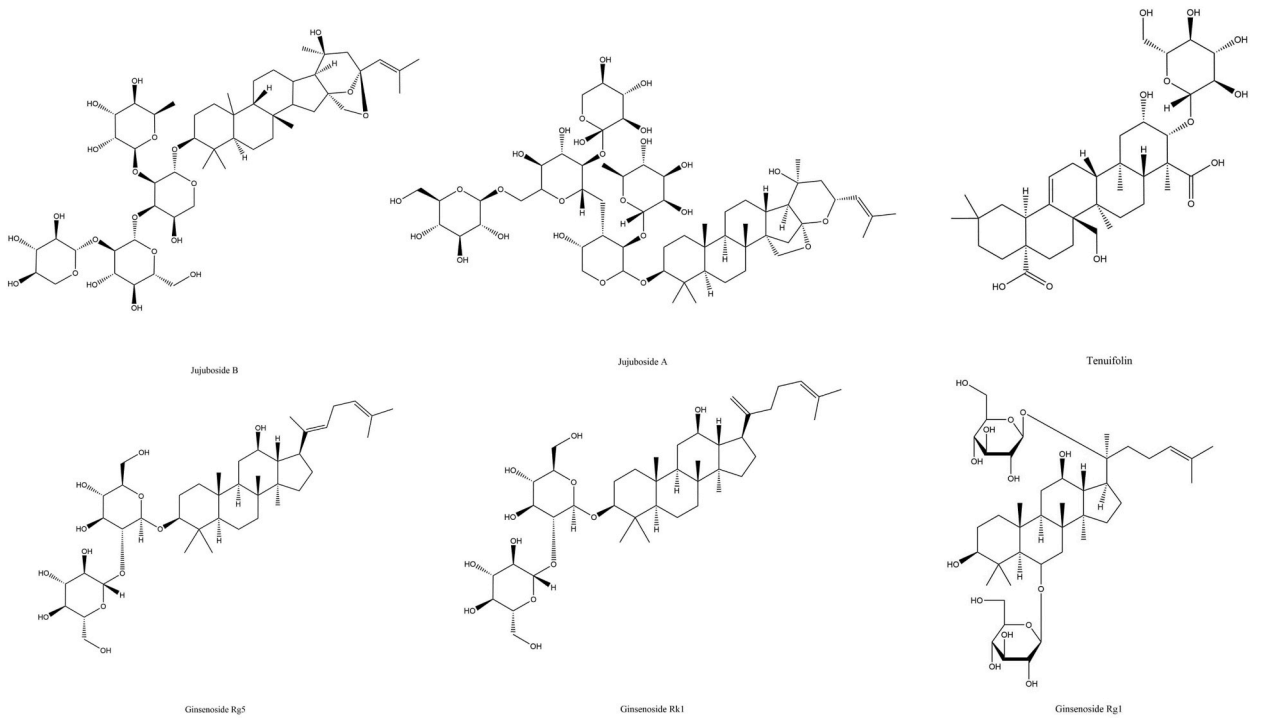

Fig. 2. The structure of the saponins mentioned in the paper (draw by software ChemDraw Profession 17.1).

Chaihu-Longgu-Muli Decoction, Shuangxia decoction, and HuoxueAnshen Recipe work better in controlling bodily functions and enhancing the quality of sleep. As a consequence, it is worth noting that insomnia symptoms vary over the course of the disease, and from individual to individual, it's not feasible to study the role of just one pathway. While the single ingredient can benefit many organs, the formula's mix of constituents will work in concert with one another.

At present, there are still a lot of study topics worth to be explored. First of all, MFH plants have complex compositions and a diverse range of compounds. The active ingredients in plants that help aid sleep are mostly saponins, flavonoids, while the rest of the compounds have received less research. Finding a particular chemical component will pave the way for more research in the future, enabling the use of pharmacokinetics and other technologies to identify potential pharmacodynamic chemicals. Second, given the intricacy of the pathophysiology of insomnia and the features of TCM's multi-pathway and multi-target therapy, combining several plants to create a combination formula and investigating their synergistic effects through the use of multi-omics and other biological research strategies will be more beneficial to the development of drug clinical treatment and the use of MFH resources. Finally, applying the theory of TCM to explore the effect and mechanism of pharmacodynamic components is rarely documented in the literature. This suggests we fully utilize the benefits of TCM theory by integrating dietetics, food science, TCM, and other disciplines. By combining the established pathways and TCM treatment concepts, we can better understand the mechanism underlying its role.

CRediT authorship contribution statement

Jingxuan Ma: Writing – original draft. **Shan Huang:** Writing – review & editing. **Lin Shi:** Supervision. **Yixiao Shen:** Writing – review & editing. **Shiyu Gao:** Visualization. **Zhaoxia Wu:** Supervision.

Data availability statement

No data associated in this work has been deposited into a publicly available repository.

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because no human or animal studies were involved.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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