International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Research Advances in the Efficacy and Mechanism of Guipi Capsule in Reducing Insomnia

Shikang Li[1], Xuemei Feng[2]

[1]School of Health Economics and Management, Nanjing University of Chinese Medicine, Nanjing, 210023, People's Republic of China; [2]School of Basic Medical Sciences, Shanghai Jiaotong University, Shanghai, 200240, People's Republic of China

Correspondence: Xuemei Feng, Email fxm0118@163.com

Abstract: Insomnia is a common clinical disorder characterized by difficulty falling asleep or maintaining sleep with daytime irritability or fatigue. The annual prevalence of insomnia symptoms in the global adult population is 35–50% and the prevalence of insomnia disorders is 12–20%. Most patients with insomnia cost a lot but fail to receive effective treatment. First-line treatments for insomnia include cognitive-behavioral therapy (CBT-I) and medication, but they both have limitations such as expensive and serious side effects. Traditional Chinese herbal remedies, such as the Guipi capsule, are selected as an alternative strategy of treatment because of more convenient, affordable, and fewer side-effects. Here, we review the potential pathogenesis of insomnia, the pharmacological ingredients of the Guipi capsule, and its effects and mechanisms in treating insomnia.

Keywords: Guipi capsule, insomnia, mechanisms, pathogenesis, pharmacological ingredients

Introduction

Insomnia, characterized by difficulty falling or staying asleep, affects 12–20% of the global population, impairing mental and physical health and even increasing risks of hypertension, depression, and cardiovascular diseases.[1–3] Insomnia patients usually suffer heavy burdens, partly due to higher healthcare costs and cognitive dysfunction, and even increased risk of developing various serious diseases (eg, hypertension and cardiovascular disease)[1,2] (Figure 1). The main therapeutic strategies for insomnia are cognitive-behavioral therapy (CBT) and pharmacotherapy.[1–3] CBT is widely recognized as the first-line standard treatment for chronic insomnia, using various cognitive and behavioral techniques to correct dysfunctional beliefs and behavioral patterns that perpetuate insomnia.[4,5] CBT can significantly improve quality of sleep, offering long-term benefits, while medications (eg, benzodiazepines, melatonin receptor agonists, and orexin receptor antagonists) provide short-term relief but with dependency risks.[4] However, the accessibility of CBT remains a challenge as it requires specially trained therapists.

Alternative therapies like traditional herbal remedy (eg, Guipi capsule) have caught increasingly attentions due to their efficacy, affordable, and fewer side effects, although lack of convincingly scientific evidence.[6] Herbal medicine for insomnia has a history of thousands of years.[6] Guipi capsule is constituted of a traditional Chinese herbal formula. Its major components are same with the traditional herbal medicine Guipi tang (Chinese for Guipi tang or Japanese for kihi-to) that is a mixture of 12 herbs used to treat insomnia, forgetfulness, fatigue, poor memory or amnesia, anorexia, anemia, palpitations, and other neurological symptoms.[7] This review will introduce the potential pathogenesis of insomnia, and the therapeutic efficacy and potential mechanisms of Guipi capsule for treating insomnia.

Potential Pathogenesis of Insomnia

Biofeedback Between Insomnia and Stomach Dysfunction

The classical theory of traditional Chinese medicine argues "if the stomach is not harmonized, one cannot lie peacefully.[8] This theory indicates that dysfunction or imbalance of gastrointestinal system may cause insomnia. A survey study found that 68% of patients with functional dyspepsia, 71.2% of those with both functional dyspepsia and irritable bowel

Received: 8 April 2025
Accepted: 24 September 2025
Published: 1 December 2025

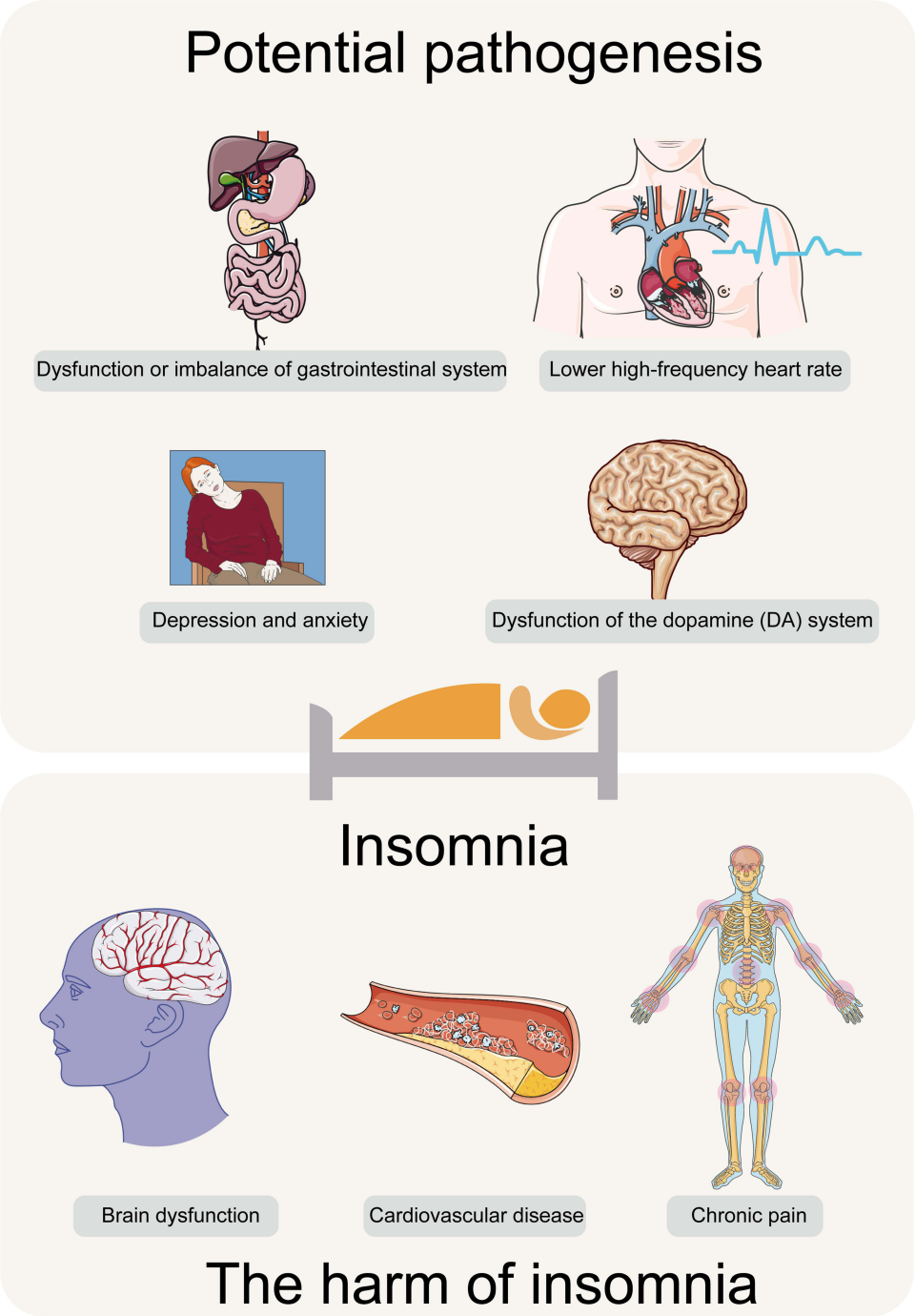

Figure 1 The potential pathogenesis and harm of insomnia.

syndrome (IBS), and 50.2% of those with IBS alone self-reported sleep disturbances.[9] Patients with functional gastrointestinal diseases often experience sleep problems, which may be attributed to the chronic pain stimuli they endure, such as persistent gastrointestinal discomfort leading to difficulty in falling asleep, disrupted sleep preventing them from falling back asleep, and overall reduced sleep duration. Individuals with digestive system disorders experience impaired sleep, while in turn, decreased sleep quality may exacerbate or trigger gastrointestinal symptoms, creating a vicious cycle of mutual influence. Therefore, improving sleep can alleviate digestive discomfort, and conversely, a better digestive state can benefit sleep quality.[8]

The current understanding of the pathophysiology of functional gastrointestinal diseases involves dysregulation of central autonomic function, visceral hypersensitivity, and neuroendocrine changes in response to stress.[10] Some neurotransmitter systems involved in regulating these abnormalities, such as the ascending serotonergic system, cholinergic system, and noradrenergic arousal system, also play a vital role in sleep regulation, potentially contributing to sleep disturbances. Gastrointestinal functional disorders are often accompanied by imbalances in the intestinal microbiota and the production of inflammation in the body.[11,12] The gut houses a diverse community of microorganisms with intricate metabolic processes that significantly impact various aspects of human health, sleep regulation included.

Roles of Emotion in Insomnia

Insomnia frequently occurs in people struggling with mental issues. Chronic depression and anxiety often disrupt sleep, fueling a cycle of sleeplessness.[13] In fact, depression is the most common mental health disorder accompanying insomnia, and the two are closely intertwined.[14–16] Research suggests that depression not only predicts insomnia but also worsens it—up to 90% of depressed patients experience poor quality of sleep, and nearly 58% of those with severe depression suffer from insomnia.[17] Similarly, people prone to insomnia tend to have more severe depressive symptoms and difficulty regulating emotions, reinforcing a vicious cycle where each condition exacerbates the other.[15] Anxiety-induced reductions in high-frequency heart rate variability, a marker of diminished parasympathetic nervous system activity, are associated with poorer sleep quality and increased sleep reactivity.[18,19] These findings align with existing evidence demonstrating anxiety's role in amplifying sleep reactivity, which serves as a critical mechanism through which emotional disturbances like depression and anxiety impair sleep quality.

From a neurobiological perspective, heightened sleep reactivity appears to involve three interconnected systems: (1) dysfunctional cortical networks, (2) autonomic nervous system imbalance that characterized by sympathetic dominance and parasympathetic withdrawal, and (3) hyperactivity of the hypothalamic-pituitary-adrenal axis. Preliminary research indicates that individuals with high sleep reactivity typically exhibit this pattern of increased sympathetic activation coupled with reduced parasympathetic activity.[20]

Emerging evidence suggests dopamine (DA) system dysfunction may play a key role in modulating sleep reactivity.[21] As a critical monoamine neurotransmitter, DA not only regulates motivation, reward processing, and pleasure perception but also significantly influences sleep neurobiology – particularly through its action on ventral tegmental area and substantia nigra neurons.[22] The connection between DA dysfunction and sleep disturbances appears bidirectional: disrupted DA signaling can contribute to anxiety and depression, which in turn exacerbate sleep reactivity and lead to insomnia.[23]

Pharmacological Ingredients of Guipi Capsule and Its Potential Regulatory Mechanisms

Guipi capsule's main bioactive ingredients amount to dozens of compounds, including sanjoinine A, jujuboside A, jujuboside B, and spinosyn (Table 1). Through the continuous collision of modern and traditional medicine, several studies have indicated mechanisms underlying the active pharmaceutical ingredients of Guipi for the treatment of insomnia (Figure 2).

The increased 5-hydroxytryptamine exerts anti-insominia Guipi capsule regulates HPA axis signaling and increases 5-HT levels.[7,24] Each of the individual compounds in Guipi decoction exerts anti-insomnia effects by distinct ways (Figure 2A). For example, Jujube seed contains complex bioactive ingredients for insomnia, including mountain sanjoinine A, Jujuboside A, jujuboside B, spinosin and other flavonoids. These active compounds can increase the levels of 5-HT in insomnia patients, while significantly reducing the levels of 5-HIAA. This effect of regulation can be comparable to the conventional anti-insomnia treatment with western medicines, and the anti-insomnia effect of Jujube seed is even more significant when it is combined with these western medicines.[25]

Atractylodis macrocephalae oil (AO) was able to increase the levels of IL-10 and decrease the levels of TNF-α, IL-6, 5-HT.[26] Atractylodis macrocephalae polysaccharide increases tryptophan, 5-HT.[27] The aqueous extract of Atractylodis Macrocephalae (the main components of which are atractylenolide III and β-eudesmol exhibited inhibitory effects on DOI-induced head-twitch response (HTR).[28] After administration of Angelica sinensis volatiles in a mouse model of insomnia, prostaglandin E2 (PGE2), histamine (HIS), and 5-hydroxytryptamine (5-HT) levels returned to those observed

Table 1 Bioactive Ingredients of the Guipi Capsule and Their Corresponding Effects

Bioactive Ingredients	Source of Chinese Herbal	Pharmacological Effects	Side Effects
Sanjoinine A	Jujube seed	Increase 5-HT levels and sedative effects	Mild drowsiness
Jujuboside A	Jujube seed	Increase 5-HT levels, sedative effects	Mild drowsiness
Jujuboside B	Jujube seed	GABA modulation	Nausea
Spinosin	Jujube seed	Increase 5-HT levels	Drowsiness in high doses
Atractylodis macrocephalae oil (AO)	Atractylodes	Anti-inflammatory	Mild Gastrointestinal (GI) discomfort
Astragaloside polysaccharide (APS)	Atractylodes	Increase 5-HT synthesis	Low toxicity
Atractylenolide II/III	Atractylodes	Anti-inflammatory and immune modulation	Low toxicity, allergic reactions
β-eudesmol	Atractylodes	Enhances sleep-wake cycle regulation	Low toxicity
Poria triterpenoids	Poria cocos	Regulate serotonin and anti-inflammatory	Mild GI discomfort
Astragaloside isoflavan (ASF)	Codonopsis, Astragalus, Atractylodes, and Poria cocos	GABAergic and serotonergic system effects	Low toxicity, mild allergic reactions
Liquiritigenin	Glycyrrhiza	Sedative and anti-inflammatory	Mild drowsiness
Glabridin	Glycyrrhiza	GABA modulation	Allergic reactions in high doses
Licochalcone A	Glycyrrhiza	Anti-inflammatory and anti-anxiety	Mild GI discomfort
Liquiritin	Glycyrrhiza	Reduce 5-HT metabolism and neuroprotection	Mild drowsiness
Astragaloside IV (ASI)	Astragalus	Reduce 5-HT and DA uptake	Mild GI issues
Isoliquiritin	Glycyrrhiza	Anti-inflammatory and anti-oxidative	Rare GI issues
Astragalus saponin	Astragalus	Anti-anxiety	Low toxicity, mild drowsiness

in normal controls.[29] Poria triterpenoids may modulate 5-HT receptors expressed in cells, and inhibition of 5-HT-induced inward currents occurs in a concentration-dependent and reversible manner.[30] Flavonoids, liquiritigenin, glabridin, and licochalcone A are the most potent inhibitors of 5-HT-induced currents,[31] liquiritin and isoliquiritin also significantly reduced the ratio of 5-HIAA/5-HT in the hippocampus and hypothalamus, and slowed down 5-HT metabolism.[32] Astragaloside IV or astragalus saponin restores 5-HT, and monoamine oxidase deletion levels and normalizes Tph 2 mRNA expression to control values and improves memory deficits and it improves sleep disorders by this mechanism.[33]

GABA Involves in Regulating the Sleep-Wake Cycle

The second mechanism by which Guipi capsule treats insomnia involves enhancing the expression of NR1 and Tau in the hippocampus, promoting GABA synthesis, and increasing serum GABA levels. Elevated GABA enhances Cl^-influx into neurons, leading to membrane hyperpolarization, reduced neuronal excitability, and regulation of the sleep-wake cycle (Figure 1A).[34,35] GAT, including GAT-1, GAT-2, and GAT-3 isoforms, acts as the GABA transporter that maintains GABA homeostasis. GAT-1, mainly located on GABAergic neuron membranes, mediates GABA reuptake. The down-regulation of GAT-1 expression is considered to be a mechanism of self-protection after insomnia.[36] The up-regulation of GAT-1 caused by Guipi may be related to the release of the persistent state of excitation, and the compensatory expression of GAT-1 is gradually restored, which maintains the balance of the concentration of GABA in the neurons and synapses, and exerts its neuroinhibitory effect to improve the symptoms of insomnia.[37,38]

As with the first mechanism, the various components of Guipi capsule each exert their anti-insomnia effects by directly or indirectly increasing GABA levels. Atractylenolide II/ III can maintain the activity of the recombinant GABA-A receptor.[39] Jujube seed contains a variety of effective chemical components against insomnia, including sanjoinine A,

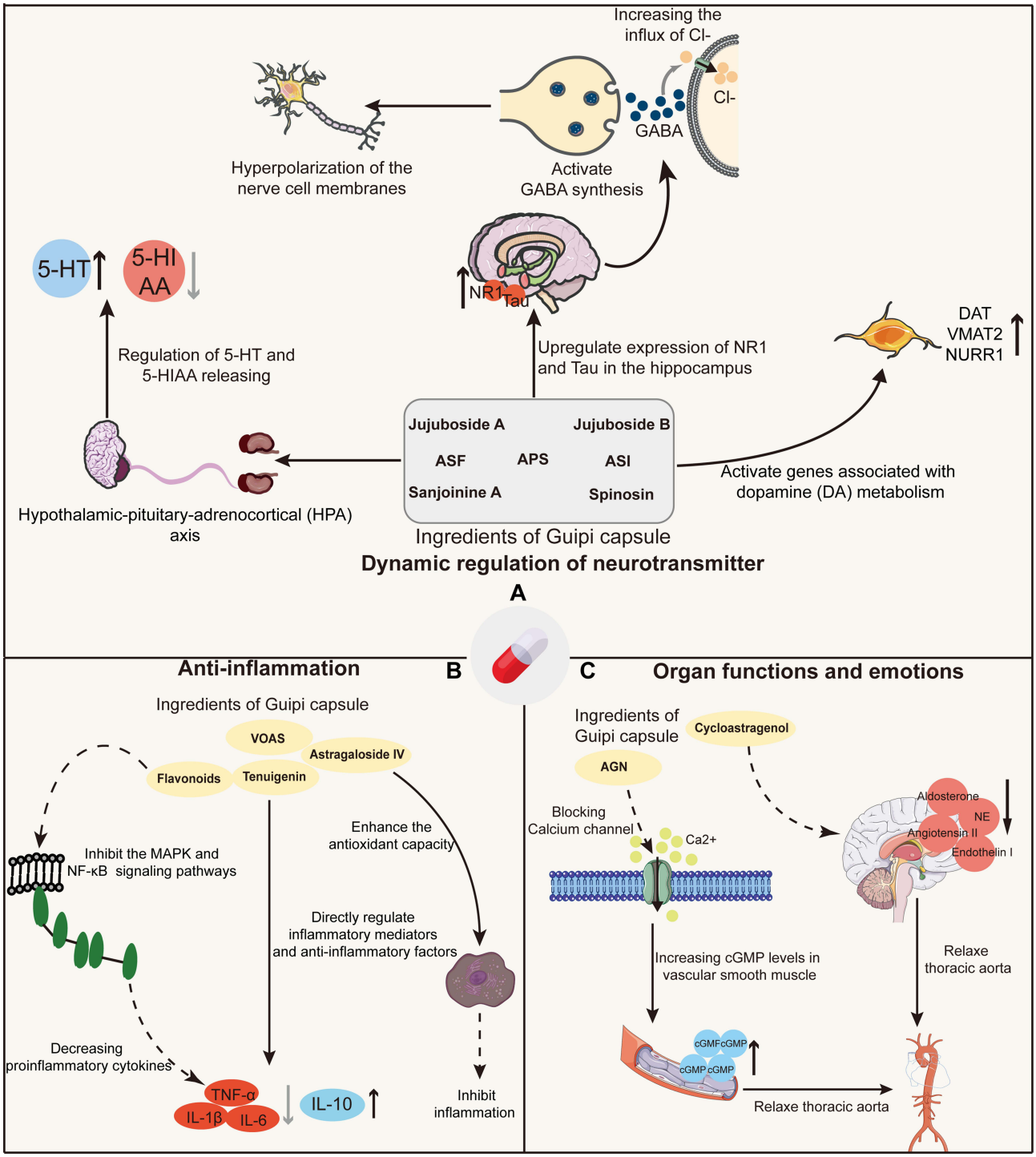

Figure 2 The mechanisms underlying the Guipi capsule for insomnia treatment. (**A**) The bioactive ingredients of Guipi capsule treat insomnia by dynamically regulating neurotransmitter. (**B**) The bioactive ingredients of Guipi capsule treat insomnia by anti-inflammation effects. (**C**) The bioactive ingredients of Guipi capsule treat insomnia by regulate organ functions and emotions. Upward arrows mean upregulate and downward arrows mean downregulate.
Abbreviations: ASF, astragaloside isoflavan; ASI, astragaloside; APS, astragaloside polysaccharide; AGN, angelica sinensis extract; AO, atractylodes macrocephala oil.

jujuboside A, spinosin and other flavonoids, which are able to mediate sedative and hypnotic functions through GABAergic and serotonergic systems,[40] jujuboside A and jujuboside B have significant effects on the expression and activation of GABA-A receptor,[41] low-dose jujuboside A induced significant increases in the mRNA of α1, α5 and β2 subunits of GABA-A receptor in both 24-hour and 72-hour treatments, and increased the frequency of the opening of

https://doi.org/10.2147/IJGM.S532993

chloride channels, which had a calming and hypnotic effect.[42] Jujuboside A not only regulates the expression of GABA receptor subunit mRNA, but also down-regulates the secretion of inflammatory cytokines related to the intestinal mucosal system, affects the cytokine network between nerve cells in the brain and exerts its specific sedative-hypnotic effect, which is a similar mechanism to that of melatonin.[43]

Poria triterpenoids, a main component in Poria cocos, can regulate the content of GABA, menthionine and glutamate in the brain, as well as regulating the expression of GAD65 and GABA,[44] with sedative and anticonvulsant effects. There are also studies specifically targeting the signaling pathway to begin with, Poria cocos water-soluble polysaccharides (PCWP) inhibited the anxiety of rats induced by chronic sleep deprivation (CSD). PCWP intervention increased the levels of 5-HT, DA, norepinephrine, and γ-aminobutyric acid in the hypothalamus and inhibited TNF-α/nuclear factor, NF-κB signaling pathway.[45] Glabridin through GABA-A receptors to enhance GABA inhibition in neurons, thereby exerting sedative and hypnotic effects.[46] Isoliquiritin activates GABA-B receptors, thereby reducing voltage-gated Ca^2+ channels and glutamate release in rat cortical nerve terminals. Additionally, it alleviates elevated levels of GABA and histamine.[47]

The Roles of DA and NE Metabolism in Insomnia

Neural stem cells (NSC) were treated with astragaloside (ASI), astragaloside polysaccharide (APS) and astragaloside isoflavan (ASF), the main active ingredients of Astragalus. Quantitative RT-PCR results showed that ASI, APS and ASF could promote the expression of tyrosine hydroxylase and dopamine transporter protein mRNA specifically expressed in DA neurons. Meanwhile, Shh, Nurr1 and Ptx3 have been suggested to stimulate the formation of DA neurons.[48] Costunolide ameliorates have anti-apoptotic activity, which may be attributed to their regulatory effects on DA metabolism-related genes. Costunolide ameliorates are involved in the regulation of genes Nurr1, DAT and VMAT2 and are closely associated with ASYN-related DA metabolism.[49] Jujube seed extract can affect DA and NE levels in insomniac mice, exerting sedative and tranquilizing effects. This suggests that Jujube seed extract may ameliorate insomnia symptoms by modulating the levels of DA and NE.[42] Liquiritin reduced dopamine levels to control levels;[50] Isoliquiritin antagonized the increase in striatal dopamine release.[51] And licorice chalcone A (Lico. A), a flavonoid isolated from licorice, was demonstrated to attenuate the reduction of DA uptake and loss of tyrosine hydroxylase immunoreactivity in an in vitro model of PD induced by Isoliquiritin,[52] as evidenced in experiments on cultured primary mesencephalic glia;[53] Lico. Isoliquiritin-induced reduction in DA uptake and loss of tyrosine hydroxylase-immunoreactive neurons in an in vitro model of PD.[52] Dose-dependent neuroprotective effects of liquiritin during subacute NE depletion of nerve endings.[50] Atractylenolide I (AT-I) is a major constituent of Atractylodes macrocephala with a wide range of activities. AT-I was able to counteract the reduction in hippocampal 5-HT and NE concentrations induced by CUMS.[54]

Anti-Inflammation Cytokines in Insomnia

As mentioned in the previous content, patients with insomnia have higher levels of inflammation, and inflammatory factors such as TNF-α and IL-1β can affect the neurotransmitter balance in the sleep center, leading to the occurrence of insomnia.[55] Therefore, reducing inflammation level is an effective method to treat insomnia (Figure 2B).

Flavonoids contained in Codonopsis, Astragalus, Atractylodes macrocephala, and Poria are natural compounds with anti-inflammatory properties.[56] Flavonoids can reduce the expression levels of inflammatory factors such as TNF-α and IL-1β as well as inhibit the NF-κB signaling pathway, suppressing the inflammatory response and thus improving the quality of sleep.[57] In addition to flavonoids, other medications have been shown to play an anti-inflammatory role in the treatment of insomnia by inhibiting the MAPK signaling pathway, including the ERK, JNK and p38 pathways. These pathways play an important role in the inflammatory response, and inhibiting their activity reduces the inflammatory response and improves sleep quality.[58] Specific drug efficacy is as follows, Astragaloside IV dose-dependently reduces serum levels of corticosterone, IL-6 and TNF-α.[59]

Atractylodes macrocephala oil (AO) was able to increase the levels of IL-10 and decrease the levels of TNF-α, IL-6, and 5-HT.[59] AO can significantly inhibit systemic inflammation triggered by acute local stimuli, and exerts anti-inflammatory activity mainly by regulating the metabolic network disorders centered on glycine and arachidonic

acid.[60] AO exerts anti-inflammatory effects by inhibiting pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), inflammatory mediators (HIS, 5-HT, PGE2, NO), and inflammation-related enzymes (iNOS and COX-2), as well as promoting the production of the anti-inflammatory cytokine IL-10.[61] Poria cocos extract inhibited the inflammatory response induced by chronic mild stress (UCMS) and reduced the expression of p38, NF-κB, and TNF-α in the frontal cortex.[62]

The Roles of Organ Dysfunctions and Emotions Instability in Insomnia

In addition, Guipi capsule plays an important role in regulating the spleen, stomach, liver and kidneys (Figure 1C). Guipi capsule exhibits broad therapeutic effects across multiple systems. Clinically, it demonstrates efficacy in treating non-acidic gastroesophageal reflux disease (GERD) with mood disorders when combined with omeprazole, improving gastrointestinal motility, reducing esophageal hypersensitivity, and modulating beneficial gut bacteria.[63,64] In neuropsychiatric applications, Guipi capsule shows antidepressant effects comparable to fluoxetine but with faster onset and better safety. Clinical trials reveal significant hamilton depression scale (HAMD) score improvements as early as 1 week post-treatment ($P < 0.01$ vs fluoxetine), with no reported adverse reactions versus fluoxetine's 3.33% incidence ($P < 0.01$).[65] Mechanistically, its active components (eg, Astragalus extracts) reduce oxidative damage by suppressing ROS production and reversing 6-OHDA-induced oxidative stress.[66] Although Guipi capsule in treating insomnia show good efficacy and relatively higher safety,[65] the results are easily influenced by potential resources of bias, including publication bias and size of patients, and designs of clinical trials, the efficacy and safety of Guipi capsule need to be more strictly demonstrated based on more and better clinical trials in future. In addition, there are some other limitations: inadequate randomization and blinding for clinical trials and methodological quality of included studies.

Guipi capsule also exerts therapeutic effects through other multiple mechanisms involving both metabolic regulation and emotional modulation. The capsule influences key amino acid metabolic pathways while also regulating intestinal flora composition and promoting short-chain fatty acid production. The capsule's emotional regulation properties are majorly mediated by its active components like astragaloside IV (ASIV) and astragalus saponins.[67] Additionally, they have been shown to mitigate anxiety responses and inflammatory reactions induced by restraint stress.[59]

Furthermore, the active ingredients in Guipi capsules exert antidepressant effects by modulating the serotonin (5-HT) system, a key neurotransmitter pathway involved in mood regulation.[33] Similarly, licorice extracts appear to enhance norepinephrine (NE) and dopamine (DA) levels in the brain, contributing to their antidepressant properties.[50] Angelica sinensis extract (AGN) has been shown to mitigate stress-induced helpless behavior in rats, likely through its influence on the central noradrenergic system and upregulation of brain-derived neurotrophic factor (BDNF).[68] Meanwhile, Hairy Angelica serrulata demonstrates vasorelaxant effects in rat thoracic aorta, mediated by calcium channel blockade and increased cGMP levels in vascular smooth muscle.[69] Cycloastragenol exhibits neuroendocrine regulatory effects, reducing serum levels of stress-related factors such as NE, aldosterone, angiotensin II, and endothelin-1.[70] Additionally, pCWP has been found to counteract anxiety behaviors induced by chronic sleep deprivation in rodent models.[45]

Conclusions and Discussion

Guipi capsule, a traditional Chinese herbal remedy, has been widely used in the treatment of insomnia.[7] As mentioned above, numerous studies have shown that Guipi capsule is effective in regulating hormones and neurotransmitters, enhancing GABAergic activity,[71] DA[49] and NE[50] metabolism, anti-inflammatory effects,[59–62] as well as improving gastrointestinal function and emotional health.[65] However, there are some limitations in this review: (1) The underlying mechanisms by which Guipi capsule regulates insomnia were revealed by using the single bioactive ingredient. Therefore, research should further explore the mechanism of action of Guipi capsule in depth because Guipi capsule inevitably suffers from the problem that its efficacy varies according to individual constitution and condition like most herbal medicines. (2) We could not convincingly demonstrate efficacy and safety of Guipi capsule as limited robust and well-designed clinical trials.

Overall, the application of Guipi capsule in the treatment of insomnia is potential promising, but its therapeutic efficacy and safety is expected to be further improved through in-depth research technological innovation, and well-designed clinical trials. The combination of Chinese and Western medicine in the treatment of insomnia may provide

patients with more comprehensive and effective treatment options, and promote the development of the field of insomnia treatment.

Data Sharing Statement

All of data and materials can be found in references.

Acknowledgments

X. F. was supported by the 2023 Shanghai Jiao Tong University Teaching Development Fund (CTLD23J0104).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests.

References

1. Buysse DJ. Insomnia. *JAMA*. 2013;309(7):706–716. doi:10.1001/jama.2013.193
2. Patel D, Steinberg J, Patel P. Insomnia in the elderly: a review. *J Clin Sleep Med JCSM off Publ Am Acad Sleep Med*. 2018;14:1017–1024.
3. Roach M, Juday T, Tuly R, et al. Challenges and opportunities in insomnia disorder. *Int J Neurosci*. 2021;131(11):1058–1065. doi:10.1080/00207454.2020.1773460
4. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American academy of sleep medicine clinical practice guideline. *J Clin Sleep Med JCSM off Publ Am Acad Sleep Med*. 2021;17:255–262.
5. Riemann D, Baglioni C, Bassetti C, et al. European guideline for the diagnosis and treatment of insomnia. *J Sleep Res*. 2017;26(6):675–700. doi:10.1111/jsr.12594
6. Poon MM-K, Chung K-F, Yeung W-F, Yau VH-K, Zhang S-P. Classification of insomnia using the traditional Chinese medicine system: a systematic review. *Evid-Based Compl Altern Med ECAM*. 2012;2012:735078. doi:10.1155/2012/735078
7. Li M, Lan R, Wen Y, Shi K, Yang D. Guipi decoction for insomnia: systematic review and meta-analysis. *Medicine*. 2020;99(27):e21031. doi:10.1097/MD.0000000000021031
8. Johnson DA, Orr WC, Crawley JA, et al. Effect of esomeprazole on nighttime heartburn and sleep quality in patients with GERD: a randomized, placebo-controlled trial. *Am J Gastroenterol*. 2005;100(9):1914–1922. doi:10.1111/j.1572-0241.2005.00285.x
9. Fass R, Fullerton S, Tung S, Mayer EA. Sleep disturbances in clinic patients with functional bowel disorders. *Am J Gastroenterol*. 2000;95(5):1195–1200. doi:10.1111/j.1572-0241.2000.02009.x
10. Schmulson MJ, Mayer EA. Evolving concepts in irritable bowel syndrome. *Curr Opin Gastroenterol*. 1999;15(1):16–21. doi:10.1097/00001574-199901000-00004
11. Farcas RA, Grad S, Grad C, Dumitrașcu DL. Microbiota and digestive metabolites alterations in functional dyspepsia. *J Gastrointest Liver Dis JGLD*. 2024;33(1):102–106. doi:10.15403/jgld-5024
12. Feng W, Yang Z, Liu Y, et al. Gut microbiota: a new target of traditional Chinese medicine for insomnia. *Biomed Pharmacother Biomedecine Pharmacother*. 2023;160:114344. doi:10.1016/j.biopha.2023.114344
13. Peng C, Wang K, Wang J, et al. Neural correlates of insomnia with depression and anxiety from a neuroimaging perspective: a systematic review. *Sleep Med Rev*. 2025;81:102093. doi:10.1016/j.smrv.2025.102093
14. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. *Dialogues Clin Neurosci*. 2008;10(3):329–336. doi:10.31887/DCNS.2008.10.3/dnutt
15. Predatu R, Voinescu BI, David DO. The role of emotion regulation difficulties in the relation between insomnia and depressive symptoms. *Int J Behav Med*. 2020;27(6):615–622. doi:10.1007/s12529-020-09903-7
16. Bjorøy I, Jørgensen VA, Pallesen S, Bjorvatn B. The prevalence of insomnia subtypes in relation to demographic characteristics, anxiety, depression, alcohol consumption and use of hypnotics. *Front Psychol*. 2020;11:527. doi:10.3389/fpsyg.2020.00527
17. Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: a review on a bidirectional relationship, mechanisms and treatment. *J Cell Mol Med*. 2019;23(4):2324–2332. doi:10.1111/jcmm.14170
18. Chalmers JA, Quintana DS, Abbott MJ-A, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. *Front Psychiatry*. 2014;5:80. doi:10.3389/fpsyt.2014.00080
19. Drake CL, Pillai V, Roth T. Stress and sleep reactivity: a prospective investigation of the stress-diathesis model of insomnia. *Sleep*. 2014;37(8):1295–1304. doi:10.5665/sleep.3916
20. Bonnet MH, Arand DL. Hyperarousal and insomnia: state of the science. *Sleep Med Rev*. 2010;14(1):9–15. doi:10.1016/j.smrv.2009.05.002
21. Eban-Rothschild A, Rothschild G, Giardino WJ, Jones JR, de Lecea L. VTA dopaminergic neurons regulate ethologically relevant sleep-wake behaviors. *Nat Neurosci*. 2016;19(10):1356–1366. doi:10.1038/nn.4377

22. Monti JM, Monti D. The involvement of dopamine in the modulation of sleep and waking. *Sleep Med Rev*. 2007;11(2):113–133. doi:10.1016/j.smrv.2006.08.003
23. Tye KM, Mirzabekov JJ, Warden MR, et al. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature*. 2013;493(7433):537–541. doi:10.1038/nature11740
24. Chen L, Ye T, Wang X, et al. The mechanisms underlying the pharmacological effects of guipi decoction on major depressive disorder based on network pharmacology and molecular docking. *Comb Chem High Throughput Screen*. 2023;26(9):1701–1728. doi:10.2174/1386207325666220831152959
25. Lu Y, Bao T, Mo J, Ni J, Chen W. Research advances in bioactive components and health benefits of jujube (Ziziphus jujuba Mill.) fruit. *J Zhejiang Univ Sci B*. 2021;22(6):431–449. doi:10.1631/jzus.B2000594
26. Xie Y, Zhan X, Tu J, et al. Atractylodes oil alleviates diarrhea-predominant irritable bowel syndrome by regulating intestinal inflammation and intestinal barrier via SCF/c-kit and MLCK/MLC2 pathways. *J Ethnopharmacol*. 2021;272:113925. doi:10.1016/j.jep.2021.113925
27. Yang H, Wu C, Chen L, et al. A. macrocephala polysaccharide induces alterations to gut microbiome and serum metabolome in constipated mice. *Microb Pathog*. 2023;178:106084. doi:10.1016/j.micpath.2023.106084
28. Murayama C, Wang -C-C, Michihara S, Norimoto H. Pharmacological effects of 'jutsu' (Atractylodis rhizome and Atractylodis lanceae rhizome) on 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI)-induced head twitch response in mice (I). *Mol*. 2014;19:14979–14986.
29. Zhong L-J, Zhang WQ, Hua YL, et al. Metabolomic evaluation for anti-inflammatory effect of volatile oils from different preparations of Angelicae sinensis radix. *Zhongguo Zhong Yao Za Zhi Zhongguo Zhongyao Zazhi China J Chin Mater Medica*. 2016;41:2061–2069.
30. Lee J-H, Lee YJ, Shin J-K, et al. Effects of triterpenoids from Poria cocos wolf on the serotonin type 3a receptor-mediated ion current in xenopus oocytes. *Eur J Pharmacol*. 2009;615(1–3):27–32. doi:10.1016/j.ejphar.2009.04.063
31. Herbrechter R, Ziemba PM, Hoffmann KM, et al. Identification of Glycyrrhiza as the rikkunshito constituent with the highest antagonistic potential on heterologously expressed 5-HT3A receptors due to the action of flavonoids. *Front Pharmacol*. 2015;6:130. doi:10.3389/fphar.2015.00130
32. Wang W, Hu X, Zhao Z, et al. Antidepressant-like effects of liquiritin and isoliquiritin from Glycyrrhiza uralensis in the forced swimming test and tail suspension test in mice. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(5):1179–1184. doi:10.1016/j.pnpbp.2007.12.021
33. Abd Elkader H-TAE, Abdou HM, Khamiss OA, Essawy AE. Anti-anxiety and antidepressant-like effects of astragaloside IV and saponins extracted from Astragalus spinosus against the bisphenol A-induced motor and cognitive impairments in a postnatal rat model of schizophrenia. *Environ Sci Pollut Res Int*. 2021;28(26):35171–35187. doi:10.1007/s11356-021-12927-5
34. Oh D-R, Kim Y, Jo A, et al. Sedative and hypnotic effects of Vaccinium bracteatum Thunb. through the regulation of serotonegic and GABAA-ergic systems: involvement of 5-HT1A receptor agonistic activity. *Biomed Pharmacother Biomedecine Pharmacother*. 2019;109:2218–2227. doi:10.1016/j.biopha.2018.10.003
35. Jiang N, Wei S, Zhang Y, et al. Protective effects and mechanism of radix polygalae against neurological diseases as well as effective substance. *Front Psychiatry*. 2021;12:688703. doi:10.3389/fpsyt.2021.688703
36. Fattorini G, Melone M, Sánchez-Gómez MV, et al. GAT-1 mediated GABA uptake in rat oligodendrocytes. *Glia*. 2017;65(3):514–522. doi:10.1002/glia.23108
37. Chiu C-S, Brickley S, Jensen K, et al. GABA transporter deficiency causes tremor, ataxia, nervousness, and increased GABA-induced tonic conductance in cerebellum. *J Neurosci off J Soc Neurosci*. 2005;25(12):3234–3245. doi:10.1523/JNEUROSCI.3364-04.2005
38. Sarris J, Panossian A, Schweitzer I, Stough C, Scholey A. Herbal medicine for depression, anxiety and insomnia: a review of psychopharmacology and clinical evidence. *Eur Neuropsychopharmacol J Eur Coll Neuropsychopharmacol*. 2011;21(12):841–860. doi:10.1016/j.euroneuro.2011.04.002
39. Singhuber J, Baburin I, Kählig H, Urban E, Kopp B, Hering S. GABA(A) receptor modulators from Chinese herbal medicines traditionally applied against insomnia and anxiety. *Phytomedicine Int J Phytother Phytopharm*. 2012;19:334–340.
40. Zhou Q-H, Zhou X-L, Xu M-B, et al. Suanzaoren formulae for insomnia: updated clinical evidence and possible mechanisms. *Front Pharmacol*. 2018;9:76. doi:10.3389/fphar.2018.00076
41. Bian Z, Zhang W, Tang J, et al. Mechanisms underlying the action of ziziphi spinosae semen in the treatment of insomnia: a study involving network pharmacology and experimental validation. *Front Pharmacol*. 2021;12:752211. doi:10.3389/fphar.2021.752211
42. You Z, Xia Q, Liang F-R, et al. Effects on the expression of GABAA receptor subunits by jujuboside A treatment in rat hippocampal neurons. *J Ethnopharmacol*. 2010;128(2):419–423. doi:10.1016/j.jep.2010.01.034
43. Wang -X-X, Ma G-I, Xie J-B, Pang G-C. Influence of JuA in evoking communication changes between the small intestines and brain tissues of rats and the GABAA and GABAB receptor transcription levels of hippocampal neurons. *J Ethnopharmacol*. 2015;159:215–223. doi:10.1016/j.jep.2014.11.012
44. Shah VK, Choi JJ, Han J-Y, et al. Pachymic acid enhances pentobarbital-induced sleeping behaviors via GABAA -ergic systems in mice. *Biomol Ther*. 2014;22(4):314–320. doi:10.4062/biomolther.2014.045
45. Zhang -D-D, Li H-J, Zhang H-R, Ye X-C. Poria cocos water-soluble polysaccharide modulates anxiety-like behavior induced by sleep deprivation by regulating the gut dysbiosis, metabolic disorders and TNF-α/NF-κB signaling pathway. *Food Funct*. 2022;13(12):6648–6664. doi:10.1039/D2FO00811D
46. Jin Z, Kim S, Cho S, et al. Potentiating effect of glabridin on GABAA receptor-mediated responses in dorsal raphe neurons. *Planta Med*. 2013;79(15):1408–1412. doi:10.1055/s-0033-1350698
47. Lin T-Y, Lu C-W, Hsieh P-W, et al. Natural product isoliquiritigenin activates GABAB receptors to decrease voltage-gate Ca2+ channels and glutamate release in rat cerebrocortical nerve terminals. *Biomolecules*. 2021;11(10):1537. doi:10.3390/biom11101537
48. Gao H, Dou L, Shan L, Sun Y, Li W. Proliferation and committed differentiation into dopamine neurons of neural stem cells induced by the active ingredients of radix astragali. *Neuroreport*. 2018;29(7):577–582. doi:10.1097/WNR.0000000000000997
49. Ham A, Lee S-J, Shin J, Kim K-H, Mar W. Regulatory effects of costunolide on dopamine metabolism-associated genes inhibit dopamine-induced apoptosis in human dopaminergic SH-SY5Y cells. *Neurosci Lett*. 2012;507(2):101–105. doi:10.1016/j.neulet.2011.10.037
50. Ahmed-Farid OA, Haredy SA, Niazy RM, Linhardt RJ, Warda M. Dose-dependent neuroprotective effect of oriental phyto-derived glycyrrhizin on experimental neuroterminal norepinephrine depletion in a rat brain model. *Chem Biol Interact*. 2019;308:279–287. doi:10.1016/j.cbi.2019.05.045
51. Jeon J-P, Buono RJ, Han BG, et al. Proteomic and behavioral analysis of response to isoliquiritigenin in brains of acute cocaine treated rats. *J Proteome Res*. 2008;7(12):5094–5102. doi:10.1021/pr800237s

52. Huang B, Liu J, Ju C, et al. Licochalcone A prevents the loss of dopaminergic neurons by inhibiting microglial activation in lipopolysaccharide (LPS)-induced parkinson's disease models. *Int J Mol Sci*. 2017;18(10):2043. doi:10.3390/ijms18102043
53. Li X, Liu Q, Yu J, et al. Costunolide ameliorates intestinal dysfunction and depressive behaviour in mice with stress-induced irritable bowel syndrome via colonic mast cell activation and central 5-hydroxytryptamine metabolism. *Food Funct*. 2021;12(9):4142–4151. doi:10.1039/D0FO03340E
54. Gao H, Zhu X, Xi Y, et al. Anti-depressant-like effect of atractylenolide I in a mouse model of depression induced by chronic unpredictable mild stress. *Exp Ther Med*. 2018;15(2):1574–1579. doi:10.3892/etm.2017.5517
55. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/26140821/. Accessed November 21, 2025.
56. Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-inflammatory molecules: a review. *Mol*. 2022;27:2901.
57. Serafini M, Peluso I, Raguzzini A. Flavonoids as anti-inflammatory agents. *Proc Nutr Soc*. 2010;69(3):273–278. doi:10.1017/S002966511000162X
58. Chen L, Deng H, Cui H, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*. 2018;9(6):7204–7218. doi:10.18632/oncotarget.23208
59. Oh H-A, Choi HJ, Kim NJ, Kim D-H. Anti-stress effect of astragaloside IV in immobilized mice. *J Ethnopharmacol*. 2014;153(3):928–932. doi:10.1016/j.jep.2014.03.068
60. Zhang W-Q, Hua Y-L, Zhang M, et al. Metabonomic analysis of the anti-inflammatory effects of volatile oils of Angelica sinensis on rat model of acute inflammation. *Biomed Chromatogr BMC*. 2015;29(6):902–910. doi:10.1002/bmc.3372
61. Li J, Hua Y, Ji P, et al. Effects of volatile oils of Angelica sinensis on an acute inflammation rat model. *Pharm Biol*. 2016;54(9):1881–1890. doi:10.3109/13880209.2015.1133660
62. Huang Y-J, Hsu N-Y, Lu K-H, et al. Poria cocos water extract ameliorates the behavioral deficits induced by unpredictable chronic mild stress in rats by down-regulating inflammation. *J Ethnopharmacol*. 2020;258:112566. doi:10.1016/j.jep.2020.112566
63. Dai Y-K, Wu Y-B, Wen H, et al. Different traditional herbal medicines for the treatment of gastroesophageal reflux disease in adults. *Front Pharmacol*. 2020;11:884. doi:10.3389/fphar.2020.00884
64. Huang -T-T, Lai J-B, Du Y-L, et al. Current understanding of gut microbiota in mood disorders: an update of human studies. *Front Genet*. 2019;10:98. doi:10.3389/fgene.2019.00098
65. Li T, Li X, Zhang J, et al. Chemical component analysis of the traditional Chinese medicine Guipi Tang and its effects on major depressive disorder at molecular level. *Heliyon*. 2022;8(12):e12182. doi:10.1016/j.heliyon.2022.e12182
66. Guo L-Y, Shi F-L, Li M, et al. Astragalus protects PC12 cells from 6-hydroxydopamine-induced neuronal damage: a serum pharmacological study. *Chin J Physiol*. 2021;64(1):24–31. doi:10.4103/CJP.CJP_50_20
67. He Q, Han C, Huang L, et al. Astragaloside IV alleviates mouse slow transit constipation by modulating gut microbiota profile and promoting butyric acid generation. *J Cell Mol Med*. 2020;24(16):9349–9361. doi:10.1111/jcmm.15586
68. Lee B, Sur B, Shim I, Lee H, Hahm D-H. Angelica gigas ameliorate depression-like symptoms in rats following chronic corticosterone injection. *BMC Complement Altern Med*. 2015;15(1):210. doi:10.1186/s12906-015-0746-9
69. Ko FN, Wu TS, Liou MJ, Huang TF, Teng CM. Vasorelaxation of rat thoracic aorta caused by osthole isolated from Angelica pubescens. *Eur J Pharmacol*. 1992;219(1):29–34. doi:10.1016/0014-2999(92)90576-P
70. Wang J, Wu M-L, Cao S-P, et al. Cycloastragenol ameliorates experimental heart damage in rats by promoting myocardial autophagy via inhibition of AKT1-RPS6KB1 signaling. *Biomed Pharmacother Biomedecine Pharmacother*. 2018;107:1074–1081. doi:10.1016/j.biopha.2018.08.016
71. Liu L, Zou Z, Yang J, et al. Jianpi jieyu decoction, an empirical herbal formula, exerts psychotropic effects in association with modulation of gut microbial diversity and GABA activity. *Front Pharmacol*. 2021;12:645638. doi:10.3389/fphar.2021.645638