Biomedicine & Pharmacotherapy 160 (2023) 114344

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Gut microbiota: A new target of traditional Chinese medicine for insomnia

Wanying Feng [a,b,1], Zhihua Yang [a,b,1], Yangxi Liu [c], Rui Chen [d], Zhihui Song [a,b], Guiyun Pan [a,b], Yuhang Zhang [a,b], Zehui Guo [a,b], Xinya Ding [c], Lu Chen [a,b,*], Yi Wang [a,b,*]

[a] State Key Laboratory of Component-based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[b] Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[c] First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300381, China
[d] College of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

ARTICLE INFO

Keywords:
Insomnia
Gut microbiota
Traditional Chinese medicine
Brain-gut-microbiota axis

ABSTRACT

All species have a physiological need for sleep, and sleep is crucial for the preservation and restoration of many physiological processes in the body. Recent research on the effects of gut microbiota on brain function has produced essential data on the relationship between them. It has been discovered that dysregulation of the gut-brain axis is related to insomnia. Certain metabolites of gut microbiota have been linked to insomnia, and disturbances in gut microbiota can worsen insomnia. Traditional Chinese medicine (TCM) has unique advantages for the treatment of insomnia. Taking the gut microbiota as the target and determining the scientific relevance of TCM to the prevention and treatment of insomnia may lead to new concepts for the treatment of sleep disorders and improve the therapeutic effect of sleep. Taking the gut microbiota as an entry point, this paper reviews the relationship between gut microbiota and TCM, the relationship between gut microbiota and insomnia, the mechanism by which gut microbiota regulate sleep, and the mechanism by which TCM regulates gut microbiota for insomnia prevention and treatment. This review provides new ideas for the prevention and treatment of insomnia through TCM and new ideas for drug development.

1. Introduction

Insomnia, a frequently encountered clinical disorder, is defined as having trouble falling asleep or staying asleep and experiencing accompanying symptoms such as irritation or weariness when awake [1]. Between 10 % and 20 % of people have insomnia, and 50 % of those cases progress chronically [2]. It has been estimated that approximately one-fifth of people worldwide suffer from insomnia [3]. Traditional Chinese medicine (TCM) has been used to treat insomnia for more than 2000 years [4]. Numerous single herbs and TCM formulae with efficacy in enhancing sleep have been listed in medical texts throughout history. In 205 CE, Zhang Zhongjing created a number of well-known prescriptions, including Suan Zao Ren Tang, which is still used to cure sleeplessness [5]. TCM offers a variety of nutritive and pharmacological benefits through the formulae it has developed, which are usually composed of many plants that contain complex components in specific ratios and doses. Multichannel and multitargeted treatment through TCM can prevent the unfavorable therapeutic impacts of some Western medicine treatments and weakening of the drug effect. The amount of clinical data supporting the use of TCM use in the treatment of insomnia

Abbreviations: TCM, Traditional Chinese medicine; RCTs, randomized controlled trials; GGLMD, Guizhi gancao longgu muli decoction; LPS, lipopolysaccharide; BGM, brain-gut-microbiota; IL-1β, interleukin1β; IL-6, interleukin 6; IL-7, interleukin 7; TNF-α, tumor necrosis factor α; NF-κB, Nuclear factor-κB; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; GABA, γ-aminobutyric acid; CNS, central nervous system; 5-HT, serotonin; NREM, non-rapid eye movement sleep; WSC, Schisandra chinensis; BLM, Bailemian; RPE, Radix Polygalae Extract; HPA, hypothalamic-pituitary-adrenal; SCFAs, short chain fatty acids; Th17, T helper cell 17; GF mice, germ-free mice; ZSS, *Ziziphus jujuba* Mill. var.*spinosa* (Bunge) Hu ex H. F. Chou.

* Correspondence to: Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, No. 10 Poyang Lake Road, Jinghai, District, Tianjin 301617, China.

E-mail addresses: 455525081@qq.com (W. Feng), yzh2499214290@163.com (Z. Yang), liuyangxic7@163.com (Y. Liu), jbwkzchenrui@163.com (R. Chen), songzhihui22@126.com (Z. Song), 910347076@qq.com (G. Pan), zyh1830320@163.com (Y. Zhang), 424107569@qq.com (Z. Guo), dingxy_1@163.com (X. Ding), chenlutjutcm@tjutcm.edu.cn (L. Chen), wangyi@tjutcm.edu.cn (Y. Wang).

[1] These authors made equal contributions to this work.

https://doi.org/10.1016/j.biopha.2023.114344
Received 6 December 2022; Received in revised form 20 January 2023; Accepted 29 January 2023
Available online 2 February 2023

is rapidly increasing. However, in recent years, the number of people with insomnia has not shown a downward trend. How to further improve the efficacy of insomnia treatment and delay the occurrence and development of insomnia is a major challenge at present and is likely to remain so in the future.

2. Current situation and advantages of the use of TCM in the treatment of insomnia

Insomnia, known as "sleeplessness" in TCM, is a prevalent sleep disorder that is often encountered in clinics [6]. TCM can effectively enhance sleep without side effects or addiction when used as a medication to treat persistent insomnia. It has a surprising long-term impact and is receiving increasing attention [7]. The effectiveness of Yangxin Anshen Therapy as an alternative treatment for insomnia was demonstrated in a meta-analysis of randomized controlled trials (RCTs) involving 1549 patients with the condition [8]. The meta-analysis and systematic review summarized the findings made in nine RCTs that together had 681 participants. The findings of this meta-analysis confirmed that Xiao Yao San is effective in treating insomnia, while also reducing adverse responses and improving efficacy [9]. The data showed that in individuals treated with Guizhi gancao longgu muli decoction (GGLMD), the symptoms of insomnia were significantly decreased; the improvement in sleep patterns primarily manifested as extension of sleep time, improvement in sleep quality, and reduction of sleep latency, and there were no adverse reactions. The study of modified GGLMD treatment of insomnia evaluated the clinical efficacy and safety of the system.Moreover, analysis of the reports of adverse reactions revealed that adverse reactions to GGLMD in the treatment of insomnia were less frequent than adverse reactions to treatment with Western medicine and that GGLMD had higher clinical safety than Western medicine [10]. A multicentre, randomized, double-blind, placebo-controlled trial was conducted to determine the effectiveness and safety of the Chaihuguizhiganjiang-SuanZaoRen granule in patients with primary insomnia. In this trial, 50 patients with primary insomnia documented their bedtimes, rising times, total sleep time, and sleep efficiency in sleep diaries. It was discovered that combining Suan Zao Ren Tang with Chaihuguizhiganjiang decoctions improved sleep quality in patients with insomnia with few side effects [11]. In a double-blind, randomized, controlled experiment, 100 people who had insomnia and gallbladder and heart Qi deficiencies participated. It was found that Zhenjingdingzhi decoction is beneficial for treating insomnia associated with heart and gallbladder Qi deficiency, particularly for lengthening and enhancing sleep [12].

The pathogenesis of insomnia has not been fully elucidated. Previous studies have shown that the mechanisms through which TCM affects insomnia are related to central neurotransmitters, cytokines and peptides [1]. In recent years, increasing evidence has been obtained that imbalances in the gut microbiota are closely related to insomnia and that maintenance of balanced gut microbial populations plays an important role in insomnia regulation [13]. Taking gut microbiota as the starting point, this paper analyzes the relationship among gut microbiota, TCM and insomnia and the mechanism through which TCM regulates gut microbiota during the treatment of insomnia and reviews the scientific mechanism through which TCM may work in preventing and treating insomnia from the perspective of gut microbiota. This work provides new research ideas for the prevention and treatment of insomnia and drug development in TCM.

3. Basic and clinical study of TCM in improving insomnia by regulating gut microbiota

Many clinical trials show that TCM is effective in the treatment of insomnia. Studies have shown that gut microbiota can regulate host sleep and mood through the brain-gut-bacteria axis [14]. Based on this, by searching the relevant literature, this paper sorted out the basic and clinical research evidence of TCM in the treatment of insomnia from the point of adjusting gut microbiota. Many Chinese medicine compound prescriptions, herb pairs and single Chinese herb have the effect of tranquillizing spirit and stabilizing mind, thus playing a clinical effect in treating insomnia. Basic and clinical evidence showed that TCM could improve the sleep quality of insomnia patients and insomnia model animals. Its mechanism is related to the regulation of gut microbiota and the improvement of gut microbiota disorder [15–32]. See Table 1 for details.

4. The relationship between the gut microbiota and TCM

The bacteria that live in the intestine are known as the gut microbiota [33–35]. There are many different types of gut microbiota; the three major types are beneficial bacteria, conditional pathogens, and harmful bacteria. Beneficial bacteria refer to bacteria or fungi that play a positive role in human health, such as *Bifidobacterium*, *Lactobacillus*, and yeast. Harmful bacteria are aerobic bacteria represented by *Clostridium perfringens*, *Pseudomonas aeruginosa* and *Staphylococcus*, all of which can cause human disease [36]. Numerous diseases manifest with changes in the quantity and makeup of the gut microbiota [37]. When the intestinal mucosal barrier is destroyed, harmful bacteria invade, and the intestinal mucosa is colonized by these bacteria, which produce more toxic and less beneficial substances. Due to this gut dysbiosis, increased levels of proinflammatory substances such as pathogen-associated molecular pattern molecules (primarily the endotoxin lipopolysaccharide) and damage-associated molecular pattern molecules [38] appear in the blood and intestines, causing both localized intestinal damage and systemic chronic inflammation [39,40]. As a result, the body is more likely to harbor various pathogenic bacteria, and this encourages the emergence and progression of disease [41].

The gut microbiota and TCM are intimately related. The composition and metabolism of the gut microbiota can be influenced by TCM; conversely, the gut microbiota can metabolize the medicinal components of Chinese herbs (Fig. 1) [42]. Many studies have demonstrated that TCM treatment can significantly alter the gut microbiota, encourage the growth of beneficial bacteria, prevent overgrowth of harmful bacteria, and help maintain a healthy intestinal environment by balancing the numbers of probiotic and pathogenic bacteria [43,44]. Treatment with TCM has a variety of effects on the abundance of potentially helpful bacteria (such as those that produce anti-inflammatory compounds or short-chain fatty acids (SCFAs)) and harmful bacteria that may be proinflammatory and pathogenic [45,46]. The monosaccharides present in TCM formulations are broken down to create metabolites such as lactate, hydrogen, carbon dioxide, and SCFAs (formate, acetate, propionate, and butyrate) that may have an impact on host physiology [47,48]. TCM degradation products such as D-mannose may also behave as signaling molecules with distinct immunomodulatory actions and specific roles in host cells and tissues [49,50]. TCM administration frequently affects the abundance of gut bacteria that are involved in amino acid metabolism [42,51]. These include the Protists, lactobacilli, streptococci, and *Clostridium* [52]. Therefore, it is crucial to make progress in identifying the potential novel metabolites produced by the gut microbiota and understanding how TCM can change the composition of the gut microbiota [53].

5. The relationship between insomnia and gut microbiota

Previous research shows that the host's circadian rhythms interact with the circadian rhythms of gut bacteria [54]. Chronic insomnia and other sleep disorders can disrupt microbial circadian cycles, and this in turn affects the makeup and function of the bacteria in the gut [55,56]. Currently, there is evidence for a link between gut microbiota and insomnia [57], and there is increasing interest in how sleep affects the gut microbiota, as the microbiota play a crucial role in the pathophysiology of sleep disorders. According to clinical studies, patients with

Table 1
Basic and clinical study of TCM in improving insomnia by regulating gut microbiota.

No	Name of traditional Chinese medicine	Compositions	Clinical manifestation	Gut microbiota changes	Ref.
1	Tianwang Buxin granule	Suanzaoren (*Ziziphi Spinosae Semen*), Baiziren (*Platycladi Semen*), Tiandong (*Asparagi Radix*), Maidong (*Ophiopogonis Radix*), Renshen (*Ginseng Radix Et Rhizoma*), Fuling (*Poria*), Xuanshen (*Scrophulariae Radix*), Danshen (*Salviae Miltiorrhizae Radix Et Rhizoma*), Jiegeng (*Platycodonis Radix*), Yuanzhi (*Polygalae Radix*), Wuweizi (*Schisandrea Chinensis*), Danggui (*Angelicae Sinensis Radix*), Dihuang (*Rehmanniae Radix*)	1. Improve TCM syndrome score 2. Improve insomnia, significantly reduce pittsburgh sleep quality index (PSQI) score, reduce athens insomnia scale score, reduced insomnia severity index (ISI) score 3. Improve anxiety and depression, and reduce hamilton depression scale (HAMD) score and Hamilton Anxiety Scale (HAMA) score	• Adjust the structure of bacterial community. • Decrease the abundance of *Roseburia intestinalis, Ruminococcus, and Prevotella* • Improve the abundance of *Faecalibacterium Prausnitzii, Bacteroides, Bifidobacterium, and Lactobacillus*	[15]
2	Bupiwei Xieyinhuo Shengyang decoction	Chaihu (*Bupleuri Radix*), Zhigancao (*Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle*), Huangqi (*Astragali Radix*), Cangzhu (*Atractylodis Rhizoma*), Qianghuo (*Notopterygii Rhizoma Et Radix*), Shengma (*Cimicifugae Rhizoma*), Dangshen (*Codonopsis Radix*), Huangqin (*Scutellariae Radix*), Huanglian (*Coptidis Rhizoma*), Shigao (*Gypsum Fibrosum*)	1. Improve sleep quality, reduce PSQI score, such as subjective sleep quality score, sleep latency score, sleep duration score, use of sleep drugs total score, reduce ISI score, reduce Polysomnography total sleep time, improve sleep efficiency	• Decrease the abundance of *Fusobacteria, Cyanobacteria, Gemmatimonadetes, and Acidobacteria, Chloroflexi* • Increase the abundance of *Lactobacillaceae* • F/B ratio↓	[16]
3	Suanzaoren decoction	Suanzaoren (*Ziziphi Spinosae Semen*), Fuling (*Poria*), Zhimu (*Anemarrhenae Rhizoma*), Chuanxiong (*Chuanxiong Rhizoma*), Gancao (*Glycyrrhizae Radix Et Rhizoma*)	1. Reduce TCM syndrome score 2. Reduce PSQI score 3. Improve treatment efficiency	• Increase the number of *Lactobacillus and Bifidobacterium*	[17]
4	Buzhong Yiqi decoction	Huangqi (*Astragali Radix*), Zhigancao (*Glycyrrhizae Radix Et Rhizoma Praeparata Cum Melle*), Dangshen (*Codonopsis Radix*), Danggui (*Angelicae Sinensis Radix*), Chenpi (*Citri Reticulatae Pericarpium*), Shengma (*Cimicifugae Rhizoma*), Chaihu (*Bupleuri Radix*), Baizhu (*Atractylodis Macrocephalae Rhizoma*)	1. Reduce the total score of PSQI and each factor score, except the total score of habitual sleep efficiency and the total score of sleep medication use, and reduce the score of ISI 2. No serious adverse events occurred during the study	• Increase the number of *Verrucomicrobia and Synergistetes colonies* • Decrease the number of *Epsilonbacteraeota and Spirochetes colonies*	[18]
5	Wumei pill	Wumei (*Mume Fructus*), Fuzi (*Aconiti Lateralis Radix Praeparata*), Xixin (*Asari Radix Et Rhizoma*), Guizhi (*Cinnamomi Ramulus*), Huajiao (*Zanthoxyli Pericarpium*), Ganjiang (*Zingiberis Rhizoma*), Danggui (*Angelicae Sinensis Radix*), Dangshen (*Codonopsis Radix*), Huanglian (*Coptidis Rhizoma*), Huangbai (*Phellodendri Chinensis Cortex*), Maidong (*Ophiopogonis Radix*)	1. Reduce TCM syndrome score 2. Reduce PSQI total score and score of sleep quality, sleep time, sleep latency, sleep disturbance, sleep efficiency and hypnotic drug score 3. Improve the total effective rate of treatment	• Improve α diversity of gut microbiota • Increase number of *Firmicutes and Proteobacteria* • Decrease the number of *Bacteroidetes and Actinomyces*	[19]
6	Chaihu Longgu Muli decoction	Chaihu (*Bupleuri Radix*), Guizhi (*Cinnamomi Ramulus*), Longgu (*Fossilia Ossis Mastodi*), Muli (*Ostreae Concha*), Renshen (*Ginseng Radix Et Rhizoma*), Fuling (*Poria*), Huangqin (*Scutellariae Radix*), Shengjiang (*Zingiberis Rhizoma Recens*), Dazao (*Jujubae Fructus*), Fabanxia (*Pinelliae Rhizoma Praeparatum*), Dahuang (*Rhei Radix Et Rhizoma*), Qiandan (*Minium*)	1. Improve the total effective rate of treatment 2. Reduce TCM syndrome score 3. Lower PSQI score 4. Reduce the incidence of adverse reactions 5. Improve rapid eye movement sleep deprivation rats insomnia and its accompanying bad mood	• Increase the diversity of gut microbiota in sleep-deprived rats • Regulate the abundance of *Enterococcus*	[20,21]
7 8	Bailemian	Baihe (*Lilii Bulbus*), Ciwujia (*Acanthopanacis Senticosi Radix Et Rhizoma Seu Caulis*), Shouwuteng (*Polygoni Multiflori Caulis*), HehHehuanhua (*Albiziae Flos*), Zhenzhumu (*Margaritifera Concha*), Shigao (*Gypsum Fibrosum*), Suanzaoren (*Ziziphi Spinosae Semen*), Fuling (*Poria*), Yuanzhi (*Polygalae Radix*), Xuanshen (*Scrophulariae Radix*), Dihuang (*Rehmanniae Radix*), Maidong (*Ophiopogonis Radix*), Wuweizi (*Schisandrea Chinensis*), Dengxincao (*Juncus effusus L.*), Danshen (*Salviae Miltiorrhizae Radix Et Rhizoma*)	1. Bailemian significantly reversed the insomnia activities in p-chlorophenylalanine-treated mice 2. Improve the total effective rate of clinical treatment 3. Lower PSQI score 4. Reduce the incidence of adverse reactions	• Modulate the diversity of gut microbiota. • Enrich the beneficial bacteria of gut microbiota	[22,23]
9	Banxia Xiexin decoction	Banxia (*Pinelliae Rhizoma*), Huangqin (*Scutellariae Radix*), Ganjiang (*Zingiberis Rhizoma*), Renshen (*Ginseng Radix Et Rhizoma*), Huanglian (*Coptidis Rhizoma*), Dazao (*Jujubae Fructus*), Gancao (*Glycyrrhizae Radix Et Rhizoma*)	1. Improve overall efficiency 2. Reduce clinical symptom score 3. Improve sleep quality, increase the length of deep sleep and reduce the length of sleep waiting	• Increase the abundance of Bacteroidetes, Proteobacteria, Actinobacteria, and Verrucomicrobia • Decrease the relative abundance of Firmicutes • Increase the relative abundance of beneficial bacteria	[24,25]

(*continued on next page*)

Table 1 (*continued*)

No	Name of traditional Chinese medicine	Compositions	Clinical manifestation	Gut microbiota changes	Ref.
10	Jiaotai pill	Huanglian (*Coptidis Rhizoma*), Rougui (*Cinnamomi Cortex*)	1. Lower PSQI score 2. Improve TCM syndrome score 3. Increase serum levels of melatonin and adenosine	• Decrease the relative abundance of pathogenic bacteria • Increase the abundance of *Lachnospiraceae, Bacteroides, and Akkermansia* • Decrease abundance of *Ruminococcaceae* • Inhibit inflammation of the gut-brain axis • Reduce intestinal permeability	[26–28]
11	Baihe	Baihe (*Lilii Bulbus*)	Unreported	• Restore the imbalance in the diversity induced by PCPA • Adjust the abundance of gut microbiota, such as *Porphyromonadaceae, Lactobacillus and Escherichia at the genus level*	[29,30]
12	Total saponins of Suanzaoren	Total saponins of Suanzaoren	1. Reduce the autonomic activity of mice, prolong the sleep time of mice with threshold dose of pentobarbital sodium, and reduce the sleep latency of mice	• Increase the diversity of gut microbiota • F/B ratio↓	[31]
13	Renshen-Suanzaoren	Renshen (*Ginseng Radix Et Rhizoma*), Suanzaoren (*Ziziphi Spinosae Semen*)	2. Shorten sleep latency and significantly prolong sleep time in sleep-deprived model rats	• Improve the diversity of gut microbiota • Adjust the structure of gut microbiota. • Bacteroidetes↑, Actinomyces↓, • F/B ratio↓	[32]

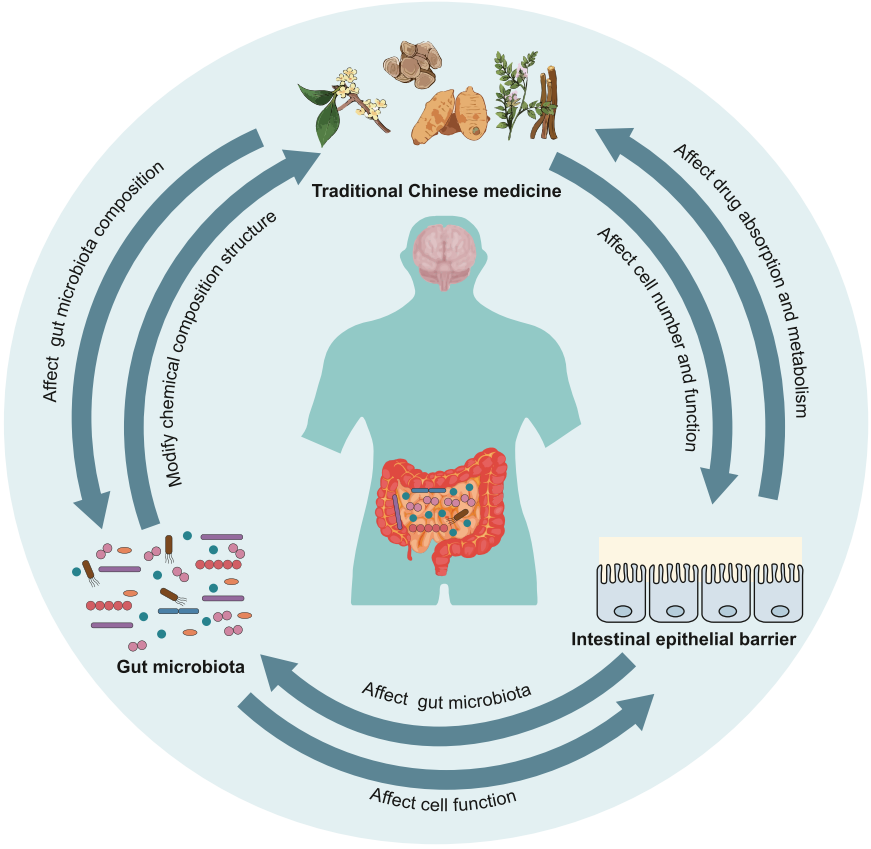

Fig. 1. The interaction between TCM and gut microbiota.

insomnia have significantly altered gut microbiota composition and diversity. Comparison of the relative abundances of various gut bacteria in individuals with insomnia and healthy individuals showed that Firmicutes and Proteobacteria were enriched in the healthy group, resulting in a decreased ratio of Firmicutes to Bacteroidetes, while Bacteroidetes were the dominant taxa in the insomnia group [58]. Another clinical study found marked changes in the composition of gut microbiota in patients with insomnia disorder compared with healthy

controls. Prevotellaceae significantly increased in patients with insomnia disorder, while Bacteroidaceae and Ruminococcaceae significantly decreased [59]. Clinical studies have found associations between sleep quality and cognitive performance with variations in gut microbiota composition and with the abundance of specific genera in older adults with insomnia [60]. Moreover, increases in the abundance of Lachnospiraceae are associated with ageing [61]. Studies have also shown negative associations between *Lachnospiraceae* and sleep deprivation [62]. Thaiss et al. [63] found that disrupting the sleep pattern of mice changed the structure and diversity of the animals' gut microbiota, and Reynolds et al. [13] reported similar findings in sleep-deprived shift workers. Moreover, the gut microbiota-derived metabolites SCFAs alter circadian rhythms [64]. SCFAs influence clock gene expression, and a relationship to sleep patterns has been confirmed [65].

It has been documented that signaling through both interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α) in the central nervous system (CNS) regulates sleep-wake behavior [66]. Zhong et al. found that the Toll-like receptor 4/nuclear factor-B signaling pathway was activated after transplantation of "SD microbiota" into germ-free (GF) mice. A clinical study showed that individuals with chronic insomnia had significantly increased levels of IL-1β compared with healthy controls and an increased abundance of signature bacteria associated with inflammatory cytokines in insomnia [67]. Therefore, loss of sleep causes inflammation, which in certain cases may be mediated by the gut flora [65]. This suggests that gut dysbiosis contributes to both peripheral and central inflammatory processes, a finding that may open the door to the development of interventions that can alleviate the negative consequences of sleep loss [68]. The gastrointestinal tract is an important target for the modulation of inflammation and its involvement in centrally mediated events such as circadian rhythm control. Future research should concentrate on the role of gut inflammation and the immune system's response to gut microbiota in circadian rhythm control [64] (Fig. 2).

6. Mechanism of the induction of insomnia by the brain-gut-microbe axis

The brain-gut-microbiota (BGM) axis, a complex bidirectional communication system that largely consists of neurological, immunological, metabolic, and endocrine pathways, closely connects the gut and the brain (Fig. 3) [69].

6.1. The HPA axis

Sleep exhibits a close and reciprocal association with the ability of the HPA axis to operate [70]. In general, increased HPA activation causes lighter sleep and increases nocturnal awakening, while insufficient sleep has been shown to increase the basal activity of the HPA axis [71]. The HPA axis releases corticotropin-releasing factor (CRF) from the hypothalamus, which in turn stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH); this causes the adrenal glands to release cortisol in humans or corticosterone in animals [72]. Mean ACTH and cortisol levels were reported to be higher in insomniacs than in control subjects in a clinical study that compared the 24-hour plasma profiles of patients with insomnia with those of healthy individuals [73]. Elevated HPA activity before sleep promotes sleep fragmentation, which in turn has been shown to promote sleep loss and to increase evening cortisol levels [74]. Experimental studies in animals have found that the diversity of gut microbiota decreased in mice that were subjected to sleep deprivation and that this change coincided with an increase in the concentration of cortisol in saliva, indicating that sleep disorders activate the HPA axis [75]. In addition, the HPA axis can disrupt the gut barrier and increase intestinal permeability, resulting in a "leaky gut" with bacterial translocation across the mucosa and immune cell infiltration and further resulting in immune activation and increased levels of proinflammatory cytokines [76,77]. An experimental study found that gut probiotics can repair gut barrier damage by affecting

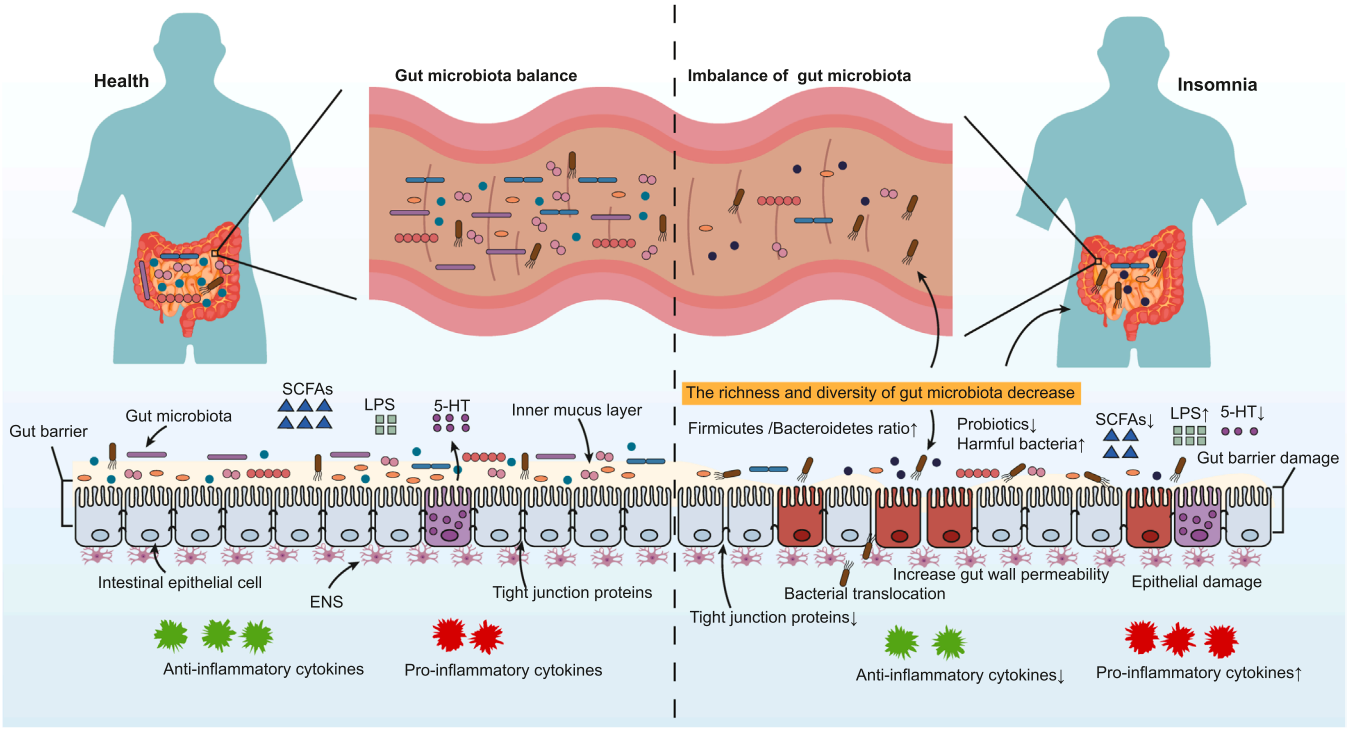

Fig. 2. The relationship between intestinal microecology and insomnia. In healthy individuals, the intestinal microecology is in dynamic balance, including the balance of gut microbiota and normal gut barrier function. Patients with insomnia have obvious disorders associated with the gut microbiota and gut barrier dysfunction, including imbalances in their gut microbiota, increased numbers of harmful bacteria, decreased numbers of beneficial bacteria, decreased gut microbiota metabolite SCFAs, increased lipopolysaccharide (LPS) levels, decreases in intestinal anti-inflammatory factors, increases in proinflammatory factors, decreases in intestinal tight junction proteins, and increased intestinal permeability.

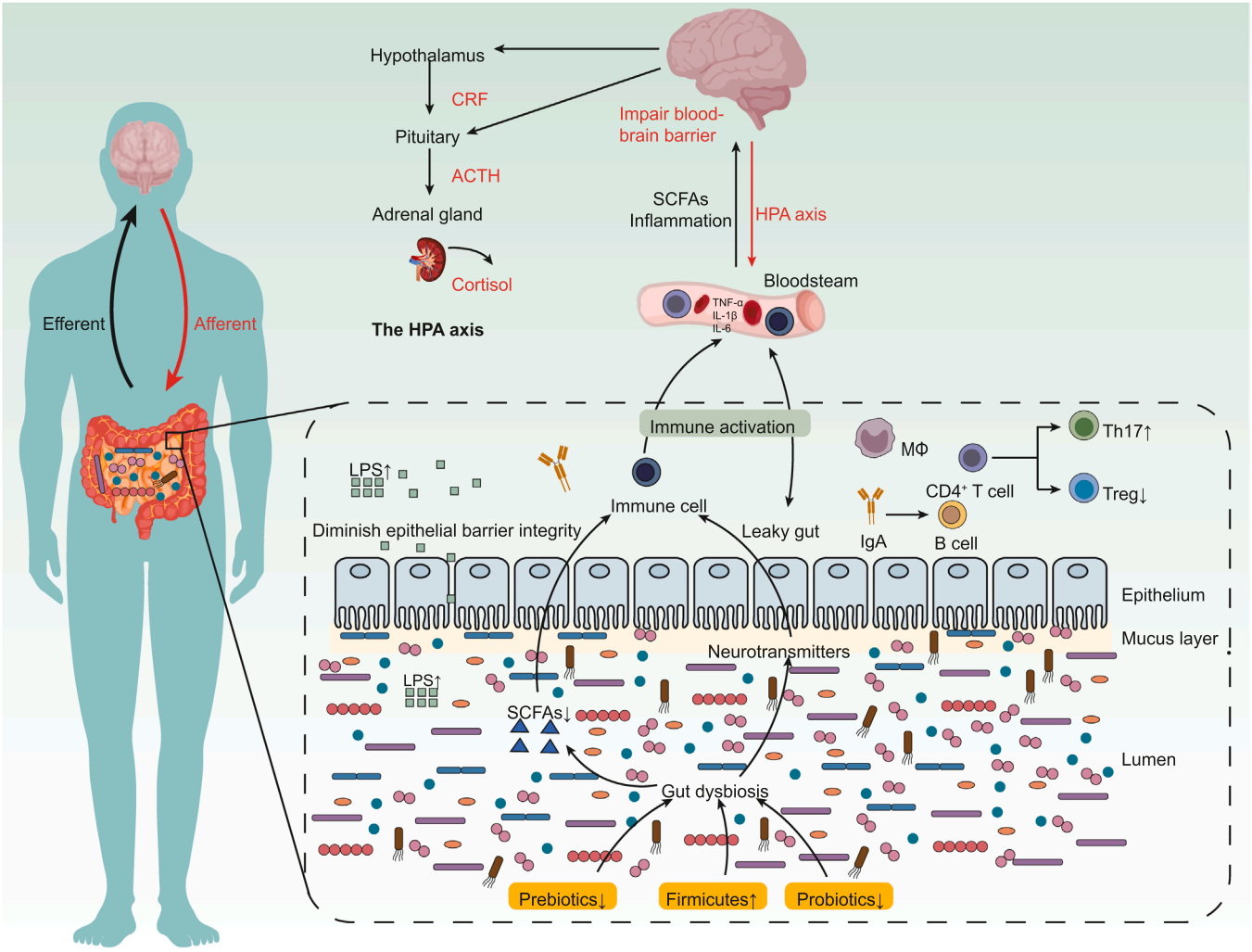

Fig. 3. Mechanism through which insomnia is induced by the BGM axis. The hypothalamic—pituitary—adrenal (HPA) axis, the vagus nerve, and enteric nerve pathways are primarily implicated in the BGM axis in insomnia, either directly or indirectly. When insomnia occurs, the HPA axis may become active and increase the release of cortisol, which interacts with immune cells and controls the release of cytokines. In addition to altering the composition of the gut microbiota and the quantity of bacterial metabolites, cortisol can also produce gut dysbiosis and "leaky gut", both of which increase intestinal barrier permeability and the production of proinflammatory cytokines that interfere with sleep. As a crucial nerve that connects the gut and the brain, the vagus nerve is able to communicate with the enteric nervous system to receive and transmit various signals from the gut that collectively affect brain function. These signals come primarily from intestinal immune cells, bacterial metabolites such as SCFAs, and gut-derived neurotransmitters such as 5-HT. Additionally, SCFAs produced by microbiota, as well as many neurotransmitters, have anti-inflammatory properties and can interact with immune cells to affect sleep.

stress responses associated with the HPA axis, suggesting that information can be transmitted from the gut to the brain via this axis [78].

6.2. *Neurotransmitters*

Neurophysiological studies have shown that insomnia is closely related to neurotransmitters. Numerous neurotransmitters produced in the gut, all of which have direct interactions with the CNS, can also communicate with the brain through γ-aminobutyric acid (GABA), an important inhibitory neurotransmitter in the brain. GABAergic neurons in various parts of the brain promote sleep, and the level of GABA in the brains of insomnia patients is low [79]. Increasing evidence supports the idea that GABA regulates sleep and that it is able to shorten sleep latency and increase sleep quality in patients with insomnia [80]. Experimental studies have found that GABA can improve sleep by regulating gut microbiota and increasing SCFA levels [81]. *Lactobacillus* and bifidobacteria have the ability to produce GABA. This suggests that GABA may improve sleep by promoting probiotics in the gut [82].

It has been confirmed that 5-HT participates in regulation of the sleep-wake cycle, that 5-HT receptor subtypes in different brain regions have different pharmacological effects, and that the content of 5-HT in the brains of patients with insomnia is abnormal [83,84]. Probiotics such as *Lactobacillus* and *Bifidobacterium* have positive effects on tryptophan metabolism and are able to convert tryptophan directly to 5-HT [85,86]. In addition, *Lactobacillus casei 327* can indirectly increase the production of 5-HT in the colon [87]. In animal studies, it was shown that dysregulation of the gut microbiota causes a dramatic decrease in 5-HT levels that impacts the sleep-wake cycle. This result indicates the likelihood that 5-HT is involved in communication between the gut microbiota and systems involved in sleep regulation [88].

6.3. *Vagus nerve*

One of the main signaling pathways connecting the brain and the gut microbiota is the vagus nerve [89]. The vagus nerve works in tandem with the enteric nervous system to regulate gut function. Probiotics have been found to regulate sleep by increasing the expression of central GABA receptors in mice. This suggests that GABA and the vagus nerve

collaborate to control how the gut microbiota affect brain function [90]. The vagus nerve is also thought to be a significant regulator of the immune response and appears to be important for microbiota-gut-brain communication [91]. An investigation in mice revealed that the gut microbiota-spleen and gut microbiota-vagus nerve axes are crucial in controlling systemic inflammation induced by sleep deprivation following LPS treatment [92]. Afferent signals from the gut to the brain can trigger an efferent response that reduces inflammation through interaction with immune cells.

6.4. Immune system

In recent years, some scholars have hypothesized that insomnia is a common inflammatory response [93] and that inflammation mediated by disorders associated with the intestinal microbiota may also lead to insomnia [94]. There is a balance among the intestinal flora, which play an important role in intestinal mucosal immune function. When this balance is disrupted, the number of harmful bacteria will increase, intestinal barrier function will be damaged, permeability will be increased, and the immune function of the body will be damaged [95]. The microbiota activate an inflammatory response mechanism that subsequently activates the CNS and worsens sleeplessness [96]. The production of inflammatory cytokines is directly correlated with alterations in the gut bacteria. By encouraging the production of TNF-α and interleukin 6 (IL-6) and activating T helper 17 (Th17) cells and B cells in the intestinal microenvironment, the family Prevotellaceae is recognized as a major contributor to intestinal inflammation [97]. The development of multiple immune-related diseases is facilitated by increased prevalence of *Prevotella* and similar organisms [98]. It was shown that the gut microbiota of insomniacs harbored much higher concentrations of the families Prevotellaceae and *Prevotella*, as well as significantly lower concentrations of the family Ruminococcaceae, compared to the gut microbiota of healthy controls [99,100]. Patients with insomnia may be more susceptible to immunological disorders as a result of these changes. The production of butyrate, an anti-inflammatory short-chain fatty acid, by members of the genus *Fusicatenibacter* has been linked to the presence of lower levels of proinflammatory cytokines, including IL-6, TNF-α, and IL-1β, in human serum [99,100]. Even short-term sleep disorders are linked to proinflammatory alterations; healthy volunteers with such disorders showed increased levels of C-reactive protein, IL-6, interleukin 7 (IL-7), TNF-α and myeloperoxidase [101]. These outcomes might increase systemic inflammation and reduce resistance to infection [102,103].

6.5. Metabolites of gut microbiota

Increasing evidence indicates that metabolites produced by the gut microbiota are important sources of sleep-promoting signals, especially SCFAs, which are arguably the most thoroughly studied of these signals [104]. Intestinal SCFAs, which include formic acid, acetic acid, propionic acid, and butyric acid, are produced by gut microbiota during the fermentation of food. SCFAs play a critical role in microbiota-gut-brain axis communication [105]. In older persons with insomnia, short sleep duration resulted in higher levels of SCFAs in feces than did regular sleep duration [106]. SCFAs enhance and reinforce the intestinal barrier by interacting with immune cells, reducing inflammation, and preventing the entrance of bacteria and their byproducts, and these effects may then lessen neuroinflammation in the brain [105]. Moreover, live bacteria in the intestines produce butyrate, which has potent anti-inflammatory properties. It reduces inflammation in the colon and liver, decreases nuclear factor-κB (NF-κB) activation and attenuates the production of proinflammatory cytokines induced by LPS [107]. This indicates that bacterial-derived anti-inflammatory signals from the intestinal tract have the potential to modulate sleep [108]. Recent research has found that tributyrin and butyrate robustly boost nonrapid eye movement sleep (NREM) in rats and mice [109]. This demonstrates that butyrate can potentially act as a signaling molecule to induce sleep. These results indicate that SCFAs are an important component of how the gut microbiota influence sleep physiology by interacting with the immune system.

7. TCM regulation of the gut microbiota in the prevention and treatment of insomnia

7.1. Regulation of gut microbiota structure

Modern research has shown that single Chinese herbal remedies, single TCM components, and TCM formulas can change the composition of the gut microbiota. Some TCM treatments promote the growth of symbiotic beneficial bacteria such as *Lactobacillus, Bifidobacterium,* and *Bacteroides* by acting similarly to prebiotics [58]. The majority of researchers concur that health is improved when the microbial diversity in the gut increases [110]. After sleep deprivation, there were no obvious changes in microbiota richness or composition [111]. However, another study found that alpha diversity was negatively linked to sleep fragmentation and favorably associated with sleep efficiency and total sleep time [62]. Yue et al. reported that Yi-Zhi-An-Shen granules improve sleep quality by improving intestinal alpha diversity [112]. A study discovered that *Schisandra chinensis* (WSC) can significantly increase the abundance and alpha diversity of gut microbiota and cause noticeable changes in the structure of gut microbiota [113]. Dysbiosis in the gut microbial environment can be corrected by WSC treatment, and such treatment also helps reverse changes in the abundance of Lachnospiraceae*, Lactobacillus,* and *Alloprevotella*. Bailemian (BLM) is reportedly used in the treatment of insomnia and has an impact on the variety and makeup of the gut microbiota. It can regulate the variety and composition of the bacteria that make up the gut microbiota, enrich the levels of beneficial bacteria therein, and increase the levels of neurotransmitters in the brain and colonic feces [22]. BLM can also enhance the abundance of beneficial bacteria such as *Lactobacillus*, which synthesize neurotransmitters, and restore the dysbiotic microbiota to a healthy population [22].

7.2. Regulating immunity

The powerful immunomodulatory effects of TCM are by far its greatest benefit [114]. An experimental study showed that Radix Polygalae Extract (RPE) [115], especially the probiotics *Lactobacillus* and *Bacteroides*, significantly reduced levels of proinflammatory cytokines and altered the gut microbiota. By altering the NF-κB-NLRP3 signaling pathway, RPE may change colonic homeostasis (proinflammatory responses, dysbiosis of the gut microbiota, and colonic barrier permeability). Pharmacological studies showed that Buzhong Yiqi decoction promotes the growth of intestinal probiotics in mice and helps repair damaged intestinal mucosa [116]. After *Poria cocos* treatment of rats with insomnia, the animals' sleep improved, indicating that *Poria cocos* regulates gastrointestinal hormones and reduces the levels of inflammatory factors [117]. Buzhong Yiqi decoction can effectively reduce the abundance of Epsilonbacteraeota, which causes gastroenteritis in humans, and the abundance of spirochetes, which cause an adaptive immune inflammatory response after infection. This indicates that Buzhong Yiqi decoction can effectively reduce inflammatory intestinal pathogenic bacteria and improve insomnia by reducing the intestinal immune inflammatory response [18]. A study of the relationship between gut microbiota and sleep deprivation in healthy elderly people found that the better the sleep quality of the subjects was, the higher was the proportion of Verrucobacteria, and the abundance of Verrucobacteria was found to be significantly increased after treatment with Buzhong Yiqi decoction [118].

7.3. Regulation of gut microbiota and their metabolites

The local or systemic immune activity of the host can be impacted by the gut microbiota and their metabolites. SCFAs are significant byproducts of the fermentation of dietary fiber by helpful gut bacteria. SCFAs play a crucial role in metabolism as well as in the control of inflammation and immunological homeostasis [119]. SCFAs have immunomodulatory effects that can improve the ability of intestinal epithelial cells to act as a barrier, decrease the production of proinflammatory cytokines, promote the development of regulatory T cells, promote intestinal mucosal homeostasis, prevent colonic inflammation, and enhance the proinflammatory states of intestinal epithelial cells and leukocytes [120,121]. Beneficial bacteria in the microbiota synthesize SCFAs. SFCAs are thought to play a variety of significant roles in preserving bodily health, including increasing gastrointestinal motility, decreasing inflammation, and defending the intestinal mucosal barrier [122]. The most prevalent SCFAs are propionic acid, acetic acid, and butyric acid; Firmicutes produce primarily butyrate, and Bacteroidetes produce primarily propionic acid and acetate [123]. Numerous intestinal flora have been found to be connected to both changes in SCFA content and insomnia. Butyrate may potentially function as a sleep-inducing signal molecule that increases sleep [109], and butyrate

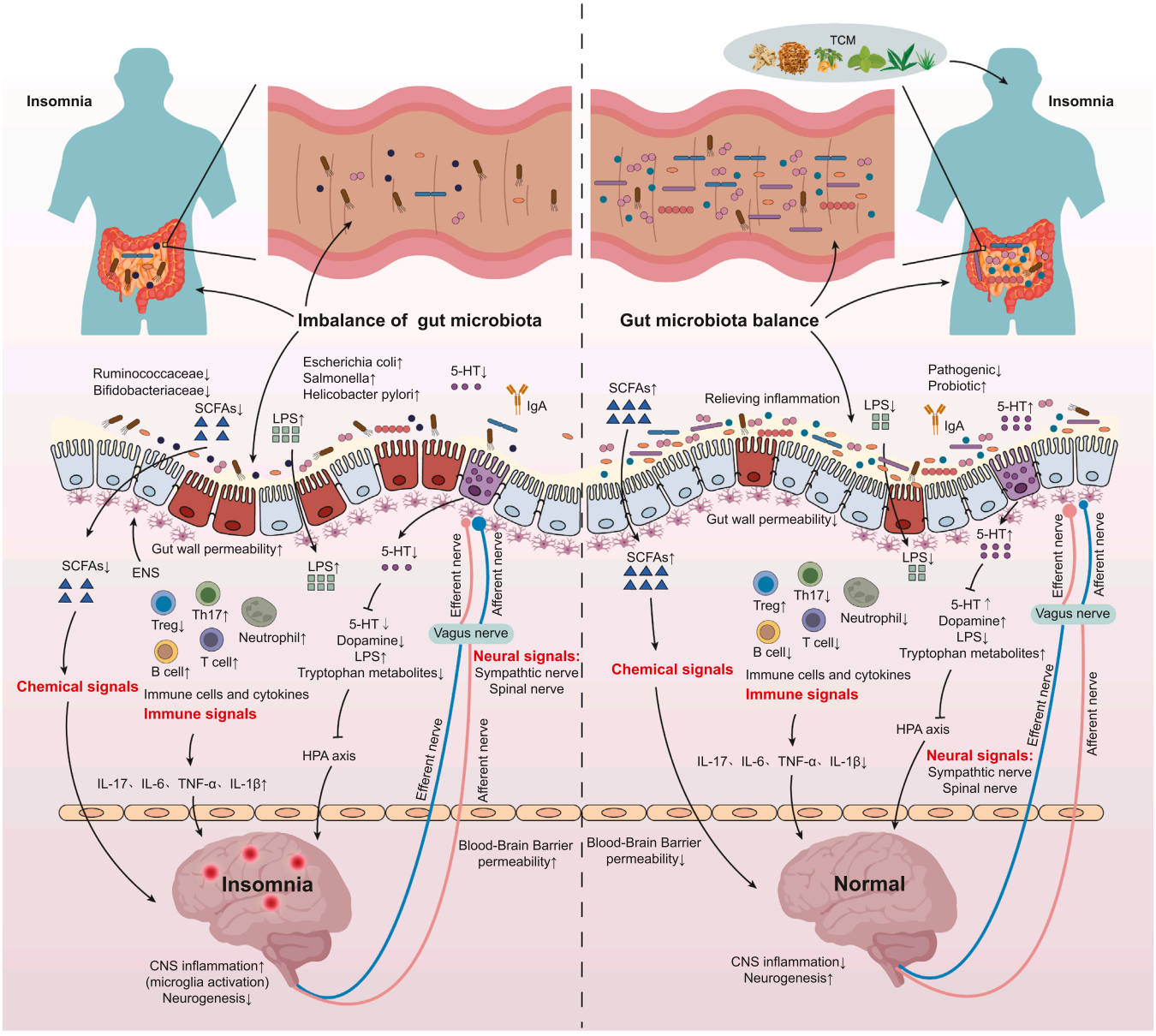

Fig. 4. Mechanism through which disorders of the gut microbiota induce insomnia and how TCM regulates the gut microbiota to prevent and treat insomnia. The CNS, periphery, and gut are shown as the three main parts of the BGM axis. A significant portion of the BGM axis is made up of a network of neurological signals, immunological signals, and chemical signals. Changes in this network result in intricate interactions between organs via direct (nerves) and indirect (systemic circulation) routes, and these interactions affect body homeostasis. Disruption of the intestinal mucosal barrier, imbalances in the intestinal flora (an increase in the number of harmful bacteria and a decrease in the number of beneficial bacteria), and an increase in intestinal endotoxins are all caused by insomnia. By targeting peripheral organs and tissue in response to various signals, the CNS functions through neuronal control, neurotransmitters, immunological signals, and other elements that support appropriate bidirectional brain-gut axis transmission. Insomnia may occur when this equilibrium is lost. TCM reduces the imbalance among intestinal flora, promotes the growth of beneficial bacteria, inhibits the excessive reproduction of harmful bacteria, and promotes the production of SCFAs; on the other hand, TCM can also help maintain the immune barrier function of the intestinal mucosa, thereby improving body immunity and preventing deterioration of the host's condition.

producers such as *Blautia* and *Coprococcus* may have an impact on the quality of sleep [62]. The expression of the clock gene, which is strongly linked to circadian rhythm and sleep quality, is influenced by butyrate and acetate [124]. *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou (ZSS, called "Suan zao ren" in China) can increase the amount of SCFAs in rat faeces, with acetic acid having a notable reversal effect. This further demonstrates that ZSS can reduce insomnia by altering the composition of the gut microbiota [125]. Fig. 4 shows how TCM regulates the gut microbiota in a way that can prevent and treat insomnia.

8. Conclusion

Targeting gut microbiota in the treatment of insomnia is a very promising treatment mode. Attaching importance to the gut microbiota as research targets related to insomnia and broadening the general train of thought regarding research on and treatment of insomnia has great potential for the future development of resistance to microbial infections and for solving the existing medical dilemma regarding the treatment of chronic insomnia. Research on the pathways through which gut microbiota are involved in the development of insomnia is not only aimed at exploring the causes of insomnia but also provides a large number of new targets for the clinical treatment of insomnia, such as the artificial production of microbial metabolites that regulate sleep and the selection of drugs based on intestinal metabolic characteristics. At present, research on the relationship between gut microbiota and insomnia is still in the initial stage, and the methods used in this research are not sufficiently mature. In addition, because the relationship between the gut microbiota and the human body is very complex and is easily affected by diet, exercise, the use of other drugs, psychological factors and other factors, this should be considered when studying the relationship between the gut microbiota and insomnia. Therefore, future research should focus on the internal mechanism through which insomnia is related to microbiota.

An increasing number of studies have confirmed that TCM can be successfully used to treat insomnia by regulating the gut microbiota. However, most of these studies are based on animal experiments and lack verification in clinical trials. Moreover, TCM has the problems of complex composition, difficulty in purifying a single active ingredient in large quantities, and low bioavailability. Most of the experiments conducted to date focus on the effect of drugs on insomnia and the corresponding structural changes in the gut microbiota, and they lack in-depth research on the specific mechanisms and targets through which TCM intervention with the gut microbiota improves sleep. Moreover, some TCMs regulate specific gut microbiota in a way that promotes the absorption of TCMs in the body. Clarification of the molecular mechanism through which TCM and compound drugs interact with the gut microbiota, identification of the targets of their action on insomnia, and screening for TCM compounds that affect bacteria related to insomnia may offer a new way to treat insomnia.

In conclusion, the gut microbiota play an important role in the occurrence and development of insomnia, and interference with the gut microbiota through TCM is expected to become a new way to prevent and treat insomnia. Therefore, taking gut microbiota as the target, paying attention to the effects of TCM on gut microbiota, and defining the scientific relevance of TCM to the prevention and treatment of insomnia may revitalize ideas regarding the treatment of insomnia and improve the treatment of insomnia.

CRediT authorship contribution statement

Lu Chen and Yi Wang designed and supervised this work, Wanying Feng, Zhihua Yang, Yangxi Liu, and Rui Chen performed the literature search, selected relevant articles, interpreted data, and wrote the report. Zhihui Song, Guiyun Pan, Yuhang Zhang, and Xinya Ding contributed to draw diagram. Wanying Feng and Zhihua Yang contributed equally to this work and shared the first authorship; Wanying Feng, Zhihua Yang, and Yangxi Liu were responsible for the entire manuscript; All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors of manuscript that titled"Gut microbiota: A new target of traditional Chinese medicine for insomnia" declared that there are no conflicts of interest.

Data Availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by the Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (No: ZYYCXTD-C-202203).

References

[1] E.J.W. Van Someren, Brain mechanisms of insomnia: new perspectives on causes and consequences, Physiol. Rev. 101 (3) (2021) 995–1046.
[2] D.J. Buysse, Insomnia, Jama 309 (7) (2013) 706–716.
[3] L. Li, Y. Gan, X. Zhou, H. Jiang, Y. Zhao, Q. Tian, Y. He, Q. Liu, Q. Mei, C. Wu, Z. Lu, Insomnia and the risk of hypertension: a meta-analysis of prospective cohort studies, Sleep Med. Rev. 56 (2021), 101403.
[4] W.F. Yeung, K.F. Chung, M.M. Poon, F.Y. Ho, S.P. Zhang, Z.J. Zhang, E.T. Ziea, V. T. Wong, Chinese herbal medicine for insomnia: a systematic review of randomized controlled trials, Sleep Med. Rev. 16 (6) (2012) 497–507.
[5] M.M. Shi, J.H. Piao, X.L. Xu, L. Zhu, L. Yang, F.L. Lin, J. Chen, J.G. Jiang, Chinese medicines with sedative-hypnotic effects and their active components, Sleep Med. Rev. 29 (2016) 108–118.
[6] D. Patel, J. Steinberg, P. Patel, Insomnia in the elderly: a review, J. Clin. Sleep Med.: JCSM: Off. Publ. Am. Acad. Sleep Med. 14 (6) (2018) 1017–1024.
[7] L. Liu, C. Li, Q. Yang, W. Zhang, Y. Liu, H. Zhu, Clinical and neuroimaging features of a Chinese patient with fatal familial insomnia, Sleep Med. 32 (2017) 280–281.
[8] F. Li, B. Xu, H. Shi, T. Zhang, Z. Song, Y. Chen, L. Liu, P. Wang, Efficacy and safety of TCM Yangxin Anshen Therapy for insomnia: a systematic review and meta-analysis, Medicine 99 (8) (2020), e19330.
[9] J. Hu, J. Teng, W. Wang, N. Yang, H. Tian, W. Zhang, X. Peng, J. Zhang, Clinical efficacy and safety of traditional Chinese medicine Xiao Yao San in insomnia combined with anxiety, Medicine 100 (43) (2021), e27608.
[10] F. Chen, Z. Chen, Y. Cheng, J. Li, R. Liao, Z. Zhao, K. Wu, J. Liu, Meta analysis for insomnia Guizhi Gancao Longgu Muli decoction for insomnia a meta-analysis, Complement. Ther. Clin. Pract. 47 (2022), 101550.
[11] Q.Q. Liu, J. Zhang, R.J. Guo, Y.Z. Xie, Q.N. Fu, T. He, X.Q. Zhu, J. Du, J. Yang, J. L. Wang, M.M. Wei, Q.Q. Li, G.X. Shi, C.Z. Liu, Efficacy and safety of the Chaihuguizhiganjiang-suanzaoren granule on primary insomnia: study protocol for a randomised controlled trial, BMJ Open 6 (2) (2016), e008459.
[12] Q. Ye, J. Zhou, X. Yuan, C. Yuan, X. Yang, Efficacy of Zhenjingdingzhi decoction in treating insomnia with Qi-deficiency of heart and gallbladder: a randomized, double-blind, controlled trial, J. Tradit. Chin. Med. 35 (4) (2015) 381–388.
[13] A.C. Reynolds, J.L. Paterson, S.A. Ferguson, D. Stanley, K.P. Wright, D. Dawson, The shift work and health research agenda: considering changes in gut microbiota as a pathway linking shift work, sleep loss and circadian misalignment, and metabolic disease, Sleep Med. Rev. 34 (2017) 3–9.
[14] Y. Li, Y. Hao, F. Fan, B. Zhang, The role of microbiome in insomnia, circadian disturbance and depression, Front Psychiatry 9 (2018) 669.
[15] X.Q. Yang, Study on the efficacy and mechanism of Tianwang Buxin granule on perimenopausal insomnia based on intestinal flora, Hubei Univ. Chin. Med. (2020).
[16] C.Y. Zhao, To explore the changes of insomnia due to spleen deficiency and the intervention effect of invigorating spleen and stomach, Purging Yin and promoting Yang decoction from intestinal flora, Guangzhou Univ. Chin. Med. (2020).
[17] X.W. Wen, B. Xu, Q. He, Observation on the curative effect of Suanzaoren decoction in the treatment of insomnia due to deficiency of liver Yin and its effect on intestinal probiotics in patients, Chin. J. Tradit. Med. Sci. Technol. 29 (03) (2022) 405–407.
[18] C.Y. Zhao, R. Xiao, L.L. Yang, Y. Li, L.M. Zheng, J. Zhang, Observation of therapeutic effect of Buzhong Yiqi decoction on insomnia due to spleen deficiency and investigation of intestinal flora, J. Guangzhou Univ. Tradit. Chin. Med. 37 (11) (2020) 2057–2063.
[19] X.S. Zhu, S.X. Peng, Z.W. Zuo, Z.Q. Sun, L. Li, F.J. Zhuo, Sleep quality of patients with insomnia after oral administration of modified Wumei Pills and changes in intestinal flora, Shandong Med. J. 62 (11) (2022) 47–49.

[20] E.B. Feng, H.J. Fang, L.Y. Li, M.L. Deng, M. Su, Clinical study on the treatment of psychogenic insomnia with Chaihu and Longgu oyster decoction, Guangming J. Chin. Med. 37 (05) (2022) 738–740.

[21] H.J. Chen, Effect of Chaihu, Longgu Muli Decoction on Intestinal Flora in REM Sleep Deprivation Rats, Beijing University of Chinese Medicine, 2020.

[22] H.F. Wang, X.J. Qin, Z.H. Gui, W.H. Chu, The effect of Bailemian on neurotransmitters and gut microbiota in p-chlorophenylalanine induced insomnia mice, Microb. Pathog. 148 (2020).

[23] M. Chen, M.J. Cheng, X.Y. Ceng, J. Liang, Clinical observation on Bailemian capsules combined with estazolam in treatment of insomnia, Drugs Clin. 35 (04) (2020) 697–700.

[24] X.R. Lan, Effect of Banxia Xiexin decoction combined with metformin in the treatment of type 2 diabetes patients with insomnia, Diabetes New World 24 (23) (2021) 63–66.

[25] F.Q. Zhao, M.X. An, Y. Zhao, Y.J. Gou, J.Y. Liu, L.H. Na, Effect of Banxia Xiexin decoction on intestinal microflora and glycolipid metabolism in PCOS rats from the perspective of "Spleen governs transportation", Lishizhen Med. Mater. Med. Res. 33 (08) (2022) 1850–1855.

[26] C.C. Ceng, Y.Y. Xie, C.X. Dai, Z.Z. Yuan, Double-blind randomized controlled study on Jiaotai pills for insomnia of noninteraction between the heart and the kidney type in perimenopausal perio, New Chin. Med. 54 (08) (2022) 41–44.

[27] Y. Wang, Z. Li, M. Feng, L. Li, S. Gao, C.Q. Yu, Effects of Jiaotai Pills on intestinal flora in depression model mice with chronic unpredictable mild stress, J. Tianjin Univ. Tradit. Chin. Med. 41 (02) (2022) 204–211.

[28] H. Su, C. Zhang, X. Zou, F.E. Lu, Y. Zeng, H.W. Guan, Y.L. Ren, F. Yuan, L.J. Xu, M.M. Zhang, H. Dong, Jiao-tai-wan inhibits inflammation of the gut-brain-axis and attenuates cognitive impairment in insomnic rats, J. Ethnopharmacol. 250 (2020).

[29] Y. Si, X. Chen, T. Guo, W. Wei, L. Wang, F. Zhang, X. Sun, M. Liu, Comprehensive 16S rDNA sequencing and LC-MS/MS-based metabolomics to investigate intestinal flora and metabolic profiles of the serum, hypothalamus and hippocampus in p-chlorophenylalanine-induced insomnia rats treated with lilium brownie, Neurochem. Res. 47 (3) (2022) 574–589.

[30] Y. Si, W. Wei, X. Chen, X. Xie, T. Guo, Y. Sasaki, Y. Zhang, L. Wang, F. Zhang, S. Feng, A comprehensive study on the relieving effect of Lilium brownii on the intestinal flora and metabolic disorder in p-chlorphenylalanine induced insomnia rats, Pharm. Biol. 60 (1) (2022) 131–143.

[31] X.F. Cui, Study on metabolic transformation of Ziziphi Spinosae Semen saponins by intestinal microflora in vitro, Shanxi Univ. Chin. Med. (2020).

[32] Y. Wang, Based on "Brain and Intestine Axis", explore the effect of Renshen and Suanzaoren on insomnia rats with deficiency of heart and spleen, Liaoning Univ. Tradit. Chin. Med. (2022).

[33] C.S. Lin, C.J. Chang, C.C. Lu, J. Martel, D.M. Ojcius, Y.F. Ko, J.D. Young, H.C. Lai, Impact of the gut microbiota, prebiotics, and probiotics on human health and disease, Biomed. J. 37 (5) (2014) 259–268.

[34] Y.L. Tsai, T.L. Lin, C.J. Chang, T.R. Wu, W.F. Lai, C.C. Lu, H.C. Lai, Probiotics, prebiotics and amelioration of diseases, J. Biomed. Sci. 26 (1) (2019) 3.

[35] N. Zmora, J. Suez, E. Elinav, You are what you eat: diet, health and the gut microbiota, Nat. Rev. Gastroenterol. Hepat. 16 (1) (2019) 35–56.

[36] H. Zafar, M.H. Saier Jr., Gut Bacteroides species in health and disease, Gut Microbes 13 (1) (2021) 1–20.

[37] X. Gong, X. Li, A. Bo, R.Y. Shi, Q.Y. Li, L.J. Lei, L. Zhang, M.H. Li, The interactions between gut microbiota and bioactive ingredients of traditional Chinese medicines: a review, Pharm. Res. 157 (2020).

[38] D.L. Tang, R. Kang, C.B. Coyne, H.J. Zeh, M.T. Lotze, PAMPs and DAMPs: signal 0s that spur autophagy and immunity, Immunol. Rev. 249 (2012) 158–175.

[39] Q. Yan, Neuroimmune imbalances and Yin-Yang dynamics in stress, anxiety, and depression, Methods Mol. Biol. 2018 (1781) 77–85.

[40] P.N. Alexandrov, Y.H. Zhai, W.H. Li, W.J. Lukiw, Lipopolysaccharide-stimulated, NF-kB-, miRNA-146a-and miRNA-155-mediated molecular-genetic communication between the human gastrointestinal tract microbiome and the brain, Folia Neuropathol. 57 (3) (2019) 211–219.

[41] S. Heinonen, T. Nurmi, K. Liukkonen, K. Poutanen, K. Wahala, T. Deyama, S. Nishibe, H. Adlercreutz, In vitro metabolism of plant lignans: new precursors of mammalian lignans enterolactone and enterodiol, J. Agric. Food Chem. 49 (7) (2001) 3178–3186.

[42] W.W. Feng, H. Ao, C. Peng, D. Yan, Gut microbiota, a new frontier to understand traditional Chinese medicines, Pharm. Res. 142 (2019) 176–191.

[43] Z.H. Yang, Y.X. Liu, L. Wang, S.S. Lin, X.D. Dai, H.F. Yan, Z. Ge, Q.A. Ren, H. Wang, F. Zhu, S.P. Wang, Traditional Chinese medicine against COVID-19: role of the gut microbiota, Biomed. Pharmacother. 149 (2022).

[44] D.X. Jin, J.F. He, K.Q. Zhang, X.G. Luo, T.C. Zhang, EtOAc extract of H. attenuatum Choisy inhibits inflammation by suppressing the NF-κB and MAPK pathways and modulating the gut microbiota, Phytomedicine 57 (2019) 292–304.

[45] X.L. Tong, J. Xu, F.M. Lian, X.T. Yu, Y.F. Zhao, L.P. Xu, M.H. Zhang, X.Y. Zhao, J. Shen, S.P. Wu, X.Y. Pang, J.X. Tian, C.H. Zhang, Q. Zhou, L.H. Wang, B. Pang, F. Chen, Z.P. Peng, J. Wang, Z. Zhen, C. Fang, M. Li, L.M. Chen, L.P. Zhao, Structural alteration of gut microbiota during the amelioration of human type 2 diabetes with hyperlipidemia by metformin and a traditional Chinese herbal formula: a multicenter, randomized, open label clinical trial, Mbio 9 (3) (2018).

[46] Q.X. Nie, H.H. Chen, J.L. Hu, S.T. Fan, S.P. Nie, Dietary compounds and traditional Chinese medicine ameliorate type 2 diabetes by modulating gut microbiota, Crit. Rev. Food Sci. 59 (6) (2019) 848–863.

[47] A. Burokas, S. Arboleya, R.D. Moloney, V.L. Peterson, K. Murphy, G. Clarke, C. Stanton, T.G. Dinan, J.F. Cryan, Targeting the microbiota-gut-brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice, Biol. Psychiatry 82 (7) (2017) 472–487.

[48] J. Martel, Y.F. Ko, D.M. Ojcius, C.C. Lu, C.J. Chang, C.S. Lin, H.C. Lai, J.D. Young, Immunomodulatory properties of plants and mushrooms, Trends Pharm. Sci. 38 (11) (2017) 967–981.

[49] D.F. Zhang, C. Chia, X. Jiao, W.W. Jin, S. Kasagi, R.Q. Wu, J.E. Konkel, H. Nakatsukasa, P. Zanvit, N. Goldberg, Q.M. Chen, L.Y. Sun, Z.J. Chen, W. J. Chen, D-mannose induces regulatory T cells and suppresses immunopathology, Nat. Med. 23 (9) (2017) 1036.

[50] T.H. Zhang, Y. Yang, Y. Liang, X. Jiao, C.H. Zhao, Beneficial effect of intestinal fermentation of natural polysaccharides, Nutrients 10 (8) (2018).

[51] T.R. Wu, C.S. Lin, C.J. Chang, T.L. Lin, J. Martel, Y.F. Ko, D.M. Ojcius, C.C. Lu, J. D. Young, H.C. Lai, Gut commensal Parabacteroides goldsteinii plays a predominant role in the anti-obesity effects of polysaccharides isolated from Hirsutella sinensis, Gut 68 (2) (2019) 248–262.

[52] E.P.J.G. Neis, C.H.C. Dejong, S.S. Rensen, The role of microbial amino acid metabolism in host metabolism, Nutrients 7 (4) (2015) 2930–2946.

[53] Y.L. Zhang, L.T. Cai, J.Y. Qi, Y.Z. Lin, Y.C. Dal, N. Jiao, Y.L. Chen, L. Zheng, B. B. Wang, L.X. Zhu, Z.P. Tang, R.X. Zhu, Gut microbiota contributes to the distinction between two traditional Chinese medicine syndromes of ulcerative colitis, World J. Gastroenterol. 25 (25) (2019) 3242–3255.

[54] H. Choi, M.C. Rao, E.B. Chang, Gut microbiota as a transducer of dietary cues to regulate host circadian rhythms and metabolism, Nat. Rev. Gastroenterol. Hepat. 18 (10) (2021) 679–689.

[55] A. Segers, I. Depoortere, Circadian clocks in the digestive system, Nat. Rev. Gastroenterol. Hepat. 18 (4) (2021) 239–251.

[56] J. Triplett, D. Ellis, A. Braddock, E. Roberts, K. Ingram, E. Perez, A. Short, D. Brown, V. Hutzley, C. Webb, A. Soto, V. Chan, Temporal and region-specific effects of sleep fragmentation on gut microbiota and intestinal morphology in Sprague Dawley rats, Gut Microbes 11 (4) (2020).

[57] Z.L. Jiang, L.B. Zhuo, Y. He, Y.Q. Fu, L.Q. Shen, F.Z. Xu, W.L. Gou, Z.L. Miao, M. L. Shuai, Y.H. Liang, C.M. Xiao, X.X. Liang, Y.Y. Tian, J.L. Wang, J. Tang, K. Deng, H.W. Zhou, Y.M. Chen, J.S. Zheng, The gut microbiota-bile acid axis links the positive association between chronic insomnia and cardiometabolic diseases, Nat. Commun. 13 (1) (2022).

[58] J. Xu, H.B. Chen, S.L. Li, Understanding the molecular mechanisms of the interplay between herbal medicines and gut microbiota, Med. Res. Rev. 37 (5) (2017) 1140–1185.

[59] J. Zhou, X.L. Wu, Z.L. Li, Z. Zou, S.W. Dou, G. Li, F.S. Yan, B.R. Chen, Y.L. Li, Alterations in gut microbiota are correlated with serum metabolites in patients with insomnia disorder, Front. Cell Infect. Microbiol. 12 (2022).

[60] I. Haimov, F. Magzal, S. Tamir, M. Lalzar, K. Asraf, U. Milman, M. Agmon, T. Shochat, Variation in gut microbiota composition is associated with sleep quality and cognitive performance in older adults with insomnia, Nat. Sci. Sleep 14 (2022) 1753–1767.

[61] C.M. Xu, H.Q. Zhu, P. Qiu, Aging progression of human gut microbiota, Bmc Microbiol. 19 (1) (2019).

[62] R.P. Smith, C. Easson, S.M. Lyle, R. Kapoor, C.P. Donnelly, E.J. Davidson, E. Parikh, J.V. Lopez, J.L. Tartar, Gut microbiome diversity is associated with sleep physiology in humans, PLoS One 14 (10) (2019).

[63] C.A. Thaiss, M. Levy, T. Korem, L. Dohnalova, H. Shapiro, D.A. Jaitin, E. David, D. R. Winter, M. Gury-BenAri, E. Tatirovsky, T. Tuganbaev, S. Federici, N. Zmora, D. Zeevi, M. Dori-Bachash, M. Pevsner-Fischer, E. Kartvelishvily, A. Brandis, A. Harmelin, O. Shibolet, Z. Halpern, K. Honda, I. Amit, E. Segal, E. Elinav, Microbiota diurnal rhythmicity programs host transcriptome oscillations, Cell 167 (6) (2016) 1495–1510 (e12).

[64] E.M. Teichman, K.J. O'Riordan, C.G.M. Gahan, T.G. Dinan, J.F. Cryan, When rhythms meet the blues: circadian interactions with the microbiota-gut-brain axis, Cell Metab. 31 (3) (2020) 448–471.

[65] B.A. Matenchuk, P.J. Mandhane, A.L. Kozyrskyj, Sleep, circadian rhythm, and gut microbiota, Sleep Med. Rev. 53 (2020).

[66] L. Imeri, M.R. Opp, How (and why) the immune system makes us sleep, Nat. Rev. Neurosci. 10 (3) (2009) 199–210.

[67] Y.Y. Li, B. Zhang, Y. Zhou, D.M. Wang, X.C. Liu, L. Li, T. Wang, Y.C. Zhang, M. Jiang, H.L. Tang, L.V. Amsel, F. Fan, C.W. Hoven, Gut microbiota changes and their relationship with inflammation in patients with acute and chronic insomnia, Nat. Sci. Sleep 12 (2020) 895–905.

[68] Z. Wang, W.H. Chen, S.X. Li, Z.M. He, W.L. Zhu, Y.B. Ji, Z. Wang, X.M. Zhu, K. Yuan, Y.P. Bao, L. Shi, S.Q. Meng, Y.X. Xue, W. Xie, J. Shi, W. Yan, H. Wei, L. Lu, Y. Han, Gut microbiota modulates the inflammatory response and cognitive impairment induced by sleep deprivation, Mol. Psychiatry 26 (11) (2021) 6277–6292.

[69] C.R. Martin, V. Osadchiy, A. Kalani, E.A. Mayer, The brain-gut-microbiome axis, Cell Mol. Gastroenterol. 6 (2) (2018) 133–148.

[70] M. Balbo, R. Leproult, E. Van Cauter, Impact of sleep and its disturbances on hypothalamo-pituitary-adrenal axis activity, Int. J. Endocrinol. 2010 (2010), 759234.

[71] P. Meerlo, A. Sgoifo, D. Suchecki, Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity, Sleep Med. Rev. 12 (3) (2008) 197–210.

[72] A. Steiger, Sleep and the hypothalamo-pituitary-adrenocortical system, Sleep Med. Rev. 6 (2) (2002) 125–138.

[73] A.N. Vgontzas, E.O. Bixler, H.M. Lin, P. Prolo, G. Mastorakos, A. Vela-Bueno, A. Kales, G.P. Chrousos, Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications, J. Clin. Endocr. Metab. 86 (8) (2001) 3787–3794.

[74] B.S. McEwen, Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators, Eur. J. Pharm. 583 (2–3) (2008) 174–185.
[75] Z. Wang, W.H. Chen, S.X. Li, Z.M. He, W.L. Zhu, Y.B. Ji, Z. Wang, X.M. Zhu, K. Yuan, Y.P. Bao, L. Shi, S.Q. Meng, Y.X. Xue, W. Xie, J. Shi, W. Yan, H. Wei, L. Lu, Y. Han, Gut microbiota modulates the inflammatory response and cognitive impairment induced by sleep deprivation, Mol. Psychiatry 26 (11) (2021) 6277–6292.
[76] T.G. Dinan, R.M. Stilling, C. Stanton, J.F. Cryan, Collective unconscious: How gut microbes shape human behavior, J. Psychiatr. Res. 63 (2015) 1–9.
[77] J.R. Kelly, P.J. Kennedy, J.F. Cryan, T.G. Dinan, G. Clarke, N. Hyland, Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders, Front. Cell Neurosci. 9 (2015).
[78] A. Ait-Belgnaoui, H. Durand, C. Cartier, G. Chaumaz, H. Eutamene, L. Ferrier, E. Houdeau, J. Fioramonti, L. Bueno, V. Theodorou, Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats, Psychoneuroendocrinology 37 (11) (2012) 1885–1895.
[79] D.F.N. Mabunga, E.L.T. Gonzales, H.J. Kim, S.Y. Choung, Treatment of GABA from fermented rice germ ameliorates caffeine-induced sleep disturbance in mice, Biomol. Ther. 23 (3) (2015) 268–274.
[80] J.I. Byun, Y.Y. Shin, S.E. Chung, W.C. Shin, Safety and efficacy of gamma-aminobutyric acid from fermented rice germ in patients with insomnia symptoms: a randomized, double-blind trial, J. Clin. Neurol. 14 (3) (2018) 291–295.
[81] L.L. Yu, X. Han, S. Cen, H. Duan, S.S. Feng, Y.Z. Xue, F.W. Tian, J.X. Zhao, H. Zhang, Q.X. Zhai, W. Chen, Beneficial effect of GABA-rich fermented milk on insomnia involving regulation of gut microbiota, Microbiol. Res. 233 (2020).
[82] R.A. Yunes, E.U. Poluektova, M.S. Dyachkova, K.M. Klimina, A.S. Kovtun, O. V. Averina, V.S. Orlova, V.N. Danilenko, GABA production and structure of gadB/gadC genes in Lactobacillus and Bifidobacterium strains from human microbiota, Anaerobe 42 (2016) 197–204.
[83] K. Biard, A.B. Douglass, J. De Koninck, The effects of galantamine and buspirone on sleep structure: implications for understanding sleep abnormalities in major depression, J. Psychopharmacol. 29 (10) (2015) 1106–1111.
[84] S. Fidalgo, D.K. Ivanov, S.H. Wood, Serotonin: from top to bottom, Biogerontology 14 (1) (2013) 21–45.
[85] S.M. O'Mahony, G. Clarke, Y.E. Borre, T.G. Dinan, J.F. Cryan, Serotonin, tryptophan metabolism and the brain-gut-microbiome axis, Behav. Brain Res. 277 (2015) 32–48.
[86] A. Agus, J. Planchais, H. Sokol, Gut microbiota regulation of tryptophan metabolism in health and disease, Cell Host Microbe 23 (6) (2018) 716–724.
[87] T. Hara, T. Mihara, M. Ishibashi, T. Kumagai, T. Joh, Heat-killed Lactobacillus casei subsp casei 327 promotes colonic serotonin synthesis in mice, J. Funct. Foods 47 (2018) 585–589.
[88] Y. Ogawa, C. Miyoshi, N. Obana, K. Yajima, N. Hotta-Hirashima, A. Ikkyu, S. Kanno, T. Soga, S. Fukuda, M. Yanagisawa, Gut microbiota depletion by chronic antibiotic treatment alters the sleep/wake architecture and sleep EEG power spectra in mice, Sci. Rep. 10 (1) (2020).
[89] B. Bonaz, T. Bazin, S. Pellissier, The vagus nerve at the interface of the microbiota-gut-brain axis, Front. Neurosci. 12 (2018).
[90] J.A. Bravo, P. Forsythe, M.V. Chew, E. Escaravage, H.M. Savignac, T.G. Dinan, J. Bienenstock, J.F. Cryan, Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve, Proc. Natl. Acad. Sci. USA 108 (38) (2011) 16050–16055.
[91] Y.P. Liu, M.F. Mian, K.A.M. Neufeld, P. Forsythe, CD4(+)CD25(+) T cells are essential for behavioral effects of Lactobacillus rhamnosus JB-1 in male BALB/c mice, Brain Behav. Immun. 88 (2020) 451–460.
[92] Y.J. Zhang, B. Xie, X.Y. Chen, J.C. Zhang, S.Y. Yuan, A key role of gut microbiota-vagus nerve/spleen axis in sleep deprivation-mediated aggravation of systemic inflammation after LPS administration, Life Sci. 265 (2021).
[93] G. Hurtado-Alvarado, E. Dominguez-Salazar, L. Pavon, J. Velazquez-Moctezuma, B. Gomez-Gonzalez, Blood-brain barrier disruption induced by chronic sleep loss: low-grade inflammation may be the link, J. Immunol. Res (2016) (2016).
[94] J.M. Krueger, M.R. Opp, Sleep and microbes, Int. Rev. Neurobiol. 131 (2016) 207–225.
[95] W. Peng, Z.F. Shen, Y.N. Wang, Y.N. Huang, Y.P. Hu, Advances in intestinal florain sleep regulation, Chongqing Med. 48 (19) (2019) 3346–3350.
[96] E.Y. Hsiao, S.W. McBride, S. Hsien, G. Sharon, E.R. Hyde, T. McCue, J.A. Codelli, J. Chow, S.E. Reisman, J.F. Petrosino, P.H. Patterson, S.K. Mazmanian, Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders, Cell 155 (7) (2013) 1451–1463.
[97] J.B. Grigg, G.F. Sonnenberg, Host-microbiota interactions shape local and systemic inflammatory diseases, J. Immunol. 198 (2) (2017) 564–571.
[98] J.M. Larsen, The immune response to Prevotella bacteria in chronic inflammatory disease, Immunology 151 (4) (2017) 363–374.
[99] A.E. Slingerland, Z. Schwabkey, D.H. Wiesnoski, R.R. Jenq, Clinical evidence for the microbiome in inflammatory diseases, Front. Immunol. 8 (2017) 400.
[100] A.A. Voorhies, C.M. Ott, S. Mehta, D.L. Pierson, B.E. Crucian, A. Feiveson, C. M. Oubre, M. Torralba, K. Moncera, Y. Zhang, E. Zurek, H.A. Lorenzi, Study of the impact of long-duration space missions at the International Space Station on the astronaut microbiome, Sci. Rep. 9 (2019).
[101] B. Faraut, K.Z. Boudjeltia, L. Vanhamme, M. Kerkhofs, Immune, inflammatory and cardiovascular consequences of sleep restriction and recovery, Sleep Med. Rev. 16 (2) (2012) 137–149.
[102] L. Besedovsky, T. Lange, M. Haack, The sleep-immune crosstalk in health and disease, Physiol. Rev. 99 (3) (2019) 1325–1380.
[103] W. Alazawi, N. Pirmadjid, R. Lahiri, S. Bhattacharya, Inflammatory and immune responses to surgery and their clinical impact, Ann. Surg. 264 (1) (2016) 73–80.
[104] Y.P. Silva, A. Bernardi, R.L. Frozza, The role of short-chain fatty acids from gut microbiota in gut-brain communication, Front. Endocrinol. 11 (2020).
[105] B. Dalile, L. Van Oudenhove, B. Vervliet, K. Verbeke, The role of short-chain fatty acids in microbiota-gut-brain communication, Nat. Rev. Gastroenterol. Hepat. 16 (8) (2019) 461–478.
[106] F. Magzal, C. Even, I. Haimov, M. Agmon, K. Asraf, T. Shochat, S. Tamir, Associations between fecal short-chain fatty acids and sleep continuity in older adults with insomnia symptoms, Sci. Rep. 11 (1) (2021).
[107] M. Thangaraju, G.A. Cresci, K. Liu, S. Ananth, J.P. Gnanaprakasam, D. D. Browning, J.D. Mellinger, S.B. Smith, G.J. Digby, N.A. Lambert, P.D. Prasad, V. Ganapathy, GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon, Cancer Res. 69 (7) (2009) 2826–2832.
[108] W.N. D'Souza, J. Douangpanya, S. Mu, P. Jaeckel, M. Zhang, J.R. Maxwell, J. B. Rottman, K. Labitzke, A. Willee, H. Beckmann, Y. Wang, Y. Li, R. Schwandner, J.A. Johnston, J.E. Towne, H. Hsu, Differing roles for short chain fatty acids and GPR43 agonism in the regulation of intestinal barrier function and immune responses, PLoS One 12 (7) (2017), e0180190.
[109] E. Szentirmai, N.S. Millican, A.R. Massie, L. Kapas, Butyrate, a metabolite of intestinal bacteria, enhances sleep, Sci. Rep. 9 (2019).
[110] K. Matsuoka, T. Kanai, The gut microbiota and inflammatory bowel disease, Semin. Immunopathol. 37 (1) (2015) 47–55.
[111] S.L. Zhang, L. Bai, N. Goel, A. Bailey, C.J. Jang, F.D. Bushman, P. Meerlo, D. F. Dinges, A. Sehgal, Human and rat gut microbiome composition is maintained following sleep restriction, Proc. Natl. Acad. Sci. USA 114 (8) (2017) E1564–E1571.
[112] S.N. Yue, T. He, B.Y. Li, Y.Q. Qu, H.M. Peng, J.X. Chen, M. Lei, C.L. Chen, W. B. Wu, Effectiveness of Yi-Zhi-An-Shen granules on cognition and sleep quality in older adults with amnestic mild cognitive impairment: protocol for a randomized, double-blind, placebo-controlled trial, Trials 20 (1) (2019).
[113] Y.G. Song, B.X. Shan, S.F. Zeng, J. Zhang, C. Jin, Z. Liao, T.T. Wang, Q. Zeng, H. W. He, F.Q. Wei, Z.F. Ai, D. Su, Raw and wine processed Schisandra chinensis attenuate anxiety like behavior via modulating gut microbiota and lipid metabolism pathway, J. Ethnopharmacol. 266 (2021).
[114] H.D. Ma, Y.R. Deng, Z.G. Tian, Z.X. Lian, Traditional Chinese medicine and immune regulation, Clin. Rev. Allergy Immunol. 44 (3) (2013) 229–241.
[115] C.C. Li, F. Ye, C.X. Xu, Q. Chang, X.M. Liu, R.L. Pan, Effect of Radix Polygalae extract on the colonic dysfunction in rats induced by chronic restraint stress, J. Ethnopharmacol. 294 (2022), 115349.
[116] D.V. Bohorquez, R.A. Liddle, The gut connectome: making sense of what you eat, J. Clin. Invest. 125 (3) (2015) 888–890.
[117] D.D. Zhang, X.C. Ye, Mechanism of Poria cocos acidic polysaccharide in quieting the spirit based on intestinal flora and metabonomics, China J. Tradit. Chin. Med. Pharm. 37 (05) (2022) 2575–2583.
[118] J.R. Anderson, I. Carroll, M.A. Azcarate-Peril, A.D. Rochette, L.J. Heinberg, C. Peat, K. Steffen, L.M. Manderino, J. Mitchell, J. Gunstad, A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults, Sleep Med. 38 (2017) 104–107.
[119] A.T. Dang, B.J. Marsland, Microbes, metabolites, and the gut-lung axis, Mucosal Immunol. 12 (4) (2019) 843–850.
[120] J. Park, M. Kim, S.G. Kang, A.H. Jannasch, B. Cooper, J. Patterson, C.H. Kim, Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway, Mucosal Immunol. 8 (1) (2015) 80–93.
[121] M.G. Rooks, W.S. Garrett, Gut microbiota, metabolites and host immunity, Nat. Rev. Immunol. 16 (6) (2016) 341–352.
[122] D. Rios-Covian, P. Ruas-Madiedo, A. Margolles, M. Gueimonde, C.G. de los Reyes-Gavilan, N. Salazar, Intestinal short chain fatty acids and their link with diet and human health, Front. Microbiol. 7 (2016).
[123] G. den Besten, K. van Eunen, A.K. Groen, K. Venema, D.J. Reijngoud, B.M. Bakker, The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism, J. Lipid Res. 54 (9) (2013) 2325–2340.
[124] N. Jiao, S.S. Baker, C.A. Nugent, M. Tsompana, L.T. Cai, Y. Wang, M.J. Buck, R. J. Genco, R.D. Baker, R.X. Zhu, L.X. Zhu, Gut microbiome may contribute to insulin resistance and systemic inflammation in obese rodents: a meta-analysis, Physiol. Genom. 50 (4) (2018) 244–254.
[125] Y. Hua, S. Guo, H. Xie, Y. Zhu, H. Yan, W.W. Tao, E.X. Shang, D.W. Qian, J. A. Duan, Ziziphus jujuba Mill. var. spinosa (Bunge) Hu ex H. F. Chou seed ameliorates insomnia in rats by regulating metabolomics and intestinal flora composition, Front. Pharm. 12 (2021), 653767.