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Molecular mechanisms of polyphenols for the treatment of insomnia through the modulation of gut-brain axis and mitochondrial metabolism

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ABSTRACT

Insomnia is one of the neurodegenerative disorders in which the duration or quality of sleep is insufficient and is accompanied by severe distress and daytime dysfunction. However, current pharmacological interventions were accomponied with unavoidable side effects. In recent years, natural polypheonls were in the spotlight of treating insomnia with high efficacy and less side effects. This review systematically examines the therapeutic effects of polyphenols on insomnia, focusing on the underlying molecular mechanisms involving the neurotransmitters, gut-brain axis and mitochondrial function. Evidence suggests that polyphenols enhance sleep quality by modulating γ-aminobutyric acid receptors, serotonin 5-hydroxytryptamine, and dopamine levels within the central nervous system. Meanwhile, polyphenols could improve the intestinal environment by improving insomnia-induced intestinal barrier disorders, gut flora disorders, and down-regulation of metabolite and neurotransmitter expression. Polyphenols also inhibits the production of inflammatory factors in the gut, hypothalamic-pituitary-adrenal axis, vagus nerve, and brain to alleviate insomnia-induced neuroinflammation from the gut-brain axis pathway. In addition, polyphenols have the ability to restore mitochondrial function *via* inhibiting the expression of inflammatory factors and pathways, and reactivating mitochondrial autophagy, thereby improving insomnia. This review provides deep insights for the development of therapeutic strategies against insomnia, as well as other neurodegenerative disorders.

1. Introduction

Insomnia has been recognized as a common symptom or risk factor for many neurodegenerative diseases and has been considered a major public health problem. Insomnia is mainly characterized by dissatisfaction with the duration or quality of sleep and difficulty in initiating or maintaining sleep, accompanied by severe distress and daytime dysfunction, such as inability to concentrate, reduced energy, impaired cognitive functioning and memory decline[1]. Insomnia occurs as influenced by a variety of factors such as aging, anxiety, depression, cardiovascular disease, chronic pain, and mental illness[2]. Recent studies have shown that insomnia causes disruptions in circadian rhythms, which in turn cascade to disruptions in biological clock rhythms and hormone levels (e.g., melatonin), as well as reductions in neuronal cell size and total number[3]. Long term insomnia can cause neuroinflammation in the brain, and triggers the development of other more serious neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD)[3]. Medications based on benzodiazepines and related compounds are available to treat insomnia, but these medicines also bring serious side effects for patients, including tolerance, dependence, amnesia, and withdrawal problems, especially after prolonged use or in the elderly[4]. Although aware of these side

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effects, many insomnia sufferers still have to get prescription of sleeping pills or over-the-counter sleep aids[5]. It is therefore necessary to consider other alternatives with high efficacy but less side effects for the treatment of insomnia.

Polyphenols are secondary plant metabolites found in plant-sourced herbs, fruits and vegetables[6]. Numerous studies have proved that polyphenols could support the defense system in dealing with oxidative stress, inflammation, cardiovascular diseases, and even cancer[7-8]. In recent years, major interests in polyphenols has arisen due to its effect on neurodegenerative diseases[6]. The neuromodulatory effects of polyphenols stem from their antioxidant and anti-inflammatory activities, modulation of neuronal signaling cascades, and improvement of peripheral and cerebral blood flow[9]. Currently, there have been many studies through different animals or models that have demonstrated that polyphenols have the ability to improve insomnia by improving neurotransmitters or the sleep cycle[10-12]. Furthermore, fundamental neural processes such as development, myelin formation, neurogenesis, and microglial activation have been shown to be critically dependent on the composition of gut flora (GF)[13]. Increasing evidence indicates that GF composition varies throughout the day, with microbial species abundance and metabolism exhibiting circadian rhythms[14-15]. The GF not only influences the host's digestive, metabolic, and immune functions but also plays a crucial role in regulating sleep and mental states[16]. These effects are mediated through the gut-brain axis (GBA), which is closely linked to mood, physiological stress, and circadian rhythms[17]. Moreover, numerous studies have demonstrated that polyphenols can improve disorders of the GF within the intestinal system[9]. Thus, investigating the mechanisms by which polyphenols may alleviate insomnia through modulation of the GBA presents a valuable avenue for research.

In addition, the role of mitochondria in sleep disorders has attracted considerable attention in recent years. Insomnia not only impairs mitochondrial morphology, but also reduces mitochondrial numbers and triggers mitochondrial dysfunction[18]. Research has demonstrated that mitochondrial dysfunction in sleep disorders not only leads to impaired electron transport chain activity, resulting in disrupted energy metabolism[19], but also causes impaired autophagy, which in turn disrupts mitosis[20]. These mitochondrial abnormalities cause a rise in the expression of inflammatory factors and trigger neuroinflammation, leading to more severe insomnia. A growing body of research suggests that polyphenols may reduce the expression of inflammatory factors to alleviate mitochondrial dysfunction[18,21]. Therefore, it is crucial to explore the mechanisms by which polyphenols modulate mitochondrial metabolism to treat insomnia.

In this review, the molecular mechanisms of polyphenols in the treatment of insomnia were systematically reviewed from the perspective of GBA and mitochondria modulation, which provides new insights for the development of therapeutic strategies against insomnia-related neurological disorders.

2. Polyphenols with therapeutic effects on insomnia

As shown in Table 1, results from several randomized animal trials have shown that ingesting polyphenols are more likely to have a higher quality of sleep[22]. Therefore, it is crucial to understand whether polyphenols can treat insomnia.

2.1 Flavonoids

Flavonoids are the largest group of dietary polyphenols and are of different types such as isoflavones, flavonols, flavanols, flavonoids and anthocyanins, which are composed mainly through the C6-C3-C6 skeleton[33]. Xu et al.[34] found that quercetin and kaempferol in have a treatment effect on insomnia through a network pharmacology study, and that they act as direct inhibitors of insomnia-related glycosyl ceramidase and inhibitors of insulin receptor tyrosine phosphatase in the upstream insulin signaling pathway, affecting the insomnia target of the downstream pathway to achieve the treatment of insomnia. It has also been shown that pentobarbital-induced sleep in a mouse model fed epigallocatechin-3-*O*-gallate (5–20 mg/kg) resulted in an increase in sleep duration and a decrease in sleep onset latency (SOL) compared to controls[35]. In addition, ingestion of isoglycyrrhizin in chalcone (25 and 50 mg/kg) also resulted in prolonged sleep duration and reduced SOL by modulating γ-aminobutyric acid (GABA) metabolism in the pentobarbital-induced mouse sleep model[36]. In clinical studies, Peng et al.[37] found that the flavonoids in acanthopanax can shorten sleep latency and prolong sleep duration by increasing the levels of the neurotransmitters 5-hydroxytryptamine (5-HT) and GABA in the brains of insomnia patients.

2.2 Phenolic acids

Phenolic acids are mainly composed of 2 subgroups, hydroxycinnamic acid and hydroxybenzoic acid[38]. Hydroxycinnamic acid is now more well-studied in the treatment of insomnia. For example, supplementation of mice with ferulic acid prior to pentobarbital-induced sleep modeling, starting at a dose of $\geq$ 15 mg/kg, resulted in a prolongation of sleep duration and a decrease in SOL, which was similar to the effect of the 2 mg/kg diazepam drug when a dose of 30 mg/kg was reached[39]. Similarly, it has also been shown that supplementation with rosmarinic acid (0.5–30.0 mg/kg) increased sleep duration and decreased SOL in mice compared to non-supplemented controls[40]. In addition, a clinical study investigating 1 936 adult subjects found a significant direct correlation between the intake of hydroxycinnamic acid in the daily diet and sleep quality[41].

2.3 Tannins

Tannins are classified into 4 main groups: hydrolyzable tannins, condensed tannins, complex tannins, and phlorotannins[42]. Currently, phlorotannins play a significant role in the treatment of insomnia[43]. It has been shown that ellagic acid from eugenol has the ability to attenuate cognitive deficits and anxiety in a SD model of mice, and to prevent histopathological and morphological damage to hippocampal neurons[44]. It has also been shown that phlorotannin supplementation (500 mg/kg) has similar effects as 10 mg/kg of zolpidem in reducing SOL and increasing non-rapid eye movement sleep (NREMS) time in a caffeine-induced sleep model in mice[28]. Moreover, a clinical human study found that 24 subjects with insomnia who took phlorotannin supplements (500 mg/day) 30–60 min before bedtime for 1 week had longer sleep duration and rapid eye movement sleep (REMS), as well as significant reductions in post-sleep wakefulness and dyspnea scores, compared to those who took a placebo[45].

Table 1
Polyphenols with improved insomnia.

Phenolic class	Polyphenolic compound	Dose	Model	Duration	Target	Main outcomes	References
Flavonoids	Baicalin	50 and 100 μmol/L	Sprague-Dawley rats (M)	5 days	$GABA_A$, IL-1	↓ SWS during the light period; ↑ SWS and REMS during the dark	[23]
	Rhusflavone	125, 250, 500 and 1 000 mg/kg	Pentobarbital mice (M)	Single dose	$GABA_A$	↓ SOL; ↑ TST	[24]
	Spinosin	35 mg/kg	Pentobarbital mice (M)	Single dose	$5\text{-}HT_{1A}$	↓ SOL; ↑TST, NREMS and REMS	[25]
Phenolic acids	Rosmarinic acid	0.5, 1.0 and 2.0 mg/kg	Pentobarbital mice (M)	Single dose	$GABA_A$	↓ SOL, REMS; ↑ TST, NREMS	[26]
	Rosmarinic acid	200 and 500 mg/kg	Sleep deprivation (SD) rats (M)	6 days	5-HT	↓ Anxious behavior; ↑ TST	[27]
	Dieckol	30, 45 mg/kg	SD rats (M)	Single dose	$GABA_A$	↓ SOL; ↑ TST	[12]
Tannins	Phlorotannin	500 mg/kg	Pentobarbital mice (M)	Single dose	$GABA_A$	↓ SOL; ↑ NREMS	[28]
	Triphlorethol A	5, 10, 25, and 50 mg/kg	Pentobarbital mice (M)	Single dose	$GABA_A$	↓ SOL; ↑ TST, NREMS	[29]
Stilbenes	Resveratrol	200 mg/kg	Gray mouse lemur	3 weeks	SIRT1, PGC1-α	↓ SWS; ↑ Active wake time	[10]
Lignans	Magnolol	5, 25 mg/kg	Pentobarbital mice (M)	Single dose	$GABA_A$	↓SOL; ↑ NREMS, REMS	[30]
	Honokiol	40, 50 mg/kg	SD rats (F)	Single dose	$GABA_A$	↓ Wake episodes; ↑ NREMS	[11]
Mixed extract	*Schisandrae chinensis*	50, 100 and 200 mg/kg	Pentobarbital mice (M)	Single dose	5-HT, GABA	↓ SOL; ↑ TST	[31]
	Pure cocoa incorporated	2% cocoa powder added with meals	C3H/HeN mice (M)	30 days	Hspa1a	↓ Nocturnal activity ↑ Wakefulness, NREMS	[32]

Note: M, male; F, female.

2.4 Stilbenes

Resveratrol is a stilbene-based phytochemical with a variety of pharmacological activities[46]. One study found that microcebus murinus with 3 weeks of continuous resveratrol intake (200 mg/kg) had an increase in active arousal time, a 95% reduction in paradoxical sleep, and a 38% reduction in slow-wave sleep (SWS)[10]. In addition, Pennisi et al.[47] found in clinical studies of 60 patients with chronic hepatitis, resveratrol improved their sleep quality and reduced their sleep disorder symptoms.

2.5 Lignans

Lignin is derived from hydroxycinnamic acid dimers and is found in food, mainly in most fiber-rich plants[48]. It was shown that ingestion of 20 mg/kg of lignans honoiol stimulated the benzodiazepine site of GABA to increase NREMS and decrease SOL in a conventional sleep model, with effects similar to those of diazepam (6 mg/kg)[49]. It has also been shown that in a pentobarbital-induced mouse sleep model, magnolol selectively increases the alpha subunit of the receptor $GABA_A$ to reduce SOL and increase the total number of episodes and episodes of REMS and NREMS to achieve prolonged sleep duration[50].

2.6 Natural food or complex extracts

Some studies have tested the treatment of insomnia through natural foods and mixed polyphenol extracts. Li et al.[27] found that polyphenols extracted with rosemary in a mouse model of SD could be effective in treating insomnia by improving serotonergic synapses and thereby. It was also found that polyphenols from *Thymus kochyanus* (200 mg/kg) in a pentobarbital-induced sleep model were effective in alleviating convulsions, anxiety, and insomnia in mice, possibly due to their ability to stimulate α1-containing $GABA_A$ receptors[51]. In clinical studies, it has been shown that in 89 patients with subclinical sleep disorders who ingested a polyphenol plant mixture containing rosemarinic acid and epigallocatechin gallate 30 min before bedtime each day, as well as a placebo, those who ingested the polyphenol mixture improved sleep quality, insomnia severity, and neurocognitive functioning better, compared to those in the placebo group[52].

3. Molecular mechanisms of polyphenols in the brain for the treatment of insomnia

3.1 Regulation of GABA receptors by polyphenols

GABA is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) and promotes sleep primarily by

inhibiting neuronal activity[53], which can be synthesized *via* glutamate decarboxylation catalyzed by glutamate decarboxylase and GABA transaminase[54]. Stored in presynaptic vesicles, GABA is response for stimulation after releasing into the synaptic gap, where it activates postsynaptic GABA receptors. Then, the action of GABA at the synapse is terminated by its reuptake into the presynaptic nerve endings and surrounding glial cells[55]. GABA activates both $GABA_A$ and $GABA_B$ receptors upon release. Insomnia affects $GABA_A$ inhibition of neuronal activity, therefore, $GABA_A$ is a high-value therapeutic target for treating CNS disorders including insomnia[55].

A growing number of studies have demonstrated that polyphenols can directly or indirectly protect neuronal cells in the brain and increase GABA activity in them[56]. Besides, polyphenols can also exert orthosteric modulatory effects on the benzodiazepine-like sites of $GABA_A$ ($GABA_A$-BZD) receptor[49]. It has been shown that in a pentobarbital-induced sleep model, the use of the flavonoid glabrol from glycyrrhiza glabra induces sleep through positive allosteric modulation of the $GABA_A$-BZD receptor thereby increasing sleep duration and decreasing SOL content in mice[57].

3.2 Regulation of 5-HT metabolism by polyphenols

5-HT, an inhibitory transmitter in the brain, is strongly associated with circadian rhythms and sleep disorders[54]. It is synthesized centrally within enteric neurons, peripheral enterochromaffin cells, and raphe neurons in the brainstem. 5-HT receptors can be categorized into seven groups ($5\text{-}HT_1$ to $5\text{-}HT_7$) based on their structure and characteristics, with $5\text{-}HT_{1A}$, $5\text{-}HT_{1B}$, and $5\text{-}HT_{1D}$ receptors being the key factors for insomnia[58]. On one hand, 5-HT can be released *via* axonal nerve endings during awakening to influence the synthesis of hypnotic substances in the brain. On the other hand, 5-HT is involved in perinuclear silencing in an autoinhibitory manner when it is released from dendrites of 5-HT neurons into the dorsal nucleus of the middle suture[58]. The current study found that serotonergic neurons are the most active neurons during sleep, have reduced activity rates during NREMS, and are unable to remain silent during REMS[59]. Decreased 5-HT down-regulates extracellular signaling to the cell, resulting in neuronal cell activation and a concomitant rise in rapid eye movement (REM)[27]. Therefore, 5-HT can promote wakefulness and inhibit REMS[60].

It has now been revealed that polyphenols can be therapeutic for insomnia by affecting 5-HT in neuronal and synaptic function[61]. It has been shown that spinosin (5 mg/kg) from sour dates acts as an antagonist of the $5\text{-}HT_{1A}$ receptor in a pentobarbital sleep model to reduce SOL and prolong sleep duration, NREMS, and REMS in mice[25]. It has also been demonstrated that Schisandrin B (5 mg/kg), an isoflavone from *Schisandra chinensis*, not only upregulated the expression of $GABA_A$ receptor α1 and $GABA_A$ receptor γ2 in the epithalamus, but also upregulated the expression of $5\text{-}HT_{1A}$ in a rat model of chlorpheniramine-induced insomnia, which reduced SOL and prolonged the sleep time[62]. In addition, spinal glycosides and ferulic acid also improved total sleep duration and reduced SOL in mice in the pentobarbital sleep model, and this inhibition was achieved by elevating the rate of 5-HT synthesis through tryptophan hydroxylase blockade for the treatment of insomnia[9].

3.3 Regulation of dopamine metabolism by polyphenols

Dopamine, a neurotransmitter in the catecholamine family, is produced by dopaminergic neurons and gastrointestinal epithelial cells in the brain, kidneys, and gut[63]. Receptors for dopamine are abundantly present in key structures of the superior reticular activating system, which are critical for the regulation of sleep[64]. During insomnia, dopamine levels are elevated as a result of a process of balanced regulation of the direct innervation system of the suprachromaffin cell nucleus (SCN) with the striatum and midbrain[65].

The dopaminergic system is a potential system for the treatment of insomnia by polyphenols through modulation of dopamine[9]. It has been shown that the flavonoid spinosin (5 mg/kg) prevents sleep reduction in mice *via* the dopaminergic tract in the pentobarbital sleep model[66].

4. Molecular mechanism of polyphenols in regulating insomnia *via* GBA

There has been tremendous research showing that GF are not only important in maintaining the homeostasis of the body but also play a pivotal role in regulating the brain function[13]. Moreover, GF are also responsible for the production of hundreds of metabolites that directly affect most systems and organs[54]. Therefore, the GF not only allows the host to maintain health, appetite regulation, energy acquisition, and metabolism, but also associates the host to maintain sleep quality by regulating signaling pathways on the immune, endocrine, and nervous systems[3]. Therefore, the improvement of host insomnia through the bidirectional relationship between host sleep and GF by the GBA is an interesting area that worth exploring.

With low water solubility, chemical instability, and rapid metabolism, most polyphenols show limited bioavailability[67]. However, some polyphenols still can pass the blood-brain barrier (BBB) and directly enter the brain, which makes them effective in the treatment of neurodegenerative diseases such as insomnia, AD, PD, and other neurodegenerative diseases. Moreover, polyphenols could also modulate the intestinal environment to improve various deseases including insomnia[68]. In this section, the mechanism of polyphenols in the treatment of insomnia by modulating GF and its metabolites will be systematically summerized.

4.1 Improvement of GF to treat insomnia with polyphenols

Recent studies demonstrated that insomnia is closely related to the circadian rhythm of the GF[69]. As shown in Fig. 1, the disruptions in circadian rhythms of GF could increase intestinal permeability, alter intestinal barrier function, and change the abundance, diversity, and functionality of GF[3]. For example, a clinical study showed that there was a significant increase in Prevotellaceae and a significant decrease in Bacteroidaceae and Ruminococcaceae in insomnia patients compared to healthy populations[70]. Moreover, it was also shown that sleep quality and cognitive performance of elderly insomnia patients were associated with changes in the abundance of specific genera such as Lachnospiraceae[71]. In addition, patients with chronic insomnia had an increased abundance of signature bacteria associated with inflammation in their GF, and the level of interleukin 1β (IL-1β) in insomnia was significantly higher than that of healthy controls[69,72].

Previous study showed that dietary polyphenols can alter the cycle, amplitude, or phase of the biological clock and alleviate symptoms caused by circadian disruption[73]. For example, polyphenols could reverse the aberrant expression of biological clock genes and alleviate neural redox imbalance and mitochondrial dysfunction[74]. In the intestinal tract, polyphenols could increase the abundance of *Lactobacillus* and Bifidobacteria to inhibit various pathogens, enhance intestinal barrier function, and regulate the structure and function of GF[17]. The *α*-diversity of GF was negatively correlated with sleep fragmentation and positively correlated with sleep efficiency and total sleep time. It was found that lignans in *S. chinensis* significantly increased the abundance of Lachnospiraceae, *Lactobacillus*, and *Alloprevotella* and *α*-diversity of GF[75]. It was also proved that the complex polyphenol in Bailemian enriched the level of beneficial intestinal bacteria such as *Lactobacillus*, and increased the level of neurotransmitters in the brain, thus restoring the disordered probiotic flora of insomnia patients[76].

4.2 Improvement of GF metabolites and neurotransmitters to treat insomnia by polyphenols

The GF produces a variety of metabolites (e.g., short-chain fatty acids (SCFAs), bile acids, and choline), neurotransmitters (e.g., GABA, 5-HT, tryptophan, and dopamine), and other neuroactive substances that communicate bi-directionally with the CNS *via* the GBA to modulate insomnia[77]. SCFAs, the most abundant bacterial metabolites (containing acetate, propionate, butyrate, etc.), are neurologically active and have a profound effect on sleep function[67]. Insomnia could affect the absorption of SCFAs by small intestinal cells. One study found that older adults with insomnia had higher concentrations of SCFAs in their feces than those with normal sleep schedules[78]. Moreover, insomnia could also affect the interaction of SCFAs with immune cells, resulting in intestinal inflammation, exacerbating the penetration of bacteria and their products, and affecting the permeability and functionality of the intestinal barrier[79]. When GF abundance and diversity were improved by polyphenols,

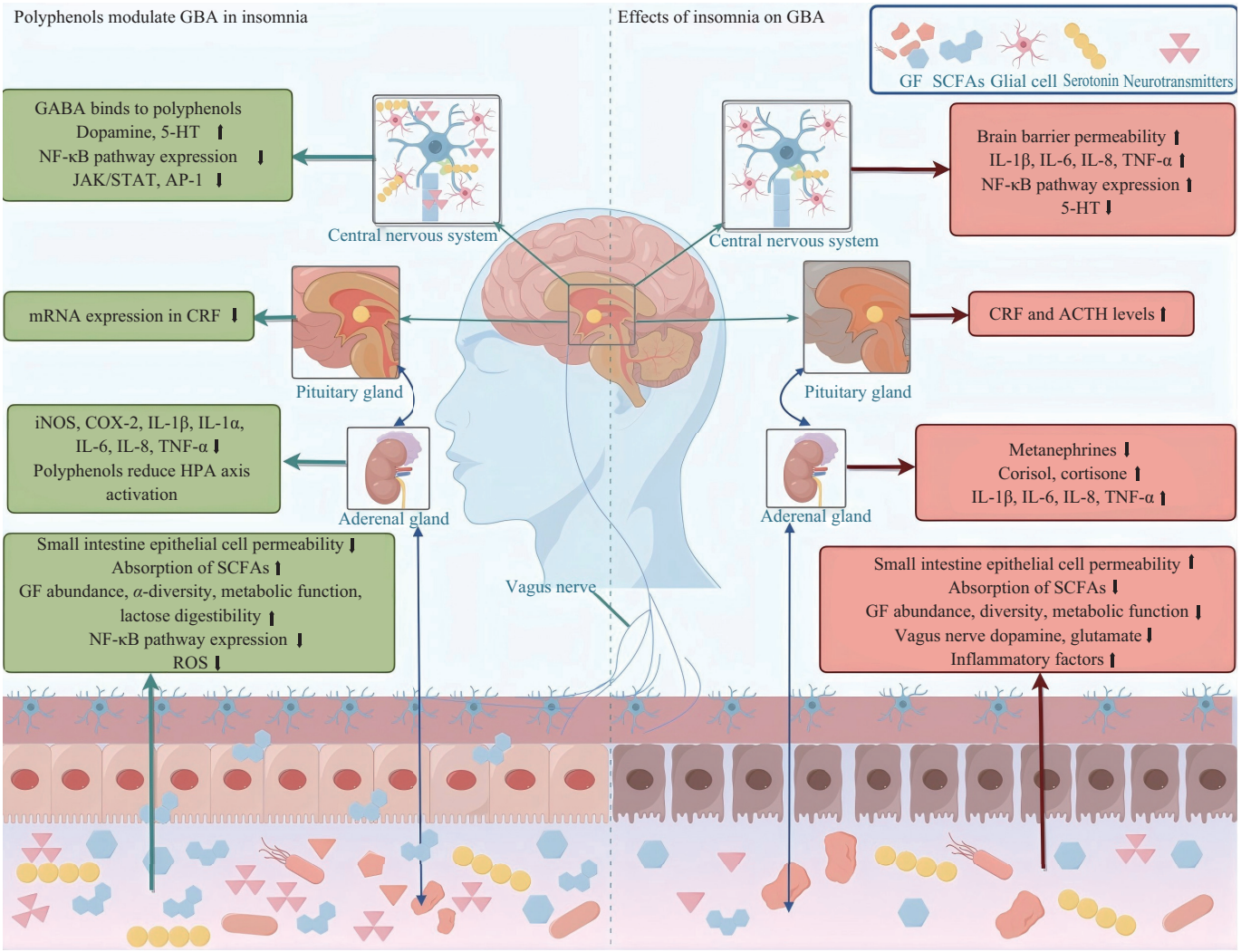

Fig. 1 Mechanisms of polyphenols in the treatment of insomnia through modulation of the GBA. Polyphenols improve small intestinal epithelial cell permeability and absorption of SCFAs in insomnia, and also improve GF enrichment, diversity, functionality and their metabolite disorders thereby improving the intestinal environment. Improvement of the intestinal environment by polyphenols results in decreased levels of systemic expression of inflammatory factors and inflammatory pathways. This information improves the immune system, the HPA axis and the vagus nerve, and through these pathways it is transmitted to the brain for the purpose of treating insomnia.

GF metabolites, especially SFCAs, were also simultaneously changed. This plays an important role in increasing gastrointestinal peristalsis, decreasing inflammation, and preserving the permeability and functionality of the intestinal mucosal barrier[69,80]. Studies showed that quercetin, chlorogenic acid, rutin, and resveratrol could affect the gut microbiota (e.g., phylum Anabaena and phylum Thicket) to increase levels of propionic acid, butyric acid, and acetate in intestinal[81].

5-HT is an important mediator that connects GF and the brain in the process of sleep regulation. Some studies have shown that insomnia causes a decrease in the amount of 5-HT in the GF, which can further lead to disruption of the sleep-wake architecture[82]. Meanwhile, the lack of 5-HT transporter proteins could alter the abundance and structure of GF, leading to further GF disruption and intestinal inflammation[83]. Polyphenols could efficiently increase the level of 5-HT in the gut through promoting the production of SCFAs. Moreover, polyphenols could also alter tryptophan metabolism, which in turn promotes 5-HT synthesis[84]. For example, besides its potent anti-inflammatory abilities, resveratrol and chlorogenic acid could change the levels of 5-HT and dopamine in GF[85-86].

In addition, GABA is also considered to be one of the most important factors for insomnia[79]. One study demonstrated that GABA significantly altered GF diversity and increased butyrate levels in the gut, thus decreasing SOL and prolonging sleep[53]. After being absorbed, polyphenols could be activated by the formation of polyphenol derivatives in the intestinal tract, which will interact with $GABA_A$-BZD receptors to improve sleep[9].

4.3 Modulation of GBA and neuroinflammation to treat insomnia by polyphenols

The above discussion proves that insomnia leads to disruption of GF and its metabolites, and triggers systemic inflammation through GBA, including the immune system, hypothalamic-pituitary-adrenal (HPA) axis, and vagus nerve[87]. Notably, insomnia causes GF to activate inflammatory response mechanisms in the immune system, promoting the production of pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α[88]. These inflammatory factors could affect brain function in different ways, such as influencing neurotransmitter synthesis and secretion, stimulating vagal afferent signaling, and activating the HPA axis, which in turn exacerbates the symptoms of insomnia[89]. The HPA axis is one of the most important pathways in the GBA that connects the brain, the kidneys, and the gut to the neuroendocrine system. Insomnia overactivates the HPA axis, causing the adrenal glands to release cortisol and corticosterone, thus causing inflammation[90]. In addition, HPA axis overexpression induced by insomnia can lead to the increasing of permeability or even disruption of the intestinal barrier. It also causes activation of the immune system as well as increased circulating levels of pro-inflammatory cytokines and endotoxins, which may further affect brain function[69]. The vagus nerve transmits gut messages to the brain[69]. The vagus nerve also provides gut-derived neurotransmitters (glutamate, GABA, etc.) and GF metabolites that act on the brain and influence brain function, cognitive function, stress response, and sleep architecture[91]. It has been shown that when the vagus nerve was severed in mice, intestinal probiotics that enhance GABA receptors in the CNS to regulate sleep and mood are blocked[92]. Insomnia stimulates the vagus nerve, leading to an increased inflammatory load, which upregulates the expression of inflammatory factors in the brain[93]. The aforementioned inflammation due to insomnia leads to an imbalance in the circadian rhythm of the host and its GF, which exacerbates insomnia through the GBA cycle[69].

Various studies showed that polyphenols were effective in reducing neuroinflammation and oxidative stress, helping to treat insomnia. At the same time, other flavonoids, such as lignans, quercetin, rutin, genistein, and soy glycosides, have shown neuroprotective effects in *in vitro* and *in vivo* models, reducing neuroinflammation[94]. For example, *Poria cocos* polyphenols can ameliorate inflammatory responses and intestinal flora dysbiosis in the colon by inhibiting the NF-κB-NLRP3 signaling pathway[95]. Also, *P. cocos* polyphenols can treat insomnia by regulating gastrointestinal hormones and decreasing the levels of inflammatory factors[96]. In addition, polyphenols have potential regulatory roles in GBA, especially in inhibiting CRF secreted by the HPA axis. It has been shown that studies have demonstrated that quercetin reduces the activation of the HPA axis by decreasing the expression of mRNAs in CRF[97]. Another *in vivo* study recently showed that resveratrol, by way of gavage, also reduces CRF levels to modulate the HPA axis in rats[98]. Although polyphenols have been extensively studied for the treatment of insomnia *via* GBA, the mechanism between these compounds' promotion of neurological function and the reduction of intestinal inflammation has not yet been clarified, and this is one of the areas of future inquiry.

5. Mitochondria modulation by polyphenols in the treatment of insomnia

Essential to the therapeutic process of polyphenols on the brain *via* GBA is the energy demand, and mitochondria are the source of the energy. Therefore, there is an intricate link between GBA and mitochondrial function, mediated by microbial metabolites, that can influence mitochondrial activity in the brain[99]. Mitochondria are key mediators of energy production in neurons and glial cells. Thus, mitochondrial signaling is critical in connecting the brain's energy metabolism to daily sleep[100]. In addition to their function in ATP synthesis, calcium signaling, cell proliferation and thermoregulation[101], more and more evidence have shown that mitochondrial dysfunction plays an important role in the development of insomnia[20].

Therefore, treating neurodegenerative diseases like insomnia from the perspective of improving mitochondrial function is an important research trend that has been emphasized in recent years. Polyphenols have now been shown to be effective in mitigating neurodegenerative diseases by modulating mitochondrial autophagy[102]. This section focuses on the effects of insomnia on mitochondria and the mechanisms of polyphenols regulation of mitochondria in insomnia.

5.1 Effects of insomnia on mitochondria

5.1.1 Effects of insomnia on mitochondrial morphology

The effects of insomnia on mitochondria are mainly characterized by 1) decreasing the density of mitochondrial cristae, 2) enlarging the outer membrane of mitochondria, 3) increasing the intermembrane space of mitochondria and inducing the formation of mitochondrial

vesicles, and 4) affecting the structure and activity of the mitochondrial synapse[103]. Cristae are sites of mitochondrial respiration, and the increase in their number can improve respiratory efficiency and ATP production. Moreover, cristae are determinants of mitochondrial function and bioenergetics, and their remodeling is a key process in cellular metabolic adaptation[104]. Furthermore, studies in *Drosophila* have shown that SD leads to an increase in the proportion of mitochondria in the total cell volume[105]. At the same time, insomnia affects *Drosophila* mitochondrial synaptic activity and structure, causing an increase in energy metabolism and inducing a response in unfolded proteins in mitochondria[105].

5.1.2 Effects of insomnia on mitochondrial function

5.1.2.1 Electron transport chain

The electron transport chain consists of 5 enzymatic complexes integrated into the inner mitochondrial membrane, whose primary function is to drive cellular production of adenosine triphosphate (ATP) through oxidative phosphorylation[106]. Complex I (NADH-ubiquinone oxidoreductase/NADH dehydrogenase) generates approximately 40% of intracellular reactive oxygen species (ROS), and is the largest enzyme in the electron transport chain[106]. Complex II (succinate-ubiquinone oxidoreductase/succinate dehydrogenase), contributes to the electron transfer in the cytochrome c redox reaction by catalyzing the oxidation of succinate to fumarate and the reduction of ubiquinone to ubiquinone in the TCA cycle[106]. Complex III (cytochrome bc1 complex/pantotactin c redox system) facilitates the transfer of electrons from the cellular pigment C to the cytochrome a/a3 complex[107]. Complex IV (cytochrome c redox system), is responsible for DNA encoding and its structural stability[108]. Complex V (ATP synthase), consisting of the F0 and F1 structual domains, could convert ADP to ATP by phosphorylation, and is responsible for facilitating proton transport[109].

Recent studies have shown that insomnia could affect the mitochondrial redox system's functions that regulating energy production, signaling, and antioxidant defenses[110]. For example, deprivation of the REM period impaired electron transfer from complex I to complex III in hypothalamic mitochondria[111]. Specifically, reduced sleep quality and efficiency were associated with downregulation of *ATP5D* mRNA and several mitochondrial proteins (NDUFB8 in complex I, SDHB in complex II, UQCRC2 in complex III, COX2 in complex IV, and ATP5O in complex V) in the dorsomedial thalamus[112]. In addition, substantial neuronal loss in insomnia patients was accompanied by reduced expression of ATP synthase and complex V subunits (F0 structural domain and hydrogen ion transport protein on ATP5H)[113]. In addition, SD in patients for 3 h could elevate the expression and activity of complex IV, whereas SD for 12 h increases the expression and activity of complex IV and V. The increases in the activities of complex IV and V will coincide with decreases in COX levels, ATP production, dehydrogenase activity, and mitochondrial membrane potential (MMP), which affects the function of the mitochondrial respiratory chain and enhances ROS production[103].

5.1.2.2 Mitochondrial oxidative stress

There is a significant correlation between sleep and mitochondrial oxidative stress. Insomnia is often coupled with oxidative stress, mitochondrial dyfunction, dyfunction of specific tissues or organs[114]. Approximately 90% of intracellular ROS are byproducts of mitochondrial oxidative phosphorylation and are generated primarily at complexes I and III of the mitochondria[115]. ROS levels above physiological thresholds can damage mtDNA and induce mutations that ultimately lead to cellular and tissue damage[114]. It has been shown that *Drosophila* mutants with shorter sleep duration are more susceptible to ROS and have lower survival rates[114].

5.1.2.3 Alterations in DNA transcription

Insomnia also has an effect on the transcription of mtDNA in mitochondria. The main reason is that insomnia affects mtDNA transcriptional expression induced by oxidative stress. It has been shown that mRNA expression with uncoupling protein 2 (*UCP2*) is blocked in the cerebral cortex of SD model mice during SD caused by ROS accumulation[116]. Meanwhile, during SD, mRNA expression of *NRF1* and *NRF2* is inhibited, which affects the transcription of oxidative phosphorylation-related genes[117]. Furthermore, by comparing identical twins with different sleep patterns, it was found that twins who slept less than 7 h had fewer copies of mtDNA in their peripheral blood leukocytes than their siblings who adhered to the recommended sleep duration of 7–9 h[111]. Therefore, insomnia can trigger the expression of relevant DNA that can further cause ROS overexpression or systemic inflammation.

5.2 Mitochondria modulation by polyphenols in the treatment of insomnia

A large number of studies have shown that polyphenols could improve circadian rhythms and biological clocks of organisms *via* regulating the function of mitochondria, to show threpative effects on various neurodegenerative diseases. As shown in Fig. 2, polyphenols can ameliorate mitochondrial abnormalities in insomnia conditions by inhibiting neuroinflammation and reactivating mitochondrial autophagy.

5.2.1 Inhibition of neuroinflammation

Insomnia could affect the mitochondria, triggering systemic and especially neurological inflammation. The ability of polyphenols to improve mitochondrial function under disorder or oxidative stress is most intuitively demonstrated by their highly effective anti-inflammatory capacity[118]. In particular, polyphenols could repair the disrupted mitochondrial electron transport chain and improve functional metabolism by inhibiting the production and gene expression of mitochondrial inflammatory factors. Polyphenols can inhibit neuroinflammation through various mechanisms, mainly including: 1) inhibition of cytokine release from microglia, including TNF-α and IL-1β; 2) inactivation of iNOS and NO production; 3) inhibition of NADPH oxidase and ROS production in microglia; and 4) reduction of NF-κB activity[21,94]. For example, tea polyphenols regulate mitochondrial dynamics and mitochondrial endothelial

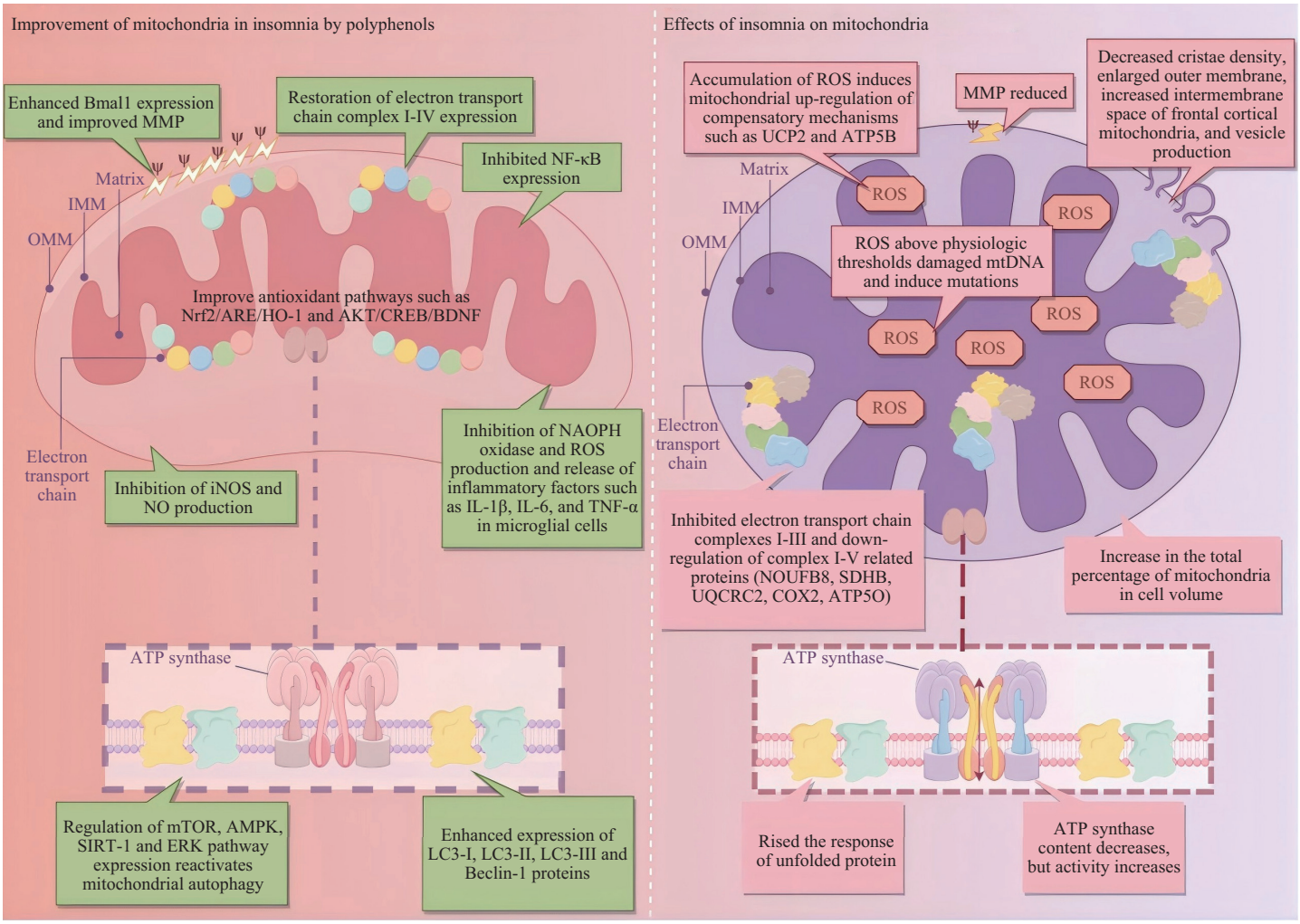

Fig. 2 Mechanisms of polyphenols in the treatment of insomnia through modulation of mitochondrial metabolism. Insomnia affects the function of the mitochondrial redox system through oxidative stress, which causes effects and damage to mitochondrial morphology, MMP, electron transport chain function, and DNA transcription. Polyphenols may ameliorate mitochondrial abnormalities in insomnia primarily by inhibiting neuroinflammation and reactivating mitochondrial autophagy.

cell growth factor, and significantly ameliorate H_2O_2-induced mitochondrial damage by up-regulating Bmal1 and restoring the expression of mitochondrial electron transport chain complex I–IV. Moreover, tea polyphenols reversed relatively shallow daily oscillations of circadian clock gene transcription and protein expression in SH-SY5Y neuronal cells under oxidative stress conditions by modulating the Bmal1-involved stimulated Nrf2/ARE/HO-1 and AKT/CREB/BDNF signaling pathways[119]. In the context of neuroinflammation, flavonoids are effective in blocking mitochondrial iNOS expression and NO production in activated glial cells[94]. Meanwhile, lignans were found to be effective in attenuating the expression of *IL-6*, *TNF-α*, *COX-2*, and *iNOS* genes and inhibiting cytokine-induced neuronal death in activated microglia[94]. In addition, quercetin has been reported to prevent inflammatory cytokine production by reducing NO production and gene expression in microglia, thereby preventing neuronal damage[120].

5.2.2 *Regulation in mitochondrial autophagy*

Mitochondrial autophagy plays an important role in maintain mitochondria function and helps prevent mitochondria against oxidative stress and inflammation[20]. During sleep, mitochondria undergo extensive metabolic reorganization to adapt to various energy supply needs, in which autophagy contributes to nutrition and cellular homeostasis[20]. Under normal conditions, the autophagic machinery is active at the basal level and plays a central role in removing unwanted or abnormal/damaged organelles, cytoplasmic protein aggregates, and intracellular bacteria *via* the ubiquitin-proteasome system (UPS) and autophagy lysosomal pathway (ALP)[21]. However, in the condition of neurodegenerative diseases such as insomnia, AD, and PD, mitochondrial autophagy is dysregulated by the disruption of circadian rhythms and systemic oxidative stress, resulting in proteopathies, mitochondrial dysfunction, and neuroinflammation[121].

Recent studies highlight that polyphenols improve neuronal mitochondrial autophagy under neuroinflammation condition through: 1) modulating the expression of anti-apoptotic factors; 2) inducing different signaling pathways; 3) scavenging free radicals and inhibiting pro-oxidant enzymes; 4) affecting mitochondrial function; 5) chelating redox-active transition metal ions; 6) preventing protein aggregation; 7) regulating major protein degradation pathways[21,121]. Polyphenols could regulate mitochondrial autophagy through mTOR, AMPK, SIRT-1, and ERK pathways, and upregulate autophagy

proteins such as beclin-1, microtubule-associated protein light chain (LC3 I and II), and sirtuin 1 (SIRT1)[121]. It was shown that kaempferol treatment not only altered the shape of the mitochondrial network in SH-SY5Y cells, but also induced mitochondrial fragmentation and increased the formation of autophagy-labeled LC3-II and other autophagic lysosomes[122]. Moreover, quercetin in olive oil could inhibit neuroinflammation through activating mitochondrial autophagy, activating the AMPK pathway, and inhibiting mTOR expression[123]. In the mice with mitochondrial autophagy injury in hippocampal neurons, 2 weeks of curcumin treatment could significantly increase the expression of LC3-II/LC3-I and beclin-1 proteins, as well as alleviate neuronal disorganization and reactivate mitochondrial autophagy[124].

6. Conclusion and prospects

Polyphenols can restore and maintain metabolic and redox homeostasis, which triggers research in their therapeutic effects in insomnia. Based on a comprehensive analysis of numerous animal and clinical studies, flavonoids, phenolic acids, tannins, stilbenes, lignans, and other mixed polyphenol extracts from plants are effective in alleviating insomnia symptoms. These mechanisms ameliorate insomnia symptoms primarily by modulating the metabolism of GABA receptors, 5-HT, and dopamine in the CNS. However, some polyphenols are limited in their ability to pass through the BBB, so this review also describes the molecular mechanisms by which polyphenols are used to treat insomnia through the modulation of 2 pathways, GBA and mitochondrial metabolism. In the intestinal environment, polyphenols not only alleviate the increased intestinal barrier permeability associated with insomnia, but also increase GF abundance and α-diversity, in addition to modulating GF metabolites and neurotransmitters, such as upregulating the expression of SCFA, GABA, 5-HT, tryptophan and dopamine. Polyphenols also inhibit the production of inflammatory factors such as IL-6, IL-1β, and TNF-α in the gut, HPA axis, vagus nerve, and brain by activating the inflammatory response mechanisms of the immune system. In addition, polyphenols can reduce the expression of CRF and inhibit the over-activation of the HPA axis, thereby improving the GBA environment for the treatment of insomnia. Furthermore, we illustrate the potential of polyphenols to ameliorate insomnia by modulating mitochondria. Polyphenols not only inhibit the expression of inflammatory pathways such as NF-κB and the production of inflammatory factors such as IL-6, TNF-α, COX-2, and iNOS in the mitochondria of insomniac hosts, but also inhibit the production of NADPH oxidase and ROS in microglial cells, thereby suppressing neuroinflammation. In addition, polyphenols regulate mitochondrial autophagy and stimulate mitochondrial mitophagy *via* mTOR, AMPK, SIRT-1 and ERK pathways, thus improving neurons in neuroinflammation.

Although there is a large body of data on polyphenols for the treatment of sleep *via* the brain-gut axis, the characteristic indicators of polyphenols' regulation of mitochondria in the treatment of insomnia are still unclear. Subsequent observations of the effects of polyphenols on mitochondrial morphology, electron transport chain metabolism, gene expression, inflammatory markers, autophagy metabolism, and markers of insomnia characteristics need to be made in animal models of insomnia. Overall, the importance of mitochondria in many aspects of physiology is just beginning to be elucidated, and the relationship between polyphenols and mitochondria and insomnia, as well as the mechanisms by which they treat insomnia, will need to be explored in depth in the future. In addition to this, the link between GBA and mitochondria is a fascinating scientific question. One of the fascinating directions is that polyphenols affect tryptophan metabolism in the gut-brain axis, which in turn affects mitochondrial metabolism in the brain. Meanwhile, despite the abundance of *in vivo* and *in vitro* data on polyphenols for the treatment of insomnia, information on their safety and efficacy remains incomplete. *In vivo* pharmacokinetic results indicate that the bioavailability of polyphenols is limited due to their low solubility, limited BBB passage, and rapid metabolism. In addition, the high concentrations of polyphenols (especially flavonoids) required to achieve biological effects may be detrimental. Nanotechnology offers a novel and promising solution to improve the bioavailability of polyphenols. Currently, there have been recent attempts by researchers to treat insomnia by making nanomaterials to encapsulate drugs across the BBB. However, it is difficult to determine the range of potentially useful dosages, and a rational regimen and optimal method of administration hinder the value of its clinical application[125]. Therefore, further pharmacological and pharmacokinetic studies of nano-encapsulated polyphenols are needed to improve the safety, purity, and bioavailability of polyphenols, and there is an urgent need for appropriate regulations on a global scale.

Declarations of interest

The authors report there are no competing interests to declare.

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