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Bidirectional Regulation of the Gut Microbiota by Insomnia via the Gut-Brain Axis Mechanism

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ABSTRACT: Insomnia, a prevalent sleep disorder, is increasingly recognized for its interaction with the gut microbiota (GM) through the bidirectional gut–brain axis (GBA). Emerging evidence indicates that insomnia disrupts central nervous system (CNS) function by inducing hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis and immune dysregulation, neurotransmitter dysfunction. These neuroendocrine disturbances extend to the gut, altering GM composition and compromising intestinal microenvironmental homeostasis. Dysbiosis, defined as an alteration in microbial diversity (e.g., a decrease in Shannon index values) and an imbalance in microbial composition, weakens intestinal barrier integrity, exacerbates systemic inflammation, and alters microbial metabolism, leading to imbalances in neuroactive compounds such as short-chain fatty acids (SCFAs), bile acids (BAs), and neurotransmitters—factors that influence CNS function and sleep quality. Conversely, the GM affects CNS activity through metabolic by-products, neurotransmitters, and immune regulation, impacting neuroinflammation, synaptic plasticity, and cognitive function. The intricate interplay between insomnia and GM is further evidenced by their shared influence on metabolic disorders and cognitive decline. This review also examines existing contradictions in insomnia-GM research, underscoring the need for standardized multi-omics approaches to resolve inconsistencies. Future research should prioritize identifying strain-specific probiotics, refining microbiota transplantation methods, and developing personalized microbiota-based interventions. Clinically, this review lays the groundwork for GM-targeted therapies for insomnia, including biomarker discovery, precision probiotics to restore microbial balance, and dietary strategies to improve GM diversity. These insights pave the way for targeted, individualized GM-based therapeutics, advancing precision medicine in sleep disorder management and addressing current knowledge gaps.

Keywords: insomnia; gut microbiota; dysbiosis; gut-brain axis; central nervous system; metabolic disorders; cognitive impairment; probiotics

1. Introduction

Insomnia is one of the most prevalent sleep disorders, characterized by difficulty falling asleep, staying asleep, or achieving restorative sleep despite adequate opportunities for sleep, and adverse effects on daytime

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functioning [1]. The prevalence of insomnia in China has been on the increase the past few years. The prevalence of insomnia in the general population currently stands at 29.2% [2], and 38.9% in healthcare workers[3]. Insomnia induces dysregulation in energy balance and glucose homeostasis, is associated with an increased risk of metabolic-related disorders, including obesity and type 2 diabetes (T2DM) [4, 5]. Insomnia is also associated with immune dysfunction [6], cognitive decline, memory impairment [7, 8], and neurodegenerative diseases, such as Alzheimer's disease (AD) [9]. Additionally, insomnia can exacerbate psychiatric disorders, such as anxiety, depression, and mood disorders [10]. The pathogenesis of insomnia is driven by changes in various hormones, neurotransmitters, and cytokines in the brain. Activation of the hypothalamic–pituitary–adrenal (HPA) axis increases cortisol production, inducing hyperarousal in specific brain regions [11]. An imbalance between excitatory and inhibitory neurotransmitters, partly driven by dysregulated tryptophan (Trp) metabolism via the serotonin (5-HT) pathway, can damage the central serotonergic signalling, disrupt sleep regulation, contributing to insomnia [12]. Inflammation may also participate in the development of insomnia. Under inflammatory conditions, the expression level of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) is increased, which triggers the secretion of inflammatory mediators such as nitric oxide (NO), further promoting inflammation. Moreover, IL-6 and TNF-α are pro-inflammatory cytokines that are known to affect the sleep cycle by regulating the interaction between the immune system and the central nervous system (CNS) [13]. In addition, disruption of the melatonergic system [14], orexin signalling [15], abnormal secretion of neurotrophic factors [16], and the limbic–cortical circuit can drive insomnia development. Notably, accumulating evidence suggests that gut microbiota (GM) may contribute to the pathophysiology of insomnia [17, 18].

Pharmacological therapy is the primary intervention for managing insomnia, particularly in acute or severe cases. Benzodiazepine receptor agonists (e.g., estazolam, flurazepam) increase the GABAA receptor affinity and amplify the neural inhibitory effects of GABA, to prevent sleep onset latency, increasing total sleep time (TST), and enhance sleep efficiency. However, prolonged use of these agonists may lead to tolerance, dependence, rebound insomnia upon withdrawal, and cognitive impairment [19]. The non-benzodiazepine receptor agonists (e.g., zolpidem, zopiclone) selectively act on GABAA receptor subtypes, more effectively enhancing sleep induction. They have shorter half-lives and few residual effects [20], but side effects such as abdominal pain, headache, dizziness, nausea, drowsiness, and sleep-related complex behaviors may still occur [21]. Dual orexin receptor antagonists (e.g., Suvorexant) can inhibit orexin-mediated arousal by selectively blocking the binding of orexin neuropeptide A/B to OX receptor 1/2 (OX1R/OX2R) [22] and may also improve subjective sleep quality [23]. However, they are associated with adverse effects such as daytime somnolence, fatigue, and abnormal dreams [24]. Doxepin, the only Food and Drug Administration-approved tricyclic antidepressant for insomnia, inhibits histamine H1 receptors, thereby improving sleep maintenance and TST [25]. However, in elderly patients, it causes headaches and drowsiness [26]. Melatonin receptor agonists (e.g., melatonin, ramelteon) target melatonin receptors 1 (MT1) and 2 (MT2) in the suprachiasmatic nucleus to ameliorate circadian rhythm sleep-wake disorders. Although generally well

tolerated, they exert weak hypnotic effects and may cause adverse reactions such as drowsiness, dizziness, and fatigue [27]. Therefore, for optimal management of insomnia researchers should develop agents that improve sleep quality and daytime functioning. Cognitive-behavioural therapy for insomnia (CBTI) is the first-line intervention and is often combined with short-term pharmacological treatment. Its management plans should be individualized based on comorbidities and patient response, and include lifestyle modifications, phytocompounds, and alternative therapies. Regular follow-up is crucial to evaluate the treatment efficacy, prevent relapse, and adjust treatment strategies in a timely manner [20]. In parallel with symptomatic treatments, there is a need to explore the underlying mechanisms of insomnia, particularly the role of GM via the gut-brain axis (GBA).

GM is a complex and dynamic community of microbes, including bacteria, archaea, fungi, and viruses, that reside in the gastrointestinal tract and are essential for maintaining host health. Taxonomically, bacteria are classified into phyla, classes, orders, families, genera and species [28]. GM is closely linked to human metabolism, intestinal homeostasis, host immune responses, and neurobehavioral effects [29]. A healthy GM is characterized by high microbial diversity, a balanced composition of beneficial bacteria, functional versatility, and resilience, which collectively support robust digestion, immune regulation, and metabolic processes while maintaining a stable and adaptable ecosystem [28]. As such, this central regulator—referred to as the "second brain,"—plays a critical role in sustaining host physiology and homeostasis [30]. However, GM dysbiosis is characterised by the altered diversity and abundance of pathogenic bacteria, along with disruptions in metabolic products [31]. These changes impact host metabolism and immune responses, contributing to various of pathophysiological conditions including endotoxemia, chronic low-grade inflammation, bile acid (BAs) metabolism dysfunction, and T2DM [32], as well as neuropsychiatric disorders such as depression [33], AD [34], Parkinson's disease (PD) [35], and poor sleep quality [36]. With ongoing advances in high-throughput sequencing, metagenomics, and third-generation sequencing technologies, significant progress has been made in GM research. Compared to traditional methods such as stool and urine culturing, these modern approaches allow precise analysis of microbial composition and function at the species level. Such techniques have unveiled potential mechanisms by which the microbiome contributes to various diseases [37]. Recent studies further support the gut’s designation as the "second brain" with growing evidence that microbiota modulates brain function and behaviour via the GBA [38]. Additionally, insomnia may influence GM through the GBA, thereby exacerbating immune dysfunction, metabolic disorders, and neuropsychiatric conditions [39].

The concept of the GBA dates back to the 1840s when Beaumont observed that emotional states influenced digestion, introducing the idea of mutual brain-gut communication [40]. GBA is a bidirectional communication system between the gastrointestinal tract and the brain, involving interactions between multiple systems, including the CNS, enteric nervous system (ENS), autonomic nervous system (ANS)—particularly the vagal nerve (VN) , immune system, and endocrine systems (HPA axis). This complex system not only regulates gut function but also plays a key role in the regulation of emotions, behaviour, cognitive performance, and overall health by linking the CNS with GM [41]. Its core lies in the

reciprocal interaction of the gut epithelium, immune system, microbiota, and the ENS within the intestinal milieu [42]. The ENS, an intrinsic neural network of the gastrointestinal tract, functions autonomously via complex neural circuits and is modulated by the CNS. Together, they mediate the interplay between GM and the GBA [43]. As the health relevance of GM gains attention, increasing evidence supports the bidirectional communication between the GM and the CNS, leading to the emergence of the "microbiota-gut-brain axis" (MGBA) concept [44]. MGBA enables the CNS to regulate gastrointestinal activity under psychological and physiological stress, influencing immune and secretory functions. Conversely, GM produces neuroactive substances, metabolites, and hormones that affect the CNS through immune, neuroendocrine, and VN pathways, ultimately resulting in behavioural and neurological changes [45].

GM plays a key role in regulating sleep mechanisms [46]. Studies have found that the GM follows circadian rhythms [47]. Insomnia disrupts these rhythms, affecting the homeostasis of the GM [48]. Dysbiosis of the gut can decrease the abundance of beneficial bacteria and increase inflammation, potentially impairing the GBA and further worsening sleep quality [18]. Sleep deprivation (SD) is a stressor that affects multiple tissues in the body. It refers to a condition resulting from either intentional sleep restriction or insufficient opportunity to sleep. SD is commonly induced in animal models to investigate its effects and has become widespread in modern society due to factors such as lifestyle, work, and environmental stressors [49]. Research has demonstrated that insomnia and SD can significantly alter the structure and function of GM in both human patients [50] and mouse models [6]. In addition to alterations in GM composition, signalling pathways and metabolic functions are also disrupted in individuals with insomnia [51]. Accordingly, many researchers propose that systemic inflammation and microbial metabolites may serve as key mediators in the relationship between GM and insomnia [52].

However, GM is shaped by multiple factors, including host genetics, age, sex, lifestyle (e.g., diet, alcohol consumption, physical activity, and sleep patterns), and chronic illnesses [53]. The complexity and individual variability of the GM community present substantial challenges to traditional experimental approaches for elucidating its regulatory or pathogenic mechanisms [54]. With the advancement of sequencing and multi-omics technologies, our understanding of the GBA has undergone a significant transformation, and GM-targeted interventions have shown promise in alleviating insomnia [55]. Mechanistically, insomnia disrupts gut barrier integrity and microbial homeostasis via neuroendocrine dysregulation (notably the HPA axis), vagal dysregulation, and immune–inflammatory activation. Conversely, altered GM communicates back to the brain via neural (vagal/enteric), endocrine, immune, and metabolic routes, thereby shaping central function and sleep regulation. This review aims to elucidate the mechanisms underlying the interaction between GM and its metabolites in insomnia, with an emphasis on the bidirectional regulatory role of the GBA in this process. This paper provides a theoretical foundation for identifying therapeutic targets for insomnia and GM-based interventions while also proposing future research directions by integrating current basic research and clinical data.

2. The Impact of Insomnia on the CNS

Recent studies have indicated that insomnia prevalence is primarily related to central neurotransmitter dysregulation [56], HPA axis dysfunction [11], inflammatory cytokine dysregulation [57], melatonin (MT) system dysfunction [14], and abnormalities in the function of the limbic-cortical system loop [58].

2.1. Insomnia-Induced Activation of the HPA Axis and Stress Response

The HPA axis is a crucial regulatory pathway within the neuroendocrine system. This axis modulates the stress response and regulates various physiological functions, including the immune response, metabolism, mood, and energy balance [59]. The widely accepted "hyperarousal" hypothesis posits that chronic insomnia, as a significant endogenous stressor, is closely associated with HPA axis hyperactivation and the subsequent release of vital molecules such as cortisol (CORT). This condition is characterised by a reduction in slow-wave sleep (SWS), increased wakefulness, and continuous physical excitement [60, 61]. The HPA axis regulation involves three key components. First, neurons in the hypothalamus' paraventricular nucleus (PVN) release the corticotropin-releasing hormone (CRH), which plays a crucial role in mediating the neuroendocrine and visceral responses to stress. CRH is then transported to the anterior pituitary gland via the bloodstream, where it stimulates the release of adrenocorticotropic hormone (ACTH). Finally, ACTH circulates through the blood to the adrenal cortex, leading to the secretion of CORT, a glucocorticoid (GC) commonly known as the "stress hormone." CORT is pivotal in the body's stress response and in regulating various physiological processes, including metabolism, immune function, and circadian rhythms [62, 63]. CRH has been shown to induce both stress-related and non-stress-related arousal, it also inhibits the secretion of growth hormone-releasing hormone (GHRH), a sleep-promoting neuropeptide primarily released during the first half of the night that stimulates SWS. Numerous studies have demonstrated that exogenous CRH administration increases electroencephalography (EEG) frequency and results in prolonged wakefulness and reduced SWS in rats, as well as in healthy male and female subjects [64]. CORT suppresses HPA axis activity by binding to and activating glucocorticoid receptors (GRs) in the hypothalamus and pituitary gland. This negative feedback loop is essential for maintaining homeostasis during stress and immune responses [65]. Studies have shown that elevated serum CORT levels are positively associated with increased wake time after sleep onset (Fig. 1A). Moreover, evening serum CORT levels correlate with the frequency of nocturnal awakenings, while sleep fragmentation (SF) disrupts circadian CORT rhythms and elevates CORT levels. In turn, HPA axis hyperactivation induces SF, creating a vicious cycle between insomnia and stress [66].

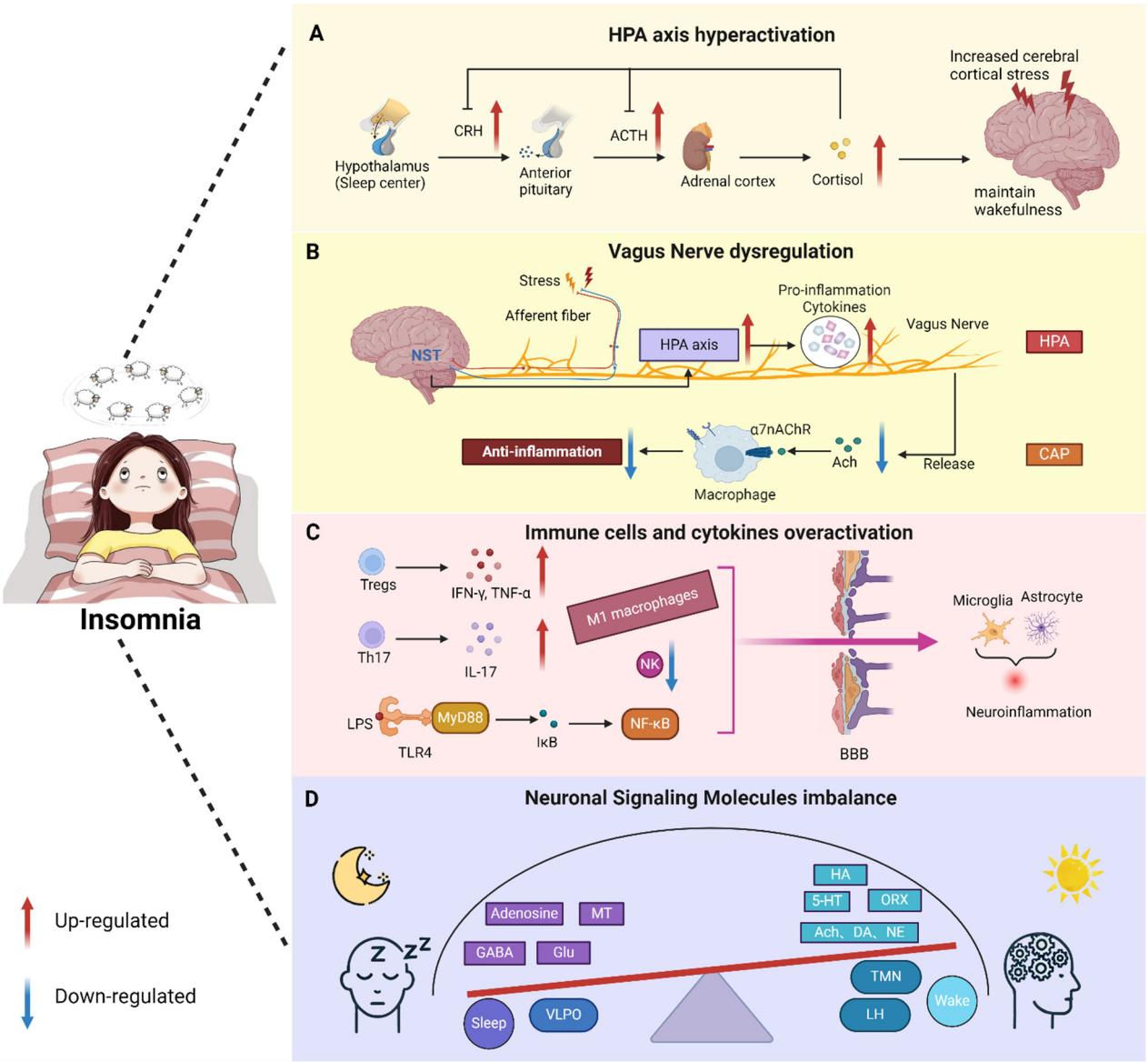

Fig. 1. The schematic diagram showing the mechanisms by which insomnia affects CNS. Illustration of the insomnia-induced HPA axis hyperactivation, vagus nerve dysregulation, inflammation and neurotransmitter imbalance. (CRH: corticotropin-releasing hormone; ACTH: adrenocorticotropic hormone; HPA: hypothalamic-pituitary-adrenal; CAP: cholinergic anti-inflammatory pathway; NST: nucleus tractus solitarius; Ach: acetylcholine; α7nAChR: α7-nicotinic acetylcholine receptors; Tregs: regulatory T cells; Th17: helper T cells; IFN-γ: interferon-gamma; TNF-α: tumor necrosis factor-alpha; IL-17: interleukin-17; NK: natural killer cells; LPS: lipopolysaccharide; TLR4: toll-like receptor 4; MyD88: myeloid differentiation factor 88; IκB: inhibitory kappa-B; NF-κB: nuclear factor kappa-B; BBB: blood-brain barrier; VLPO: ventrolateral preoptic nucleus; TMN: tuberomammillary nucleus; LH: lateral hypothalamic; MT: melatonin; GABA: gamma-aminobutyric acid; Glu: glutamate; HA: histamine; 5-TH: 5-hydroxytryptamine; ORX: orexin; DA: dopamine; NE: norepinephrine).

In recent years, growing attention has been given to Nesfatin-1—a neuropeptide widely distributed in brain regions associated with feeding and emotion—due to its role in modulating the HPA axis [67]. Research indicates that stress activates Nesfatin-1-expressing neurons in the PVN and other brain areas, leading to elevated cytoplasmic calcium concentrations in CRH neurons within the PVN and increased plasma ACTH and CORT levels in rats [68]. Additionally, Nesfatin-1 activates noradrenergic neurons in the nucleus of the solitary tract (NTS) and locus coeruleus (LC), as well as 5-hydroxytryptamine neurons in the brainstem [69]. These neurons project extensively to CRH neurons in the PVN, significantly influencing HPA axis activity [70]. Notably, Nesfatin-1 also activates the nuclear factor-κB (NF-κB) signalling pathway [71] and upon NF-κB

nuclear translocation, subsequent post-translational modifications promote CRH production and secretion[72]. Thus, the Nesfatin-1/NF-κB axis may serve as a key central mechanism through which insomnia induces HPA axis hyperactivation.

Hyperactivation of the HPA axis can promote insomnia–stress vicious cycle by sustaining central neuropeptide signalling and amplifying arousal. Studies have demonstrated that Nesfatin-1 can integrate the brainstem monoaminergic excitatory input with NF-κB-driven CRH production, thereby increasing GC overproduction. In parallel, peripheral immune activation can further reinforce this central drive, forming a self-perpetuating neuroendocrine–sleep disruption cycle that underlies chronic hyperarousal. Chronic HPA axis hyperactivation, through persistent GC exposure, induces GC resistance in immune cells, weakens systemic regulation, and biases cytokine signalling toward a pro-inflammatory profile [74]. Thus, sustained HPA activity not only maintains central hyperarousal but also predisposes to peripheral immune imbalance, creating conditions that facilitate subsequent systemic immune amplification.

2.2. Insomnia Affects CNS function through Immune System Dysfunction

Insomnia triggers widespread immune activation that extends beyond central neuroendocrine alterations. Relevant studies show that insomnia significantly activates the conserved transcriptional response to adversity in peripheral blood mononuclear cells, characterized by increased activity of transcription factors (TFs) related to immune activation (e.g., NF-κB/Rel family) and sympathetic nervous system (SNS) signalling (e.g., cAMP response element-binding protein [CREB]), along with reduced activity of TFs involved in HPA axis negative feedback regulation (e.g., GRs) [73]. This transcriptional imbalance provides a mechanistic link between sustained stress signalling and immune dysregulation, setting the stage for persistent systemic inflammation.

In chronic insomnia disorder (CID), the bidirectional interaction between the immune system and the CNS is a key component of its pathophysiology. External threats such as infection and inflammation activate the immune system, leading to cytokine release and immune cell modulation that affect sleep-regulatory brain regions, thereby disturbing sleep rhythms [75]. Conversely, insomnia can activate the immune system and induce immune dysregulation. Short sleep duration has been associated with widespread immune activation, including elevated levels of leukocytes, neutrophils, monocytes, $CD4^+$ and $CD8^+$ T cells, memory T cells, and pro-inflammatory cytokines such as IL-6, IL-17, and C-reactive protein (CRP) along with reduced natural killer (NK) cell activity (Fig. 1C) [76, 77]. Further studies have shown that the CD4/CD8 ratio—a sensitive marker of adaptive immune status—is frequently elevated in CID patients and is linked to chronic inflammatory conditions such as HIV and cardiovascular disease [78]. This elevation may not only indicate T cell dysfunction but also increase insomnia risk via disrupted amino acid metabolism, particularly altered leucine levels. Leucine competes with monoamine precursors at the blood-brain barrier (BBB), thereby modulating monoaminergic neuronal activity and disturbing the sleep–wake cycle [79].

Downstream of these transcriptional shifts, sleep loss mobilizes multiple innate-immune effectors—engaging NLRP3-inflammasome signalling and cGAS–STING pathways while amplifying

NF-κB-dependent cytokine cascades—which converge on microglial priming and increased BBB vulnerability. Inflammasomes, as key components of the innate immune system, play a critical role in insomnia-related neuroimmune activation particularly through the NLRP3/Caspase-1/IL-1β pathway and microglial activation [80]. IL-1β and other pro-inflammatory cytokines such as IL-6, can inhibit the Wnt/β-catenin/annexin A1 signalling pathway and impair BBB integrity, facilitating the entry of inflammatory mediators and macrophage migration into brain [81]. These cytokines activate glial cells and neurons in various brain regions, especially in the hippocampus, which exhibits the highest density of IL-1 receptors [82]. NF-κB, a major upstream regulator of inflammation, further amplifies the inflammatory response by upregulating IL-1β, IL-6, and TNF-α [83]. Emerging evidence also implicates the cGAS-STING pathway—an innate immune sensing mechanism—as a potential contributor in insomnia. Chronic stress associated with insomnia promotes mitochondrial damage, reactive oxygen species (ROS) production, and mitochondrial DNA leakage [84], which together activate the cGAS-STING pathway [85]. Once triggered, this pathway sustains inflammatory signalling and contributes to shaping the central inflammatory microenvironment [86]. Centrally, the cAMP/PKA/CREB signalling pathway is essential for regulating neuroinflammation, promoting neuronal survival, improving sleep and cognitive function [87, 88]. This pathway exerts neuroprotective effects through CREB activation and the expression of downstream proteins, such as c-FOS and brain-derived neurotrophic factor (BDNF), thereby enhancing neuronal repair and synaptic plasticity. Studies have shown that CID is associated with downregulation of cAMP, PKA, p-CREB and BDNF, highlighting the importance of this CID neuropathology [89].

Peripheral immune dysregulation in chronic insomnia can induce inflammation characterized by disruption of leukocyte levels, pro-inflammatory cytokines secretion, inflammasome and cGAS–STING activation—that compromises BBB integrity. This triggers glial activation, NF-κB-driven cytokine signalling, and inhibition of the cAMP/PKA/CREB–BDNF pathway, thereby impairing the neuronal repair and plasticity. These peripheral-to-central immune signals can re-excite PVN CRH neurons and weaken GR-mediated negative feedback, thereby re-engaging the HPA axis and perpetuating the insomnia–stress–immune loop. This indicates that targeting the peripheral immune–BBB interactions (e.g., cytokine blockade, inflammasome inhibition) while restoring central neuroprotective signalling (e.g., CREB–BDNF activation) can prevent sleep disruption and limit the occurrence of neuroinflammation.

2.3. Neuronal Signalling Molecules Imbalance and its Role in Sleep-Wake Regulation

The maintenance of sleep-wake cycles is dependent on coordination between multiple neural nuclei and neurotransmitters (Fig. 1D). The ascending reticular activating system activates the cerebral cortex in the CNS and maintains wakefulness by releasing wake-promoting neurotransmitters. The ventrolateral preoptic nucleus (VLPO) induces and sustains sleep by releasing gamma-aminobutyric acid (GABA) and inhibiting the activity of the arousal system [90]. The tuberomammillary nucleus (TMN), located in the posterior hypothalamus, as a wake-promoting center in the brain, has the highest number of histamine (HA)ergic neurons. HAergic neurons promote wakefulness by inhibiting GABAergic neurons in the VLPO through

controlling interneurons. HAergic neurons are also modulated by orexinergic neurons in the lateral hypothalamus (LH), which are collectively involved in the regulation of the sleep-wake cycle [91]. Studies have shown that orexins (OXs) are overexpressed in individuals with SD, circadian rhythm disruptions, and insomnia-associated conditions such as mild cognitive impairment, PD, and AD [92, 93]. The orexin system (OX/OXR) plays a central role in sleep–wake regulation and exerts neuroprotective effects through multiple signalling pathways. Orexin A (OXA) and orexin B (OXB), neuropeptides synthesized in the LH, bind to OX1R and OX2R [94]. Activation of these G protein-coupled receptors triggers several intracellular cascades, including the Gq/PLC/IP_3/DAG-mediated calcium signalling pathway, the AC/cAMP/ PKA pathway, and stress-related pathways such as ERK1/2 and p38-MAPK [95, 96]. These pathways elevate intracellular calcium levels, increase phosphatase activity, and enhance neuronal excitability, collectively amplifying arousal signalling at multiple neural levels [96]. Additionally, OXA exhibits neuroprotective properties by preventing neuronal apoptosis via activation of the protein kinase B (Akt) and caspase-3/7 signalling pathways [97].

Regarding neurotransmission, 5-HT and GABA serve as major inhibitory neurotransmitters in the CNS, while dopamine (DA), norepinephrine (NE), and glutamate (Glu) are the primary excitatory neurotransmitters. The Glu/GABA-glutamine cycle—major metabolic pathway for the interconversion of Glu and GABA—is essential for maintaining the excitatory–inhibitory balance in the CNS. Insomnia has been significantly linked to disruptions in this metabolic cycle and an elevated Glu/GABA ratio [98]. A key regulatory enzyme in this context is glutamate decarboxylase 67 (GAD67) which catalyses the conversion of Glu to GABA and functions as a molecular switch governing neural excitability [99]. Furthermore, 5-HT1A receptors modulate BDNF expression via the cAMP/PKA/CREB signalling pathway, thereby promoting neuroplasticity and supporting stable sleep architecture [100]. In line with these findings, recently proposed "5-HT-Glu/GABA Long-Feedback Neural Circuit" hypothesis suggests that 5-HT modulates the Glu/GABA excitatory/inhibitory balance through 5-HT1AR [101], playing a pivotal role in regulation of sleep-wake cycles and mitigation of insomnia-related neurological impairments.

Abnormal levels of neurotransmitters in chronic insomnia may reflect a breakdown in the excitatory–inhibitory control over the sleep–wake cycle. Orexinergic and histaminergic hyperactivation, coupled with diminished VLPO-mediated GABAergic inhibition, increases cortical excitability, and disruption of the Glu/GABA–glutamine cycle—accompanied with decreased GAD activity and elevated Glu/GABA ratio—further destabilizes network homeostasis. The proposed 5-HT–Glu/GABA long-feedback circuit suggests the existence of a link between monoaminergic regulation and excitatory–inhibitory balance, which can be targeted for to improve sleep cycle. Further in vivo studies are needed to validate and clarify their therapeutic value in chronic insomnia.

2.4. VN Dysregulation and its Role in Insomnia

The VN, a major component of the parasympathetic nervous system, is a mixed nerve composed of 80% afferent fibers and 20% efferent fibers [102]. The VN is the neuroanatomical pathway between the ENS and the CNS and serves as a critical component of the gut-brain bidirectional communication system [103]. VN exerts a

dual anti-inflammatory effect through its afferent fibers (via the HPA), and efferent fibers (via the cholinergic anti-inflammatory pathway, CAP) [104] (Fig. 1B). Neurons activated in the NTS send signals to the PVN when afferent fibers are stimulated, activating the HPA axis and inhibiting the release of pro-inflammatory factors [105, 106]. The distal VN releases acetylcholine (Ach), which binds to the α7-nicotinic acetylcholine receptors (α7nAChR) on macrophages, inhibiting the release of pro-inflammatory cytokines. This inflammatory reflex is known as the CAP [107]. Insomnia disrupts VN function and weakens its anti-inflammatory effects, which affects gut-brain communication mechanisms. This may exacerbate stress responses, mood disorders and reduce sleep quality. However, studies have shown that transcutaneous auricular vagus nerve stimulation (taVNS) can promote the secretion of MT or GABA, exhibiting sedative effects and effectively treating insomnia [108]. A clinical study also demonstrated that taVNS can regulate sleep by altering the concentrations of neurotransmitters, such as GABA, NE, and 5-HT, thereby effectively treating primary insomnia [109].

VN dysfunction in insomnia disrupts the bidirectional brain–gut communication, weakening anti-inflammatory and neuromodulatory control of sleep regulation. There is evidence that taVNS can modulate neurotransmitter release and improve sleep quality, suggesting that VN may serve as a therapeutic target, but the variability in stimulation protocols, patient heterogeneity, and unclear mechanistic pathways limit its clinical utility. This calls for further investigations to optimize stimulation parameters, delineate neurotransmitter- and inflammation-related mechanisms, and identify responder profiles to maximize therapeutic efficacy.

3. The Impact of Insomnia on the Gut Microbiota

Insomnia leads to changes in gut permeability, immune regulation, and microbial diversity, thereby triggering systemic inflammation and intestinal microenvironment dysbiosis (Fig. 2). The mechanisms linking insomnia to GM dysregulation and the characteristics of insomnia-related gut dysbiosis are highlighted below, including the profound impact of insomnia on gut health.

3.1. Manifestations of GM Dysbiosis in Insomnia

A growing body of evidence indicates that chronic insomnia significantly alters the composition and function of the GM, primarily through its impact on the HPA axis and VN function. In gut homeostasis, mitochondrial oxidative phosphorylation (OXPHOS) in colonocytes can help to maintain the physiological hypoxic state of the colonic surface, which sustains a microbiota dominated by obligate anaerobes (e.g., *Akkermansiaceae*, *Bacteroidaceae*, and *Ruminococcus*). Stressors such as insomnia activate the HPA axis, leading to the release of CRH, which subsequently upregulates CRH receptor 1 (CRHR1) expression in colonocytes. CRHR1 activation can impair the mitochondrial ultrastructure and respiratory function of colonocytes via the cAMP-Ras-MAPK signalling pathway, creating a hypoxic state in epithelial cells. This disruption increases epithelial oxygenation, triggering oxygen escape from the colonic surface into the lumen, leading to the expansion of facultative anaerobes (e.g., *Pseudomonadaceae* and *Enterobacter*) and driving GM dysbiosis [110]. Impaired mitochondria may act as a trigger of inflammasome activation, further amplifying intestinal inflammation and enhancing dysbiosis [111]. Moreover, SD-induced elevations in CORT

and sustained HPA axis activation are closely linked to alterations in VN signalling, further influencing gut–brain axis homeostasis. These effects collectively influence intestinal epithelial cells (IECs), intestinal immune cells and the intestinal muscular layer, causing changes in immune function, mucosa, permeability, etc., leading to GM alterations [112, 113]. Additionally, the VN exerts significant anti-inflammatory effects through the CAP, which mitigates peripheral inflammation and reduces intestinal permeability—factors that can substantially influence GM composition [102]. VNS has been demonstrated to restore GM homeostasis by increasing the relative abundance of beneficial genera such as *Lactobacillus* and *Bifidobacterium*, thereby improving intestinal health and reinforcing gut barrier integrity [114].

Dysbiosis may be linked to gut homeostasis, generally defined as alteration or imbalance in microbial diversity and composition [115]. Among these, alpha-diversity (e.g., Chao estimate, observed species [Sobs], abundance-based coverage estimator [ACE], Shannon and Simpson index) is often used to assess the richness and evenness of microbial communities and is generally considered a biomarker of health. Beta diversity can help to determine differences in microbial community composition between individuals [116]. Dysbiosis related to chronic insomnia is marked by reduced microbial diversity, a decreased abundance of beneficial bacteria, and an increased abundance of pathogenic bacteria (Table 1). Low bacterial diversity is a key indicator of gut dysbiosis. The diversity of the microbiome fluctuates over several stages of insomnia pathophysiology, with prolonged insomnia potentially exerting a more significant effect on patients' microbiome diversity [117]. Insomnia is associated with a diminished presence of probiotic bacteria, including *Lactobacillus, Bifidobacterium, Faecalibacterium* [118], and A*kkermansia* [119]. Probiotic bacteria have diverse functional roles, such as anti-inflammatory, antioxidant, and antimicrobial, and are essential for preserving gut barrier integrity and regulating the immune system. Pathogenic taxa, including *Klebsiella, Proteus, Staphylococcus,* and *Enterococcus*, often proliferate under dysbiosis conditions, promoting gut inflammation and gut permeability. The *genus Aeromonas*, belonging to the *phylum Proteobacteria*, is a key human pathogen responsible for intestinal and extraintestinal infections. The cell wall component of Gram-negative bacteria, such as the *phylum Proteobacteria*, is lipopolysaccharide (LPS), also known as endotoxin. LPS can cross the gut barrier into systemic circulation by increasing the permeability of the BBB, thereby inducing neuroinflammation [120]. *Klebsiella*, a prevalent pathogen found in the gut, produces various virulence factors, such as adhesins, capsular polysaccharides, and LPS, which stimulate the host immune response [121]. *Proteus*, commonly residing in the gut as a commensal bacterium, is a potential opportunistic pathogen [122]. Taken together, the stress-driven shifts in epithelial oxygenation, combined with attenuated vagal anti-inflammatory signalling, establish a brain-to-gut causal path. These changes increase susceptibility to barrier disruption and dysbiosis, thereby contributing to insomnia-related GBA pathology.

Table 1 Summary of studies investigating changes of gut microbiota in insomnia and sleep deprivation.

Subject	Sample Source	Experiment Protocols	Up-regulated flora	Down-regulated flora	Other outcomes	Ref.
Insomnia						
Insomnia patients between 26–55 years	humans	DSM-V, Duration of Insomnia, AID: >1 week, <3 months; CID: >3 months	AID: *g_Bacteroides;* CID: *g_Blautia, g_Eubacterium hallii*	AID: *g_Lachnospira;* CID: *g_Faecalibacterium, g_Prevotella 9, g_Roseburia*	In the AID group, lower *Lachnospira* and higher *Bacteroides* were associated with higher PSQI score In the CID group, lower *Faecalibacterium* and higher *Blautia* abundance were associated with higher IL-1β levels and higher PSQI score	Li et al. [117]
24 patients with insomnia between 18–60 years	humans	Diagnosis was based on the DSM-V and the CCMD-3	*g_Gemmiger, g_Fusicatenibacter, g_Prevotella*	*g_Bacteroides, g_Oscillibacter*	*Coprococcus, Oscillibacter, Fusicatenibacter* positively correlated with sleep/mood indexes *g_Clostridium XI* negatively correlated with ISI, PSQI, HAMA and HAMD	Zhou et al. [496]
Patients with primary insomnia	humans	Diagnosis was based on the criteria in the DSM-V	*g_ Bacteroides*	*g_Odoribacter, g_Megamonas, g_Lachnospira, g_Enterobacter, g_Oscillibacter, g_Dysosmobacter*	Serum butyrate levels were significantly decreased in insomnia patients 19 butyrate producers were significantly correlated with PSG	Wang et al. [497]
54 postmenopausal patients with insomnia	humans	Classified as O-IN and P-IN based on sleep Efficiency	O-IN: *g_Collinsella, g_Adlercreutzia, g_Clostridium, g_Pediococcus;* P-IN: *g_Bacteroides, g_Staphylococcus, g_Carnobacterium, g_Pseudomonas, g_Odoribacter*	*g_Lachnospira*	O-IN patients exhibited higher WASO and AN P-IN patients showed higher TST and SE O-IN and P-IN patients exhibited almost identical low scores for PSQI, elevated stress levels and higher diastolic blood pressure	Barone et al. [498]
Females insomnia patients within the perimenopause	humans	Meeting DSM-V diagnostic criteria	*g_Ruminococcus, s_Roseburia faecis, s_Prevotella copri, s_Fusicatenibacter saccharivorans, s_Blautia obeum*	*g_Bacteroides, s_Faecalibacterium prausnitzii*		Yang et al. [499]
The SPF male Wistar rats (160–180 g)	rats	400 mg/kg PCPA for 2 consecutive days	*g_Lactobacillus, g_Prevotella, g_Escherichia, g_Bacteroides, g_Sutterella, g_Blautia, g_Parabacteroides*	*o_Clostridiales, f_Porphyromonadaceae, f_Ruminococcaceae*	PCPA administration decreased the 5-HT, MT and $GABA_AR$ levels in the hypothalamus and increased the level of NE The metabolites induced by PCPA were linked to tryptophan metabolism, primary bile acid biosynthesis, etc.	Si et al. [500]

Male SPF-grade SD rats (200 ± 20 g, 3–8 weeks old)	rats	CUMS for 14 days + 450mg/kg PCPA for 2 days	*g_Coriobacteriaceae_UCG-002, g_Dubosiella, g_Bifidobacterium, g_Prevotellaceae_NK3B31_group, g_Anaerostipes*	*p_Cyanobacteria*	Insomnia was correlated with the digestive system's three energy in the gastrointestinal tract (protein digestion and absorption, bile secretion, etc.) *Dubosiella* and *Bifidobacterium* affected the metabolism of cholic acid and were negatively correlated with 5-HT	Du et al. [501]
Male rats (180−220 g, SPF grade)	rats	400 mg/kg PCPA for 2 consecutive days	Predominant bacteria*: g_Romboutsia, g_Dubosiella, g_Alloprevotella, g_Enterococcus, g_Bifidobacterium, g_Lactobacillus, s_Clostridium sensu stricto 1*	*F:B ratio*	In PCPA group, Serum levels of IL-6, TNF-α and IL-β were increased, GSH-Px and SOD were decreased *Ruminococcaceae UCG-014* and others were positively correlated with most insomnia indices but negatively associated with immune indices, whereas *Lactobacillus* and others showed the opposite pattern	Yao et al. [401]
Six-week-old male rats (160 to 180 g)	rats	300 mg/kg PCPA in the morning for 3 days	*g_Romboutsia, g_Blautia, s_Clostridium XlVa*	*g_Lactobacillus, g_Clostridium sensu stricto*	In the PCPA group, the levels of 5-HT, GABA and fecal butyrate were decreased, Ach, NE and GAT-1 were increased, the cAMP signaling pathway was activated	Yu et al. [502]
SPF-grade mice (male, 18–20 g)	mice	500 mg/kg PCPA for 3 consecutive days	*g_Muribaculaceae_unclassified, g_Paramuribaculum, g_Faecalibacterium*	*F:B ratio; g_Ligilactobacillus, g_Gardnerella*	*Faecalibacterium* et al. were negatively correlated with IL-1β, TNF-α, MT and 5-HT *Lactobacillus* et al. were positively correlated with 5-HT and MT, and strongly correlated with acetic, propionic and butyric acid.	Ren et al. [503]
C57BL/6 female mice (7–8 weeks old, 20 ± 2 g)	mice	9:00–9:30 am, 400 mg/kg PCPA for 2 days	*f_Lactobacillaceae, f_Muribaculaceae, f_Erysipelotrichaceae, g_Lactobacillus*	*F:B ratio; g_Prevotellaceae UCG-001, g_Ruminococcaceae UCG-014, s_Lactobacillus gasseri, s_Lactobacillus murinus*	In PCPA group, the 5-TH and GABA levels are decreased, the Glu/GABA ratio is elevated High levels of propionic acid were strongly associated with lower sleep quality	Cheng et al. [504]
sleep deprivation						
25 healthy participants (13 males)	humans	40 h SD		*g_Prevotella, g_Sutterella, g_Parasutterella, g_Alloprevotella, g_Anaeroplasma, g_Elusimicrobium*	SD potentiated hypothalamic–pituitary–adrenal (HPA) axis reactivity in healthy adults Most genera involved in SCFA production were significantly reduced following SD The BBB permeability marker S100β increased in serum after SD	Wang et al. [340]
Thirty 7-week-old male Sprague-Dawley rats	rats	7:00 a.m. to 7:00 p.m. (12 h/d) for 7 days Use of sleep disturbance device	*s_Vagococcus lutrae, s_Adlercreutzia equolifaciens, s_Bifidobacterium pseudolongum, s_Aerococcaceae bacterium, s_Streptococcus hyointestinalis*	*s_Akkermansia muciniphila, s_Muribaculum intestinale, s_Bacteroides caecimuris*	The total distance, average velocity, and upright numbers were positively correlated with *Akkermansia muciniphila* et al. and negatively correlated with *Prevotella spp*.	Zhang et al. [505]
Male SPF Wistar rats	rats	SD 24h daily for 7 days	*F:B ratio; g_Romboutsia, g_Enterococcus*	*p_Verrucomicrobia, p_Fusobacteria, g_Akkermansia, g_Cetobacterium*	The gut microbial abundance was decreased relative to GABAergic synapses and glutamatergic synapses following SD	Zheng et al. [506]

Eighteen 6-week-old Wistar rats	rats	Four-week chronic SD	*F:B ratio; g_Ruminiclostridium, g_Candidatus, g_Raoultella, g_Negativibacillus*	*g_Blautia, g_Lactococcus, g_Fecalitalea*	SD rats exhibited anxiety and depression-like behavior, and cognitive impairment SD reduced the intestinal concentration of SCFAs and the enhanced intestinal level of SBAs	Li et al. [254]
C57BL/6 J mice (age: 7 weeks)	mice	72-h REM-SD	*p_Actinobacteriota, p_Patescibacteria, p_Verrucomicrobiota; g_Candidatus_Arthromitus, g_Enterobacter*	*g_Enterorhabdus, g_Lactobacillus, g_Monoglobus, g_Ruminococcus, g_Parasutterella, g_Akkermansia*	*Enterobacter* et al. were positively correlated with the TNF-α, but negatively correlated with OCLN, ZO-2, and 5-HT_{1A}R *Lactobacillus* et al. were negatively correlated with TNF-α, and positively correlated with OCLN, ZO-2, and 5-HT_{1A}R	Yang et al. [48]
Healthy 8-week-old male C57BL/6J mice	mice	SD for 6h/d (8:00 am∼14:00 pm)	*f_Burkholderiaceae, f_Tannerellaceae*	*f_Ruminococcaceae, f_Prevotellaceae, f_Rikenellaceae, f_Akkermansiaceae*	SD increased pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and learning and memory impairment in mice	Zhang et al. [139]
Male ICR mice (8 weeks old; 35–40 g)	mice	SD-FMT: donor mice subjected to 3-day SD	*p_Proteobacteria; g_Turicimonas, g_Aeromonas*	*F:B ratio; Lachnospiraceae_NK4A136_group, Eubacteriumxylanophilum_group, g_Ruminococcus_1, g_Lachnospiraceae_A2*	SD-FMT mice exhibited microglia overactivation and neuronal apoptosis in the hippocampus, and cognitive decline Butyrate administration to SD mice restored inflammatory and memory impairment	Wang et al. [244]
Three-week-old C57BL/6J female mice	mice	SD from 18:00 to 14:00 h of the next day (20 h/d) for 6 weeks	*g_Kaistobacter, g_Arthrobacter, g_Flavisolibacter, g_Phenylobacterium, g_Adlercreutzia, g_Promicromonospora*	*g_Lactobacillus, g_Lactococcus, g_Pseudoalteromonas, g_Alteromonas, g_Octadecabacter, g_Candidatus Arthromitus*	Reduction of tight junction proteins such as Claudin-1, Occludin and ZO-1 is associated with increased levels of IL-6 and TNF-α SD increased immune cell infiltration in the lamina propria of the small intestine	Yan et al. [507]
Male C57BL/6J mice	mice	Propeller-based automatic SD system, 20h SD/day for 7 days	*c_Clostridia*	*c_Bacilli, c_Betaproteobacteria, c_Sphingobacteria, s_Akkermansia muciniphila*	*Akkermansia muciniphila* alleviated SD-induced cognitive dysfunction by increasing SCFAs production and maintaining microglial homeostasis SCFAs restoration mediates reduced microglial activation and synaptic engulfment	Li et al. [119]

p_: phylum; c_: class; o_: order; f_: family; g_: genus; s_: species; F:B ratio: *Firmicutes*: *Bacteroidetes* ratio; AID: acute insomnia disorder; CID: chronic insomnia disorder; DSM-V: Diagnostic and Statistical Manual of Mental Disorders, 5th edition; CCMD-3: Chinese Classification of Mental Disorders Version 3; O-IN: objective insomnia; P-IN: paradoxical insomnia; SPF: specific pathogen-free; PCPA: para-Chlorophenyl alanine; CUMS: chronic unpredictable mild stress stimulation; SD: sleep deprivation; REM: rapid eye movement; FMT: fecal microbiota transplantation; ISI: Insomnia Severity Index; PSQI: Pittsburgh Sleep Quality Index; HAMA: Hamilton Anxiety Rating Scale; HAMD: Hamilton Depression Rating Scale; PSG: Polysomnography; TST: total sleep time; WASO: wake after sleep onset; AN: awakenings' number; SE: sleep efficiency; 5-TH: 5-hydroxytryptamine; MT: melatonin; $GABA_AR$: gamma-aminobutyric acid type A receptor; NE: norepinephrine; GSH-Px: glutathione peroxidase; SOD: superoxide dismutase; Ach: acetylcholine; Glu: glutamate; GAT-1: GABA transporter 1; BBB: blood–brain barrier; SCFAs: short-chain fatty acids; SBAs: secondary bile acids; 5-HT_{1A}R: 5-hydroxytryptamine 1A receptor; tight junction genes: OCLN, ZO-2, Claudin-1, Occludin, ZO-1

3.2. Effects of Insomnia on the Intestinal Microenvironment Dysbiosis

The intestinal microenvironment is a complex and dynamic host-microecosystem, maintained by the microbial community and the host immune system. It comprises microorganisms and their metabolites, intestinal secretions, IECs, and cytokines released during host immune responses [123]. Central to this microecosystem is the intestinal barrier, which comprises mechanical, chemical, immune and microbial components, which are crucial for maintaining gut homeostasis. The mechanical barrier is formed by tight junction proteins (TJPs), including claudins, zona occludens (ZO), and occludin which regulate paracellular permeability between IECs [124]. The chemical barrier consists mainly of mucin proteins such as MUC2 secreted by goblet cells [125]. Factors such as GM dysbiosis, inflammation, or toxin exposure may lead to intestinal barrier dysfunction. Insomnia, through activation of the HPA axis, triggers the release of CORT, which downregulates the expression of TJPs, disrupting their assembly at intercellular junctions, and impairs barrier integrity [126]. This impairment is promoted by stress-related inflammatory signalling pathways, such as the c-Jun N-terminal kinase (JNK) and p38 MAPK, which mediate the downregulation of TJPs [127]. In SD mouse models, prolonged SD reduced goblet cell numbers and MUC2 protein expression, further weakened the gut barrier and increasing gut permeability, which led to microbial translocation and infection [128]. A clinical study in patients with CID reported elevated serum levels of ZO-1 and claudin-5 in , indicative of barrier compromised, likely driven by inflammation and GM dysbiosis [129]. Compared to healthy controls, CID patients also exhibit significantly lower serum levels of intestinal barrier biomarkers—diamine oxidase, D-lactic acid, intestinal fatty acid binding protein, and endotoxin—correlating with poor sleep efficiency, increased total wake time, and reduced sleep quality [130].

"Leaky gut" permits translocation of bacterial endotoxins such as LPS from Gram-negative bacteria, from the gastrointestinal tract into the bloodstream via the paracellular route [131]. The circulating LPS binds to LPS-binding protein (LBP), promoting interaction with toll-like receptor 4 (TLR4) on immune cells including monocytes, macrophages, and dendritic cells [132]. This activates downstream MyD88- and TRIF-dependent pathways, leading to nuclear translocation of transcription factors such as NF-κB and interferon regulatory factors, which upregulate pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, and interferons), driving systemic inflammation and exacerbating gut-localized immune responses [133]. The intestinal immune microenvironment—comprising immune cells such as dendritic cells, macrophages, neutrophils, T cells, B cells, and innate lymphoid cells within the epithelium, lamina propria, and gut-associated lymphoid tissues (GALTs)—closely interacts with the GM to regulate immune homeostasis [134]. Insomnia-induced GM dysbiosis can disrupt this balance, contributing to immune dysregulation. These downstream alterations can, in turn, exacerbate dysbiosis, creating a self-perpetuating positive-feedback loop. Increased intestinal permeability and mucosal enrichment of specific bacterial strains induce a transition toward a disease-associated microbiota, supporting the “common ground hypothesis” that barrier dysfunction triggers microbial imbalance [135]. Moreover, the ENS [136] and enteric glial cells (EGCs) play vital roles in barrier maintenance. EGCs, through secretion of factors like S100β and IL-22, exert immunomodulatory effects and

cooperate with the VN to stabilize the gut barrier [137]. Insomnia may disrupt EGC–immune cell communication and gut–brain axis signalling, aggravating neuroinflammation and barrier dysfunction. Collectively, insomnia damages barrier structures, weakens mucosal defences, alters immune–glial dynamics, and blunts enteric glial–vagal regulation, thereby promoting bacterial translocation and amplifying inflammatory signalling. Therefore, strategies that prevent improve barrier repair and maintain the gut microenvironment stability can effectively alleviate insomnia-related intestinal changes.

3.3 Insomnia-Induced Intestinal Microenvironment Dysbiosis Mediated by Microbiota Alterations

Notably, changes in GM are not merely outcomes but may act causally as mediators between insomnia and gut dysfunction. Systemic inflammation is considered a crucial to the link between the GM and sleep regulation [138]. Further SD studies have shown that GM alterations are related to elevated markers of inflammation in mice. Specifically, IL-1β exhibits a positive correlation with the abundance of *Muribaculaceae* and a negative correlation with *Lachnospiraceae* and *Akkermansiaceae*. Additionally, TNF-α has a positive correlation with the abundances of *Erysipelotrichaceae*, *Burkholderiaceae,* and *Tannerellaceae*, while negatively correlated with *Akkermansiaceae* [139]. Similarly, in LPS-induced intestinal inflammation, dysbiosis was observed, characterized by increased pro-inflammatory taxa (e.g., *Proteobacteria*, *Prevotella*) and reduced beneficial bacteria (e.g., *Firmicutes*, *Lactobacillus*). These effects were correlated with tight-junction disruption (Claudin-1, Occludin, ZO-1), impaired antioxidant enzyme activity (SOD, CAT, GSH-Px), and increased production of inflammatory mediators (TNF-α, IL-6, IL-17, IL-1β) and MDA. These mechanisms confirm that GM alterations can drive gut barrier dysfunction and systemic inflammation [140]. More critically, the GM plays a pivotal role in regulating the host's stress response. Glucocorticoid release, a hallmark of stress-induced HPA axis activation, has been shown to be modulated by the GM. Germ-free (GF) mice exhibit exaggerated glucocorticoid responses to stress, which can be normalized upon colonization with conventional microbiota, indicating a modulatory role of GM in stress reactivity [141]. Comparative studies using specific pathogen-free (SPF) and GF mice further demonstrate this regulatory effect in the context of SD. Following SD, SPF mice displayed significantly elevated levels of circulating pro-inflammatory cytokines and disrupted expression of gut barrier markers. In contrast, GF mice exhibited markedly attenuated systemic inflammation and preserved gut barrier function, despite prior reports of baseline abnormalities in intestinal structure in GF animals [142]. Notably SD did not exacerbate gut barrier dysfunction in GF mice, as evidenced by the absence of elevated serum endotoxin levels post-SD—suggesting that the GM is a key mediator of SD-induced gut injury [143]. Transplantation of GM from normal-sleeping donor mice into SD-affected recipients partially reversed SD-induced oxidative stress, inflammation, and gut barrier disruption [144]. These results show that the GM can regulate stress responses and gut injury in insomnia. Moreover, it affects the HPA axis and inflammatory responses, thereby influencing the severity of SD-induced barrier disruption. The protective effect observed in GF mice and the partial reversal achieved via microbiota transplantation demonstrate that maintaining a healthy microbiota could help alleviate the gut dysfunction and systemic inflammation associated with insomnia.

4. The Feedback Effects of the Gut Microbiota on the Central Nervous System

MGBA, as a bidirectional communication system between the GM and the CNS, is a vital physiological mechanism for maintaining health and regulating the brain and CNS. Notably, GM is a key mediator in MGBA, facilitating the dynamic interaction between the CNS and the gastrointestinal tract [145]. This bidirectional communication involves VN-mediated pathways, gut microbial metabolites, and local and systemic immune responses (Fig. 2).

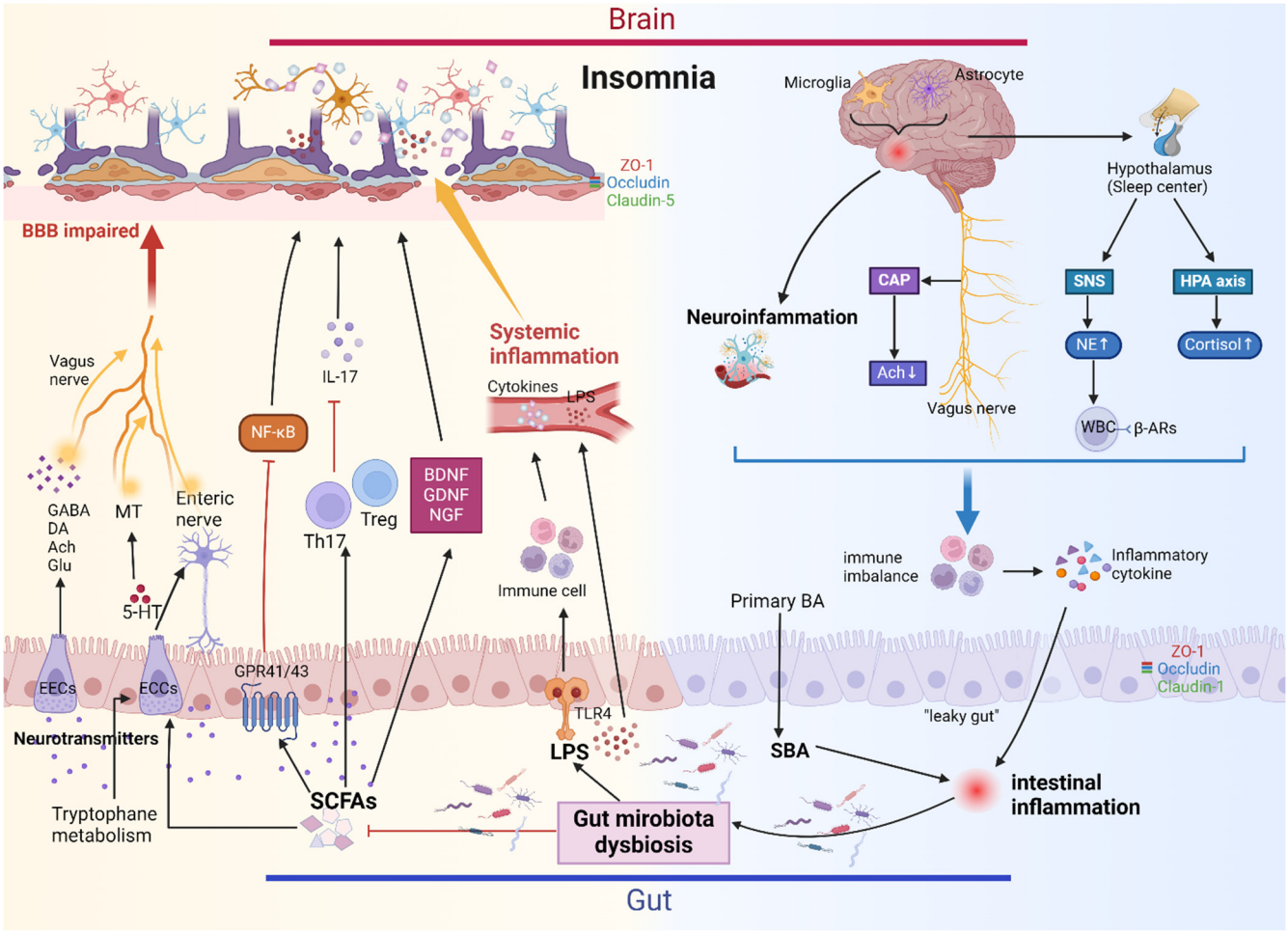

Fig. 2. A diagram illustrating the intricate network of interactions between the brain and the gut. The upper section represents the brain, containing the hypothalamus (sleep center), hypothalamic-pituitary-adrenal (HPA) axis, sympathetic nervous system (SNS), cholinergic anti-inflammatory pathway (CAP) pathway and related neurotransmitters and hormones (e.g. acetylcholine (Ach), norepinephrine (NE), Cortisol). It also includes the blood-brain barrier (BBB) disruption and neuroinflammation (activation of microglia and astrocytes) triggered insomnia. The middle section illustrates the bidirectional communication between the brain and the gut through vagus nerve, immune, neuroendocrine and metabolic pathways. The lower section represents the gut, covering elements such as the intestinal barrier breakdown, tight junction proteins, gut microbiota dysbiosis, microbial metabolites (e.g. short-chain fatty acids (SCFAs), secondary bile acid (SBA), lipopolysaccharide (LPS)), enteric nerve, enterochromaffin cells (ECCs) and enteroendocrine cells (EECs). The axis contains several molecules (e.g., gamma-aminobutyric acid (GABA), dopamine (DA), Ach, glutamate (Glu), 5-hydroxytryptamine (5-TH), melatonin (MT), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF)) and receptors (e.g., G-protein-coupled receptors 41/43 (GPR41/43), toll-like receptor 4 (TLR4)). The arrows in the figure represent mutual interactions and influences among various elements, illustrating the multiple mechanisms associated with the gut-brain axis in physiological and pathological states. These include the interplay between gut inflammation and neuroinflammation, and the regulation of brain function by the GM, providing a comprehensive visual framework for understanding the interactions among the nervous system and the intestinal system. (WBC: white blood cell; β-ARs: β-adrenergic receptors)

4.1. GM regulates CNS function through metabolic products and neurotransmitters

Recent research has shown that GM-derived metabolites are significantly associated with the pathogenesis of insomnia [146]. GM produces various bioactive compounds, including neurotransmitters, amino acids, short-chain fatty acids (SCFAs), and unsaturated fatty acids, which influence CNS function and sleep.

4.1.1. GM modulates nervous system function through SCFAs and their neuroactive effects

SCFAs, including propionate, acetate, and butyrate, are generated via the fermentation of dietary fiber in the colon by specific bacteria, including *Bifibacterium, Lactobacillus, Bacteroides, Ruminococcus, Firmicutes* and others [147]. Different microbial taxa contribute to distinct SCFAs. Specifically, *Firmicutes phylum* mainly produces butyrate, while *Bacteroidetes* primarily produce propionate and acetate [148]. SCFAs play essential roles in a wide range of physiological processes, including regulation of immune responses, metabolism, energy expenditure, intestinal and vascular integrity, circadian rhythms, sleep, and appetite control [147, 149].Their biological effects are primarily mediated through two mechanisms: interaction with G protein-coupled receptors (such as GPR43, GPR41, and GPR109A) and histone deacetylases (HDACs), which modulates gene expression and inflammatory pathways [150]. Within the CNS, SCFAs are critical for proper neurodevelopment, maturation of microglia, suppression of neuroinflammation, synthesis of neurotransmitters and neurotrophic factors, and consolidation of memory [44, 151].

(1) SCFAs indirectly affect the CNS by modulating intestinal immunity and intestinal barrier

SCFAs have shown the ability to maintain intestinal homeostasis by safeguarding the integrity of the epithelial barrier, enhancing secretion of IgA, and modulating T cell differentiation [152]. SCFAs inhibit NF-κB activation by binding to host immune cell GPR41 (FFAR3) and GPR43 (FFAR2), thus regulating colonic inflammation, promoting mucosal repair, and enhancing intestinal barrier function, providing protection for the gut [153]. SCFAs can also influence the activation of helper T cells (Th17) and regulatory T cells (Tregs), reducing the secretion of pro-inflammatory factor IL-17 by inducing Th17 while increasing Tregs levels in the gut, thereby providing protective effects [154]. Specifically, butyrate is a key energy source for intestinal cells and plays essential roles in regulating gut motility, maintaining epithelial barrier function, and supporting immune system health [155, 156]. Furthermore, butyrate enhances the strengthening of the colonic barrier by promoting the synthesis of TJPs and the production of antimicrobial peptides [157]. Butyrate also has significant anti-inflammatory properties because it can suppress pro-inflammatory cytokine secretion and inhibit NF-κB activation [158]. These anti-inflammatory effects can reduce neuroinflammation via blood circulation, suggesting that gut-derived SCFAs can regulate CNS inflammation and potentially improve sleep [159].

(2) SCFAs cross the BBB and direct action on the CNS

The permeability of the BBB is modulated by inflammatory processes within the brain and is often used as a marker of neuroinflammation [160]. SCFAs can cross the BBB via monocarboxylate transporters (MCTs), enhance the expression of TJPs, and prevent the influx of neurotoxic substances into the brain [161, 162]. They play a crucial role in alleviating neuroinflammation, enhancing neurogenesis, and sustaining general neural

function [163]. Studies have shown that supplementation with SCFAs in vagotomized mice still induces BBB repair by improving TJPs localization, indicating that SCFAs can bypass the VN and influence BBB function through other pathways [164]. These pathways may include: direct penetration of the BBB; and indirect regulation of neuroinflammation by activating FFARs on BBB endothelial cells, which exerts neuroprotective effects [149]. The protective mechanism of SCFAs on BBB integrity mainly relies on their antioxidant and anti-inflammatory properties. This is achieved through the inhibition of NF-κB and the activation of Nrf2—a transcription factor of the antioxidant response that plays a crucial role in counteracting NF-κB-driven inflammatory responses [165]. Research has shown that SCFAs can regulate the integrity of the BBB, neuroinflammation, and the maturation of microglia involved in neurogenesis in GF mice by directly interacting with the CNS [159]. Additionally, colonization of butyrate-producing bacteria or supplementation with sodium butyrate in GF mice can upregulate TJPs and reduce BBB permeability [166].

(3) SCFAs modulate neurotrophic factors and synaptic plasticity

SCFAs, such as butyrate, specifically modulate the expression of neurotrophic factors, including BDNF, glial cell line-derived neurotrophic factor, and nerve growth factor, which promote neuronal repair and regeneration, synapse formation, and synaptic plasticity, while ameliorate mood-related behaviours [167, 168]. Among these, BDNF binds to its high-affinity receptor tyrosine kinase receptor B (TrkB), which activates downstream signalling pathways such as PI3K/Akt, MAPK/ERK, and PLCγ, promoting neuronal cell survival and anti-apoptosis, which exerts neuroprotective effects [169, 170]. SD reduces BDNF levels, impairing long-term potentiation and cognitive performance. During SWS, BDNF modulates synaptic strength and postsynaptic signal transduction thereby facilitating synaptic plasticity and memory consolidation [171]. In vitro experiments further confirmed that acetic acid treatment significantly elevated BDNF and TrkB protein levels in rat hippocampal neurons, suggesting that SCFAs stimulates the BDNF/TrkB signalling pathway, which promote neuronal growth [172]. Notably, SCFAs also regulates the interaction between microglia and synapses, thereby facilitating synaptic remodelling during neurodevelopment, sleep, and memory formation [173, 174]. Additionally, GM-based interventions offer more systematic evidence. *Bifidobacterium bifidum* CCFM1163 can alter the composition of GM (e.g., increasing *Lactobacillus* and *Bacteroides* while reducing *Faecalibacterium*) and elevate the level of SCFAs (e.g., acetic and isobutyric acid). Subsequently, elevated BDNF expression triggers the BDNF-TrkB-PLC/IP_3 pathway, which upregulates the expression of Uchl1, S100β, and Acta2 genes, resulting in neuronal repair, activation of glial support functions, and restoration of intestinal smooth muscle structure, thereby coordinating enteric and CNS function [175].

(4) SCFAs regulate neuronal function

Butyrate can activate the VN and hypothalamus by crossing the BBB and binding to receptors, such as G-protein-coupled receptors, in gut cells and the brain [176]. Disruption of gut butyrate biosynthesis caused by GM dysbiosis may lead to sleep disorders by altering the dynamics of orexin neurons in the LH. However, butyrate can regulate neuronal signalling in the brain and promote sleep by inhibiting the activity of orexin

neurons in the LH [177]. *Akkermansia mucinophila* modulates butyrate production to inhibit microglia activation-mediated neuroinflammation thereby attenuating DA neuronal damage [178].

Multiple environmental and dietary factors can modulate SCFA production by modulating the composition of GM to regulate sleep via the MGBA. In SD models, the abundance of butyrate-producing taxa such as *Faecalibacterium prausnitzii* [128] and *Akkermansia muciniphila* [119] was reported to be significantly reduced, whereas depletion of *A. muciniphila* has been associated with low levels of acetate. These SCFA decreases can disrupt sleep homeostasis and exacerbate insomnia-like symptoms. It has also been shown that supplementation of these taxa can normalize SCFA levels, improve intestinal barrier integrity, prevent microglial overactivation, and prevent SD-induced sleep disturbances and related neurofunctional impairments. In chronic unpredictable mild stress (CUMS) models, the abundance of butyrate-producing taxa such as *Bifidobacterium pseudolongum* and *Lactobacillus intestinalis* was reported to be significantly reduced, leading to lower fecal and serum butyrate levels [179]. This SCFA deficiency may impair the gut and blood–brain barrier integrity, promote neuroinflammation, and disrupt HPA axis and circadian rhythm regulation. Inulin supplementation restores these taxa and SCFA levels, upregulates SCFA-signaling receptors (Olfr78, Ffar3), improves the gut–brain barrier function, attenuates TLR4/MyD88/NF-κB-mediated neuroinflammation, and enhances sleep homeostasis. In high-fat diet (HFD) models, the abundance of SCFA-producing genera, including *Alistipes*, *Allobaculum*, *Olsenella*, *Odoribacter*, and *Butyricicoccus* is reduced, resulting in low production of acetate, propionate, and butyrate [180]. This SCFA deficiency compromises gut barrier integrity, increases LPS translocation, and impairs neuronal integrity and plasticity, thereby disrupting gut–brain communication and contributing to HFD-related circadian rhythm and sleep disturbances. In contrast, ketogenic diet enriches neurovascular-protective taxa such as *Akkermansia* and *Lactobacillus*, resulting in higher SCFA production and improved sleep homeostasis [181].

Overall, evidence from prior investigations show that SCFAs regulate GBA, acting through interconnected pathways that maintain intestinal and blood–brain barrier integrity, modulate neuroimmune interactions, sustain neurotrophic signaling, and regulate neuronal excitability. Disruption of SCFA homeostasis—which often occurs in SD, chronic stress, and HFD—may serve as a shared pathological signature, that causes barrier dysfunction, increased neuroinflammation, and impaired neuronal plasticity, leading to disruption of CNS function. Strategies that restore SCFA levels such as, microbiota-targeted supplementation, dietary modulation, or metabolic reprogramming can re-establish barrier and neural homeostasis, stabilize sleep–wake cycles, and potentially prevent insomnia-related cognitive and mood impairments.

4.1.2. GM modulates nervous system function through BAs metabolism

One of the critical functions of GM is the deconjugation and subsequent biotransformation of primary BAs into secondary bile acids (SBAs). The primary BAs pool in humans, all synthesized in the liver from cholesterol, includes cholic acid, chenodeoxycholic acid, and their taurine- or glycine-conjugated derivatives. In the lower gastrointestinal tract, primary BAs are heavily modified by GM to produce a broad range of

SBAs, such as deoxycholic acid (DCA) and lithocholic acid (LCA) [182]. BAs play a pivotal role in regulating inflammation through interactions with both microbiota and host receptors [183]. Specifically, bacterial taxa such as *Lactobacillus*, *Erysipelotrichaceae*, *Lachnospiraceae*, *Clostridium*, and *Bacteroides* catalyse the deconjugation of primary BAs via bile salt hydrolase (BSH) activity. Further conversion to SBAs is primarily mediated by microbial taxa including *Lactobacillus*, *Lachnospiraceae*, *Ruminococcaceae*, *Clostridiaceae*, *Eubacterium*, and *Peptostreptococcus*, relying on 7α-dehydroxylase activity [184]. Notably, DCA and LCA inhibit Th17 and Th1 cell differentiation while promoting $FOXP3^+$ Treg cell development [185, 186]. DCA and LCA also exert anti-inflammatory effects by activating G protein-coupled bile acid receptor 1 (GPBAR1), which induces macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype and enhances IL-10 production, thereby alleviating intestinal inflammation [187]. Ursodeoxycholic acid (UDCA) activates the farnesoid X receptor (FXR) signalling pathway, suppresses NF-κB activation, and promotes M2 macrophage polarization, resulting in reduced intestinal inflammation, restoration of intestinal barrier integrity, and maintenance of mucosal homeostasis [188]. Moreover, BA receptors—particularly Takeda G protein-coupled receptor 5 (TGR5), FXR, and GPBAR1—are widely distributed throughout the CNS, including in the BBB, glial cells, and neurons [189, 190]. Studies indicate that FXR (NR1H4) and TGR5 synergistically regulate BBB integrity and neuroinflammation [191], with NR1H4 exerting neuroprotective effects by inhibiting astrocyte activation via the CEBPβ/NF-κB pathway [192]. Tauroursodeoxycholic acid (TUDCA) effectively inhibits the polarization of astrocytes into the neurotoxic A1 phenotype, thereby reducing the secretion of pro-inflammatory and neurotoxic factors and protecting adjacent neurons and oligodendrocytes [193].TUDCA also activates the cAMP-PKA and TGF-β signalling pathways in microglia, downregulates pro-inflammatory cytokines (e.g., iNOS, IL-1α, TNF-α), and enhances anti-inflammatory responses [194, 195]. Preclinical studies further demonstrate that TUDCA improves neuroplasticity via TGR5 activation, evidenced by an increased mature BDNF/proBDNF ratio, enhanced dendritic spine density, and upregulation of synaptic proteins in the hippocampus [196], highlighting its therapeutic potential in promoting neuroplasticity and mitigating neurodegenerative disorders.

Abnormalities in BAs metabolism are closely associated with GM disorders in insomnia patients. Meanwhile, reduced abundance of certain *family Ruminococcaceae* members with BSH and 7α-dehydroxylase-active in insomnia patients decreases the conversion of primary BAs to SBAs [197], which may disrupt intestinal homeostasis and trigger intestinal inflammation [198]. Experimental studies based on SD models have reproduced this SBAs-deficiency pattern seen in clinical observations. Circadian disruption can inhibit the abundance of SBA-producing taxa such as *Clostridium*_UCG-014, with high 7α-dehydroxylase activity. This microbial shift prevents the conversion from primary BAs to SBAs, lowering intestinal DCA levels. Reduced DCA compromises gut colonization resistance, disrupts intestinal immune homeostasis, increases intestinal permeability, and amplifies pro-inflammatory responses, which impairs the GBA signalling and exacerbates insomnia-related neuroinflammation and contributes to sleep–wake dysregulation [199]. In contrast, under HFD conditions with dietary cholesterol content, the intestinal environment selectively

enriches 7α-dehydroxylase-containing taxa—particularly *Lachnospiraceae* bacterium, *Dorea sp*., and *Clostridium sp*.—which is known to convert primary BAs to DCA. Elevated circulating DCA can accumulate in the hippocampus, facilitated by apical sodium-dependent bile acid transporters (ASBT) expressed in hippocampal neurons. In the neurons, excessive DCA induces mitochondrial dysfunction, activates caspase-3, and triggers neuronal apoptosis, causing cognitive dysfunction [200].

The above data show that microbial conversion of primary BAs to SBAs under physiological conditions maintains BA homeostasis and supports the gut–brain signalling. Loss of sleep disrupts the circadian rhythm of BA metabolism, suppressing the BSH-dependent deconjugation of primary BAs. This limits substrate availability for 7α-dehydroxylase-active taxa, causing their depletion and decreasing DCA levels, which interferes with the gut–brain immune signalling. In contrast, HFD with cholesterol alters BA rhythmicity while generating large amounts of substrates, increasing the expansion of bile-tolerant 7α-dehydroxylase-active taxa and ASBT-mediated hippocampal DCA uptake. Despite these opposing effects, both reflect SBA homeostasis disruption, suggesting that neuropathology may be influenced more by temporal dynamics and gut–brain distribution than by absolute levels.

4.1.3. GM modulates nervous system function through neurotransmitters

GM is a major producer of neurotransmitters and influences the synthesis of neurotransmitters by modulating amino acid metabolism and precursor availability [201], thus directly or indirectly stimulating the interconnection of intestinal afferent neurons with the CNS [202].

(1) Gamma-aminobutyric acid (GABA)

GABA, produced by bacteria, such as *Lactobacillus, Bifidobacterium, and Bacteroides* [203], is a key inhibitory neurotransmitter in the CNS and mediator in sleep regulation [204]. GABA induces sleep by suppressing the activity of noradrenergic and serotonergic wakefulness-promoting neurons [205]. It has been reported that central GABAergic neuronal excitation induces non-rapid eye movement (NREM) sleep and inhibits rapid eye movement (REM) sleep, whereas inhibition of these neurons results in sustained wakefulness [206]. GABA regulates neuronal excitability primarily through its two receptor types—GABAA and GABAB—thereby modulating sleep–wake states. Binding of GABA to GABAA receptors facilitates chloride ion influx, leading to membrane hyperpolarization and reduced neuronal excitability, which promotes sleep [207]. Activation of GABAB receptors inhibits adenylyl cyclase, decreases cAMP levels, suppresses calcium channel activity, and activates potassium channels, collectively contributing to reduced neuronal excitability and stabilization of the sleep state [208]. Some observational studies have revealed that sleep-deprived individuals have significantly lower peripheral blood GABA levels than those with regular sleep patterns. However, oral administration of medium to high doses of GABA (100-150 mg/kg) can significantly prolong deep sleep duration in SD mice [209]. Clinically used anti-insomnia medications, such as benzodiazepine receptor agonists, primarily mimic the effects of GABA by enhancing receptor affinity for GABA and promoting GABAergic neurotransmission, thereby exerting sedative, hypnotic, and anxiolytic effects [210].

Studies have shown that stress-related conditions can alter GM composition and inhibit microbial GABA synthesis to cause insomnia via the GBA. In a rhesus monkey model, SD activated the HPA axis and SAM system, increased the production of stress hormones (e.g., CORT, NE) and inflammatory cytokines, which in turn disrupted GM composition and metabolism—particularly by reducing *Lactobacillus* abundance and impairing the Glu-GABA synthesis pathway, to reducing the levels of peripheral GABA. Supplementation with *Lactobacillus* increased GABA levels and alleviated stress-related dysbiosis [211], suggesting that microbial GABA disruption forms an important pathological factor driving insomnia in stress contexts. Similarly, a human intervention study found that *Bifidobacterium breve* 207-1 alleviated stress-induced insomnia by modulating microbial GABA and SCFA production. This strain carries the gadB gene, which facilitates the Glu-to-GABA conversion, induces neurotransmission inhibition and improves sleep quality. It also promotes the enrichment of SCFA-producing genera (*Bifidobacterium*, *Blautia*, *Streptococcus*), increasing acetate and propionate levels that can cross the BBB to prevent HPA axis hyperactivation [212]. These findings demonstrate that stress-induced microbial dysbiosis disrupts GABAergic signalling, while specific probiotic strains can restore gut-derived GABA and promote sleep homeostasis.

The improvement of insomnia by GABA may be attributed to its role in multiple biological processes, including inhibition of neuroinflammatory responses, repair of oxidative damage, neuroprotection, and regulating MT [213, 214]. Studies have shown that GABA can modulate macrophages [215], microglia [216], and astrocytes [217] via GABAB receptors, inhibiting the activation of inflammatory pathways such as MAPKs and NF-κB and reducing the release of inflammatory factors. The GABAB receptor agonist baclofen inhibits cell-damaging autophagy by upregulating the Bcl-2/Bax ratio and enhancing activation of Akt, glycogen synthase kinase (GSK)-3β, and ERK, thus mitigating neuronal damage [218]. GABA also inhibits ROS, scavenges free radicals, and lowers malondialdehyde concentrations to counter oxidative stress [219, 220]. It maintains neuronal redox balance by modulatingGSK-3β and the Nrf2, thereby exerting neuroprotective effects [221]. Additionally, GABA interacts with MT, which follows a circadian rhythm, to alleviate insomnia. GABA supplementation has been observed to elevate serotonin and MT levels in rat blood, promoting sleep via the dopaminergic system [222].

(2) 5-hydroxytryptamine (5-TH)

5-HT, commonly known as serotonin, is a neurotransmitter with a variety of biological effects. In the gut, enterochromaffin cells (ECCs) absorb dietary Trp from the bloodstream and convert it to 5-HT via tryptophan hydroxylase-1 (TPH1) and aromatic L-amino acid decarboxylase, accounting for 90% of intestinal 5-HT production [223], while the remaining 10% is synthesized by TPH2 in ENS and CNS neurons [224]. Gut -derived 5-HT activates 5-HT_3 receptors on vagal afferent fibers, transmitting signals to the NTS and modulating serotonergic neurons in the dorsal raphe nucleus as well as noradrenergic neurons in the LC [225]. This process influences sleep, mood regulation, stress response, and immune modulation [226].Within the immune system, 5-HT regulates macrophage polarization and mediates anti-inflammatory effects through $5\text{-HT}_2\text{B}$ and 5-HT_7 receptors, with $5\text{-HT}_2\text{B}$ receptors predominantly expressed on M2 macrophages [227]. 5-HT upregulates

M2-associated genes (e.g., SERPINB2, THBS1), inhibits pro-inflammatory cytokine secretion, and downregulates M1-related gene expression [228]. These regulatory actions are vital for maintaining tissue homeostasis and resolving inflammation [227]. Additionally, SCFAs—particularly butyrate—enhance TPH1 expression in ECCs and increase 5-HT production [229]. Certain species within the *Firmicutes phylum*, such as probiotics *Lactobacillus* and *Bifidobacterium*, positively impact Trp metabolism and can directly convert Trp to 5-HT [230, 231]. SCFAs can also regulate VN activity, altering the expression of the serotonin transporters and receptors (5-HT_1A, 5-HT_2B, 5-HT_7), thereby influencing its levels [232] and further strengthening the MGBA [233]. Animal studies have shown that dysbiosis of GM significantly decreases 5-HT levels, thus affecting the sleep-wake cycle. These findings indicate that 5-HT may play a role in communication between the GM and the sleep regulation system [234]. In sleep regulation, activation of 5-HT_1A receptors inhibits GABAergic neurons in the lateral preoptic area and stimulates arousal systems in the basal forebrain, brainstem, and hypothalamus to initiate and sustain sleep [235]. A study further demonstrated that 5-HT_1A receptor activation also suppresses the arousal-promoting activity of orexin neurons, thereby facilitating sleep [236].

5-HT is absorbed by IECs and enters the bloodstream, mainly promoting wakefulness and suppressing REM sleep [237]. The metabolism of Trp, depends on the involvement of the GM. The microbiota particularly sways the metabolic shunting of Trp towards the kynurenine pathway, which affects the availability of 5-HT in the CNS [238]. Studies have shown that GF animals with extremely low circulating Trp levels can restore normal levels following colonization with a healthy microbiota, suggesting that circulating Trp levels are related to microbial abundance [239]. Systemic Trp levels are closely linked to inflammatory conditions. Inflammatory cytokines can induce the expression of indoleamine 2,3-dioxygenase and tryptophan-2,3-dioxygenase, which catalyse the synthesis of kynurenine during Trp metabolism, thereby reducing Trp availability for serotonin production [240]. Conversely, SCFAs mitigate inflammation and indirectly enhance Trp availability, thus limiting the overactivation of the kynurenine pathway [241]. Data from preclinical and clinical studies indicate that some gut microbes can regulate sleep via 5-HT-related pathways. In a pentobarbital-induced mouse model, administration of Ganoderma lucidum extract (GLAA) significantly shortened sleep latency and prolonged sleep duration, accompanied by increased hypothalamic 5-HT levels and upregulation of key serotonergic-synapse genes. GLAA enriched *Bifidobacterium animalis*, *Lactobacillus reuteri*, and *Odoribacter*, which positively correlated with 5-HT levels and sleep duration. Antibiotic-induced microbiota depletion abolished these effects, confirming the role of GM [242]. In patients with major depressive disorder—often presenting with disrupted sleep–wake cycles and gastrointestinal symptoms—*Bifidobacterium breve* CCFM1025 supplementation enhanced Trp, 5-HTP, and 5-HT levels but decreases the levels of 5-HIAA. These improvements are due to the increase in *Bifidobacterium*, *Desulfovibrio*, and *Faecalibaculum*, as well as indole-3-propionic acid production [243], suggesting that specific microbes can modulate Trp metabolism and serotonergic pathways to alleviate emotional and sleep-related symptoms.

(3) Melatonin (MT)

MT hormone is synthesized and secreted by the pineal gland in response to circadian rhythms. MT is also secreted by the intestines, skin, bone marrow, and other organs for its sleep-promoting effects [244]. Its synthesis is regulated by both the endocrine and nervous systems. In pineal cells, norepinephrine binds to β and α adrenergic receptors, stimulating MT synthesis via the cAMP-PKA-CREB and PLC-Ca^{2+}-PKC pathways [245]. Meanwhile, the majority of Trp (about 95%) is metabolized through the kynurenine pathway in the liver [246], with less than 5% utilized for serotonin and MT synthesis [247].Studies have reported that in insomnia patients, elevated levels of pro-inflammatory cytokines and CORT excessively activate the kynurenine pathway, generating neurotoxic metabolites and reducing Trp availability for MT and serotonin synthesis, thus contributing to mood and sleep disturbances [248]. MT exerts diverse neuroregulatory effects by binding to neuronal MT1 and MT2, activating multiple signalling pathways. For example, MT1 activates the PI3K/Akt signalling pathway, promotes neuronal growth, and promotes proliferation and survival, while MT2 participates in the cAMP/PKA/CREB signalling pathway and regulates the expression of circadian rhythm genes [249]. Additionally, MT exhibits potent antioxidant and anti-inflammatory properties, protecting synaptic connections from oxidative damage and enhancing the efficiency of signal transmission between neurons [250]. Studies have shown that MT administration increases BDNF expression by 25%–30% [251] and improves synaptic transmission by 15%–20% [252].

In the chronic unpredictable mild stress combined with sleep deprivation (CUMS+SD) model, impaired mitochondrial autophagy in the pineal gland significantly disrupts normal MT secretion. This impairment is closely associated with dysfunction in the Pink1/Parkin pathway and the AMPK/FOXO3a autophagy signalling, leading to depressive symptoms accompanied by insomnia [84, 253]. These findings suggest that MT may serve as a crucial mediator linking mitochondrial dysfunction, impaired autophagy, and sleep-emotional disorders. Moreover, MT plays an essential role in alleviating cognitive impairment induced by SD. In a mouse model combining SD with MT-treated faecal microbiota transplantation (SD+MT-FMT), MT restores microbial homeostasis by regulating the GM (e.g., reducing *Aeromonas* and increasing butyrate-producing bacteria), lowering LPS levels, and inhibiting microglia activation. This process cross-regulates central inflammatory responses and neuronal apoptosis through the TLR4/NF-κB and MCT1/HDAC3 pathways, thereby exerting neuroprotective effects [244]. MT may also influence brain signalling in MGBA by increasing the production of SCFAs and reducing the production of SBAs, thereby improving neuropsychiatric symptoms such as anxiety, depression, and cognitive impairment induced by chronic SD [254]. Studies have also shown that MT can elevate GABA concentrations in specific brain regions and modulate the serotonergic and dopaminergic systems, thereby exerting sedative, anxiolytic, anti-insomnia, and cognitive-enhancing effects [255, 256]. In contrast, insomnia may be partly driven by GM-mediated disruption of MT rhythmicity. In GF or antibiotic-treated mice, colonization with specific taxa such as *Lactobacillus reuteri* (positively associated with serum MT) or *Escherichia coli* (negatively associated with serum MT) was observed to reproduce these MT alterations. Under such colonization conditions, GM activated the TLR2/4–MyD88–NF-κB signalling in colonic epithelium, upregulating the expression of the rate-limiting

enzyme arylalkylamine N-acetyltransferase (AANAT) and increasing the local colonic MT synthesis. In contrast, the NF-κB signalling can inhibit pineal MT synthesis, which increases colonic MT but reduces serum MT [257]. This microbiota-driven disruption of MT rhythmicity may impair circadian sleep–wake regulation and contribute to neurocognitive decline. In an AANAT-knockout model of endogenous MT reduction, GM remodelling—characterized by reduced *Bacteroidetes* and increased *Lactobacillus* and *Ruminiclostridium*_5—accompanied gut barrier impairment, increase the risk of gut and systemic inflammation. This inflammatory state promoted microglial activation, Aβ deposition, and BBB disruption, thereby driving cognitive decline and circadian rhythm disturbances via the GBA [258].

Evidence from recent studies show that GABA, 5-HT, and MT can mediate the association of GM to the CNS via the MGBA. Their synthesis is regulated by specific microbial taxa and metabolites (e.g., SCFAs, Trp metabolites), which collectively modulate neuronal excitability, circadian rhythms, inflammation, and neuroendocrine balance. Dysbiosis induced by SD or chronic stress can disrupt the key microbial genera (e.g., *Lactobacillus*, *Bifidobacterium*) and related metabolic enzymes (e.g., gadB, TPH1, AANAT), disrupting GABAergic, serotonergic, and melatonergic systems and disturbing neural signalling. This process is accompanied by reduced SCFA levels, HPA axis overactivation, neuroinflammation, and abnormal VN signals, contributing to neuro–immune–endocrine dysregulation initiated by dysbiosis. Conversely, targeted supplementation of specific probiotics or their metabolites can restore neurotransmitter metabolism and signalling to improve sleep-related neural dysfunction. These findings highlight the central role of microbiota–neurotransmitter pathways in the regulation of sleep homeostasis.

4.2. GM exerts feedback on the CNS via the VN pathways

The VN receives signals from the GM and their metabolites via multiple pathways, playing a key role in signal transmission within the GBA [259]. Synaptic connections are formed between the ENS and the VN when gut bacteria stimulate afferent neurons in the ENS, allowing the transfer of gut information to the CNS. This process is known as the "gut microbiota-enteric nervous system-vagus nerve-brain pathway" [260, 261]. In cases of impaired intestinal barrier function, GM and their metabolites directly interact with vagal afferent fibres, activating neurons via specific receptors. For example, *Edwardsiella tarda* binds to transient receptor potential ankyrin A1 located on the nodose ganglia and activates intestinal epithelial enteroendocrine cells (EECs), thereby directly stimulating vagal sensory neurons and inducing structural and functional changes in the CNS neurons through the release of 5-HT [262]. EECs detects bacterial products such as LPS via surface TLRs or sense metabolites like SCFAs through other receptors. These cells activate vagal afferent fibres by releasing Glu or peptide hormones (e.g., cholecystokinin and glucagon-like peptide-1 [GLP-1]) thus transmitting gut-derived signals [263]. These mechanisms have been validated in multiple studies. Celiac vagotomy significantly attenuated cognitive dysfunction-like behaviours, hippocampal $Iba1^{+}$ microglial activation, and enhanced TNF-α expression induced by *Escherichia fergusonii* (NK2001) or *Veillonella infantium* (NK2002)-mediated LPS overproduction [264]. Moreover, neurotoxic metabolites, such as D-lactic acid and ammonia, produced by GM may enter the CNS through the VN, affecting brain function, stress

responses, and sleep architecture [260]. Neuroactive compounds and metabolites can enter the brain regions within the CNS that regulate cognition and mood, further activating the VN system and leading to corresponding changes in mood, cognition, and sleep [265]. For example, Ach produced by *Lactobacillus species* can enter the CNS via the VN pathway to regulate the sleep-wake circadian rhythms [266]. Therefore, studying the VN-mediated gut-brain pathway and related interventions can provide valuable insights into VNS-based therapeutic strategies that can help improve gastrointestinal, emotional, neuropsychiatric, and sleep disorders.

Research has shown that VNS can modulate CNS inflammatory responses through multiple mechanisms, including inflammatory signalling pathways such as the α7nAchR/JAK2/STAT3/NF-κB pathway [267]. VNS upregulates BDNF, promoting microglial polarization toward the M2 phenotype and increasing anti-inflammatory cytokines such as IL-4 and IL-10 [268, 269]. VNS also alleviates systemic inflammation resulting from GM dysbiosis by inhibiting mast cell degranulation and chymase secretion, thereby enhancing the integrity of both the gut and blood-brain barriers [270]. Moreover, VNS reduces the expression of matrix metalloproteinases (MMP)-2/9 in astrocytes surrounding damaged blood vessels, mitigating BBB damage by preventing TJPs degradation [271]. Notably, increased vagal tone relative to sympathetic tone improves sleep [272, 273], while probiotics such as *Lactobacillus brevis* have been shown to enhance vagal activity and reduce sympathetic activity in skin arteries [274, 275].

The VN transmits the GM-derived signals to the CNS under physiological conditions by integrating receptor-mediated pathways that modulate inflammation, preserve barrier integrity, and regulate sleep–wake cycles. Therefore, this pathway can transmit harmful signals such as LPS, ammonia, and D-lactate, precipitating neuroinflammation in response to impaired barrier function or dysbiosis. The combination of microbiota-directed interventions (e.g., probiotics) with therapeutic VNS can inhibit inflammatory and neuroprotective pathways to restore GBA homeostasis and improve sleep quality.

4.3 GM exerts feedback on the CNS via immune and neuroendocrine pathways

The gastrointestinal tract, as the largest immune organ in the body, plays a critical role in MGBA signalling through its immune system. Insomnia-induced intestinal inflammation leads to reduced differentiation of Tregs, diminished secretion of IL-10 and TGFβ, and promotes Th1/Th17-dependent pro-inflammatory responses, thereby further activating peripheral immune cells and exacerbating CNS inflammation [276, 277]. Clinically, patients with CID exhibit significantly elevated serum levels of 1,3-β-D-glucan, IL-1β, and NLRP3 proteins, which positively correlate with insomnia severity. Among these, 1,3-β-D-glucan—a pathogen-associated molecular pattern found in the cell walls of various intestinal microorganisms—serves as a biomarker of intestinal barrier dysfunction and microbiota dysbiosis [278]. It is associated with a decrease in *Lactobacillales*, which are crucial for maintaining mucosal barrier integrity [279]. This molecule can activate macrophages via the dectin-1 receptor, leading to enhanced pro-inflammatory cytokine production [280],and plays a central role in the pathogenesis of chronic insomnia through the activation of the NLRP3/IL-1β inflammasome pathway. Additionally, LPS, a typical pro-inflammatory

metabolite of GM, can disrupt the BBB through multiple mechanisms. It stimulates brain vascular endothelial cells to release prostaglandins and nitric oxide, activating astrocytes and microglia, inducing pericyte detachment and degradation of TJPs, thereby destabilizing the BBB [281]. LPS further exacerbates BBB damage by increasing inflammatory cytokine release and inducing MMPs, which degrade TJPs and extracellular matrix components. As permeability increases, systemic cytokines, LPS, and other microbial products infiltrate the CNS, stimulating astrocytes and microglia, amplifying neuroinflammation, damaging neurons, and impairing cognitive function [282-284].

The GM regulates HPA axis function through multiple mechanisms, thereby influencing stress responses and neuroendocrine homeostasis. Insomnia-induced microbiota dysbiosis allows pro-inflammatory cytokines to cross the BBB and activate the HPA axis [285]. Additionally, bacterial metabolites, such as LPS, SCFAs, and peptidoglycans can directly stimulate the HPA axis [286]. The GM also modulates noradrenergic neuron activity in the NTS via the VN, influencing downstream HPA axis output [287]. Moreover, GM can affect HPA axis activity by regulating gene expression in the hippocampus and hypothalamus [288]. These mechanisms highlight the GM as a core regulator of the GBA and underscore its critical role in insomnia-associated HPA axis dysfunction. Notably, HPA axis dysregulation is linked to reduced levels of *Lactobacillus* and *Bacteroides*, alongside elevated *Clostridium* levels [289]. Further studies indicate that SCFAs can attenuate HPA axis responses, indicating that modulating HPA axis activity through GM may represent a promising therapeutic strategy for insomnia [290]. In summary, the GM exerts feedback on the CNS via immune–inflammatory cascades and HPA axis pathways, thereby aggravating neuroinflammation, BBB disruption, and stress hyper-responsivity, which ultimately intensify sleep disturbances. Dysbiosis-induced metabolites and inflammatory mediators reinforce central dysfunction, establishing a closed pathogenic loop in which insomnia alters the GM and microbiota-derived signals further exacerbate CNS impairment. Together, this reciprocal chain highlights the essence of bidirectional regulation within the MGBA and provides a coherent framework for understanding the persistence and progression of chronic insomnia, as well as a mechanistic basis for microbiota-targeted interventions.

5. Combined Effects of Insomnia and GBA Dysregulation

The dysregulation of the GBA significantly impacts sleep and various physiological processes. Alterations in GM composition exacerbate the negative effects of insomnia, leading to severe disruptions in metabolism and cognitive function (Fig. 3).

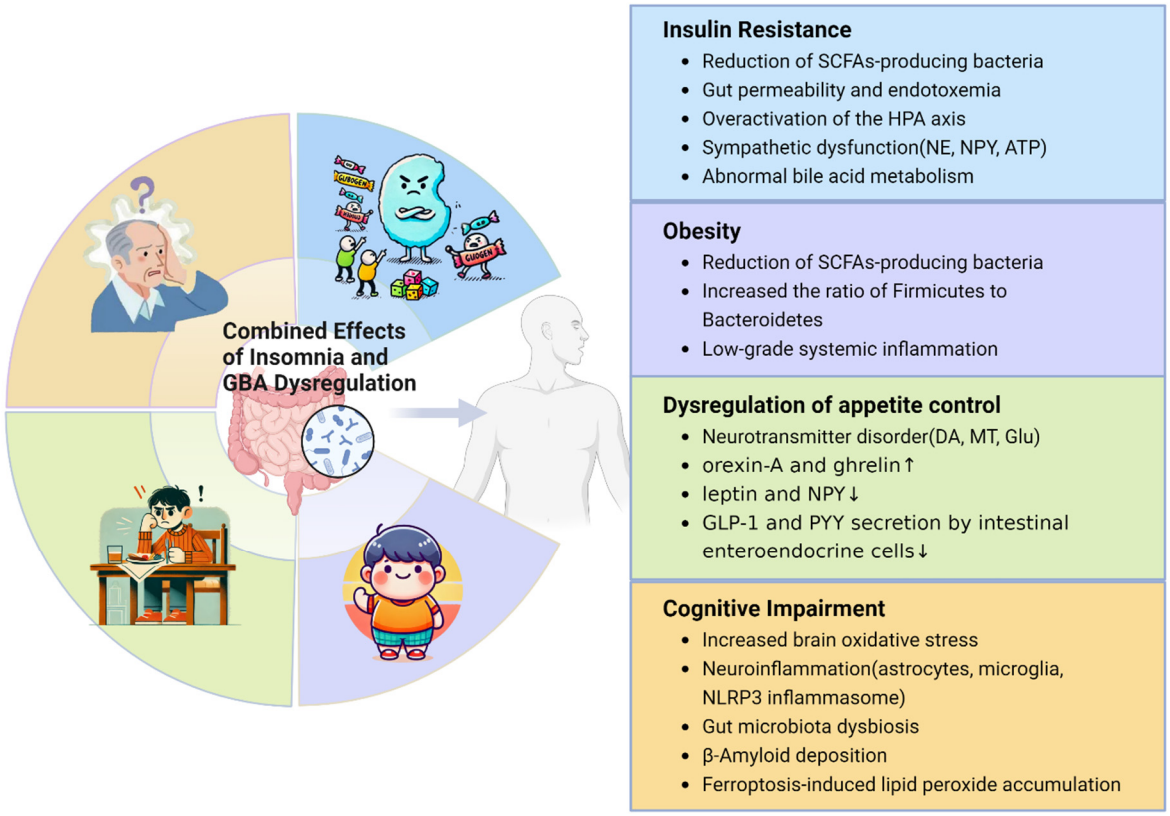

Fig. 3. Schematic illustration of the combined effects of insomnia and gut microbiota dysbiosis. This figure demonstrates the multifaceted effects of insomnia and GM dysbiosis on human health in a circular structure. Specifically, the combined effects of GM on insulin resistance, obesity, appetite regulation and cognitive function are shown, summarizing the underlying mechanisms. These mechanisms collectively highlight the complex interplay between sleep, gut health, and systemic diseases, offering a clear and concise framework for related research and therapeutic interventions. (GBA: gut-brain axis; SCFAs: short-chain fatty acids; HPA: hypothalamic–pituitary–adrenal; NE: norepinephrine; NPY: neuropeptide Y; ATP: adenosine triphosphate; DA: dopamine; MT: melatonin; Glu: glutamate; GLP-1: glucagon-like peptide-1; PYY: peptide YY; NLRP3: NOD-like receptor family pyrin domain containing 3).

5.1. Insomnia-induced GM Dysbiosis Triggers Metabolic Disorders

Insomnia-induced GM dysbiosis and neuroendocrine dysfunction can significantly affect insulin sensitivity and energy metabolism, leading to a cascade of metabolic disturbances, such as insulin resistance (IR), obesity, and chronic inflammation. These effects are mediated by changes in gut microbial composition and their metabolic byproducts [291].

5.1.1. GM dysbiosis induces Insulin resistance and lipid metabolism disorders

Chronic insomnia leads to neuroendocrine system disorders. Excessive cortisol secretion following HPA axis interferes with insulin signalling and the expression of insulin-sensitive genes, thereby inducing IR [292]. Excited sympathetic nerve fibers regulate adipose tissue function by modulating the secretion of NE, neuropeptide Y (NPY), and adenosine triphosphate. Notably, these fibers inhibit insulin secretion and decrease glucose uptake, which induces IR and glucose tolerance abnormality [293]. Neurotransmitter disorders, such as DA, MT, and Glu, interfere with the normal ingestion and satiety centers in the brain, enhancing appetite, reducing energy expenditure, and causing peripheral glucose homeostasis imbalance,

which disturbs glucose and lipid metabolism [294]. Insomnia is associated with elevated levels of orexin-A and ghrelin as well as reduced levels of leptin and NPY, contributing to IR and abnormal lipid metabolism [295].

Studies have shown that prolonged SD disrupts the circadian rhythm of Incretin hormones, including GLP-1 and glucose-dependent insulinotropic polypeptide, leading to dysregulated insulin secretion, heightened inflammatory responses, impaired glycaemic homeostasis, and ultimately the development of IR [296]. Moreover, the GM plays a critical role in maintaining metabolic homeostasis and regulates GLP-1 secretion in a circadian manner [297]. Insomnia-induced disturbances in microbial metabolism, such as the reduction of butyrate-producing bacteria (*Faecalibacterium* and *Roseburia*), significantly reduce insulin sensitivity and impact obesity development [298]. Butyrate is a health-promoting molecule that increases insulin sensitivity, exerts anti-inflammatory effects, regulates energy metabolism, and upregulates leptin gene expression [298]. Additionally, dysbiosis increases the ratio of *Firmicutes*-to-*Bacteroidetes* (F/B). An elevated F/B ratio is associated with the development of obesity because *Firmicutes* are more efficient in obtaining energy from food than *Bacteroidetes*, leading to an increase in the number of calories absorbed, thus causing weight gain and obesity [299]. It has also been shown that chronic SF induces metabolic disturbances, such as visceral fat accumulation, adipose tissue inflammation, and systemic IR. A vital mechanism underlying these effects involves alterations of the GM, characterized by an increased abundance of *Lachnospiraceae* and *Ruminococcaceae* and decreased amounts of *Lactobacillaceae*. These microbial shifts are accompanied by elevated levels of IL-6, LBP, and neutrophil gelatinase-associated lipocalin. This suggests that inflammation may be triggered by translocation of microbial products into the bloodstream due to a compromised colonic epithelial barrier [300]. This low-grade systemic inflammatory response interferes with host glucose and lipid metabolism and promotes adipose tissue production and storage, leading to the development of IR and other metabolic disorders [301]. Animal studies further confirmed that transplantation of microbiota from SF mice to GF mice replicated their inflammatory and metabolic abnormalities phenotypes. This suggests that SF-induced metabolic alterations may be partially mediated by corresponding changes in GM [300].

The liver plays an important role in lipid metabolism and the development of systemic inflammation and immune responses. Insomnia-induced GM dysbiosis and intestinal barrier disruption may expose the liver to gut-derived microbial products, thereby inducing chronic endotoxemia and gut-liver axis dysfunction. Notably, several bacterial genera observed in insomnia patients, such as *Bacteroidetes* and *Streptococcus*, have been positively associated with total cholesterol (TC) and triglyceride (TG) levels in a HFD-induced metabolic-associated fatty liver disease (MAFLD) rat model [302]. This suggests that insomnia-related GM alterations may indirectly exacerbate hepatic lipid accumulation by regulating lipid metabolism. Moreover, increased intestinal permeability promotes the translocation of microbial metabolites and endotoxins (such as LPS) into the liver via the portal circulation. LPS activate TLR4 on Kupffer cells (KCs), initiating the TLR4–IκB–NF-κB–TNF-α/IL-6 signaling cascade, potentially leading to hepatic inflammation and fibrosis [303]. LPS also promotes the release of pro-inflammatory cytokines such as IL-1β and IL-18 through inflammasome activation, thereby continuously exacerbating hepatic pathological damage [304]. Under

physiological conditions, SCFAs are transported to the liver via the portal vein and regulate lipid metabolism genes (e.g., Hmgcr, Srebp-1, Fasn), thereby modulating hepatic fatty acid synthesis and β-oxidation, and reducing excessive fat accumulation [305]. SCFAs also modulate intestinal lamina propria macrophage activity and promote Tregs recruitment to suppress hepatic immune responses and inflammation [306]. However, in insomnia patients, the abundance of multiple SCFA-producing bacteria is significantly reduced, potentially weakening the protective effects of SCFAs on liver metabolism. Ethanol is another microbiota-derived metabolite of interest. In a chlorophenylalanine (PCPA)-induced insomnia rat model, the relative abundance of *Escherichia* was elevated [307], and this bacterial genus is known to generate ethanol [308]. Ethanol metabolism increases the activity of cytochrome P450 family 2 subfamily E polypeptide 1 (CYP2E1), elevating the levels of ROS and free radicals, resulting in oxidative damage and necrosis of hepatocytes [309]. Ethanol accumulation can also activate the NF-κB signaling and impair intestinal barrier function, promoting the hepatic translocation of LPS and exacerbated hepatic inflammation [304]. Impaired BAs metabolism is another key mechanism. It has been reported that the abundance of *Ruminococcaceae* UCG-002 and UCG-003—positively correlated with SBAs such as isoLCA, LCA, and UDCA—is decreased in individuals with chronic insomnia [310]. Of note, specific SBAs (e.g., UDCA, isoLCA) can inhibit TH17 cell differentiation and promote Tregs proliferation via regulating the TH17 cell differentiation/IL-17/PPAR signaling pathway to inhibit the progression of non-alcoholic fatty liver disease (NAFLD) [311]. Since LCA is a natural agonist of FXR and TGR5, its reduction may decrease the FXR/TGR5 activity, thereby disrupting BAs-mediated metabolic and immune homeostasis regulation. Mechanistically, FXR attenuates hepatic inflammation by activating small heterodimer partner (SHP), which inhibits pro-inflammatory transcription factors NF-κB and AP-1. TGR5 decreases the NF-κB activity via mechanisms such as activating β-catenin, inhibiting IκBα phosphorylation, promoting the AKT-mTOR pathway, and promoting IL-10 transcription, thereby exerting anti-inflammatory effects in various immune cells [312]. Moreover, fibroblast growth factor 21 (FGF21), a downstream cytokines of FXR, can stimulate fatty acid β-oxidation and energy metabolism by inducing peroxisome proliferator-activated receptor α (PPARα) and peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) [313]. SCFAs also promote FGF21 expression [314], and FGF21 overexpression may increase the expression of the suppressor of cytokine signaling 2 (SOCS2), involved in the modulation of adipose tissue metabolism and immune inflammation [315].

Insomnia-related GM dysbiosis has been shown to be a potential driver of insulin resistance and lipid metabolic disorders. The interplay of inflammatory amplification, barrier disruption, and metabolic product imbalance—particularly SCFA depletion and LPS translocation—forms a self-reinforcing gut–liver–metabolic loop. Although animal studies strongly support this mechanism, causal evidence in humans is limited. Strategies that restore SCFA/BA predominance, inhibit LPS–TLR4–mediated inflammation, and repair barrier integrity can potentially break this cycle.

5.1.2 Intervention of GM metabolites in metabolic disorders

Gut microbial metabolites and their host receptors, in conjunction with dietary interventions, have emerged as promising targets for the advancement of novel therapeutic strategies for metabolic disorders [316]. Among these, SCFAs have numerous beneficial effects on metabolism and immunity [317]. SCFAs can activate FFAR2 and FFAR3 or directly inhibit HDACs, stimulating colonic L cells to secrete GLP-1 and peptide YY [318, 319]. These hormones regulate the signalling of appetite-related neuropeptides and delay gastric emptying [320]. These hormones can also promote insulin secretion and inhibit glucagon secretion, thus maintaining glucose homeostasis [321]. In energy metabolism, SCFAs activate AMPK signalling and upregulates key metabolic regulators such as PPARα and PPARγ, uncoupling protein 1, adiponectin, and resistin, resulting in reduced lipogenesis and improved glucose and lipid metabolism [322]. Emerging evidence highlights the essential role of SCFAs-producing bacteria in metabolic regulation. For example, *Intestinimonas butyriciproducens* converts dietary fructoselysine to butyrate, and its abundance negatively correlates with metabolic risk markers including BMI, TG, glycated haemoglobin, and fasting insulin levels. Oral administration of this bacterium in diet-induced obese mice reduces obesity, improves glucose metabolism, and alleviates tissue inflammation [323]. Similarly, *Bifidobacterium adolescentis* FJSSZ23M10 significantly increases the relative abundance of *Bifidobacterium*, *Faecalibaculum*, and gut butyrate levels, leading to less weight gain, improved lipid profiles, decreased adipose tissue lipid accumulation, and restored energy metabolism homeostasis [324]. *Pediococcus acidilactici* Y01 inhibits fat accumulation, dyslipidemia, and chronic low-grade inflammation, enhances glucose tolerance and IR, and reduces adipose tissue inflammation by modulating the M1/M2 polarization balance of adipose tissue macrophages. Additionally, *P. acidilactici* Y01 markedly increases the abundance of beneficial gut bacteria such as *Akkermansia*, *Bifidobacterium*, *Lachnospiraceae_NK4A136_group*, and *Lactobacillus*, indicating its potential for preventing and treating obesity and type 2 diabetes-related metabolic disorders [325].

SCFAs can ameliorate insomnia-related metabolic dysfunction since they can regulate glucose–lipid metabolism and suppress chronic inflammation. Targeted probiotic strategies that restore butyrate-producing taxa can improve metabolic homeostasis and reduce adipose inflammation. However, evidence from human insomnia cohorts is lacking. Therefore, researchers should perform causal, longitudinal trials integrating microbiome, metabolome, and circadian rhythm data to guide SCFA-centred precision interventions.

5.2. Insomnia Induces Cognitive Impairment

Sleep plays a central role in brain plasticity, memory consolidation, and optimal cognitive function. Disruptions in sleep patterns can significantly impair cognitive abilities and trigger a cascade of adverse neurological effects. Studies have demonstrated that sleep disorders contribute to cognitive decline through multiple mechanisms, including oxidative stress, neuroinflammation, gut microbiota imbalance, and neurotransmitter disruption.

5.2.1. Mechanistic Pathways of Insomnia-Induced Cognitive Impairment

(1) Insomnia-Induced Cognitive Impairment Through Oxidative Stress

Research has confirmed that SD is associated with oxidative stress. Salehpour et al. [326] found that the content of malondialdehyde in the hippocampus increases in SD in mice after 72h, while the activities of antioxidant enzymes, such as glutathione peroxidase and superoxide dismutase, are significantly reduced. SD suppresses the production of antioxidant enzymes, leading to an excessive increase in ROS, lipid peroxidation, and DNA modifications, causing neuronal damage and cognitive dysfunction [327]. Recent studies have shown that chronic SD increases brain oxidative stress by inhibiting the PI3K/AKT/GSK-3β signalling pathway, thereby leading to cognitive damage [328]. Furthermore, studies have demonstrated that ferroptosis, which is characterized by accumulation of lipid peroxides, participates in the neurogenesis of AD and PD [329]. GM par ferroptosis through its microbial composition, biological functions and metabolites, such as regulating intestinal pH to optimize dietary iron bioavailability [330]. Application of exogenous melatonin and the ferroptosis inhibitor Fer-1 was found to alleviate SD-induced hippocampal damage and cognitive deficits, supporting a mechanistic link between ferroptosis and SD-related cognitive impairment [14].

(2) Insomnia-Induced Cognitive Impairment Through Neuroinflammation

Neuroinflammation has been implicated in the initiation and development of cognitive impairment [244]. Xia et al. [331] reported that SD stimulates the activation of the NLRP3 inflammasome by inhibiting the signalling and phosphorylation of signal transducer and activator of transcription 3 in astrocytes. This leads to the activation of Akt and induces neuroinflammation. Meanwhile, SD triggers the activation of microglia, which participates in SD-induced cognitive impairment by regulating neuronal cell proliferation, differentiation, and BDNF levels [332]. Moreover, other studies have found that TNF-α triggers a cytotoxic cascade response and apoptosis. Amyloid-beta (Aβ) can trigger cytotoxicity via the TNF-α receptor 1 and have been implicated in the occurrence of neuronal apoptosis. TNF-α was also found to trigger cognitive deficits by disrupting synaptic plasticity and neurotransmitter transmission across the synapse [333]. Notably, neurons and glial cells exhibited enhanced metabolic rates and are known to generate large amounts of metabolic waste, primarily including Aβ and tau. A previous study showed that accumulation of these toxic molecules in turn impair neurons and glial cells [334]. Short-term activation of microglia can phagocytose and clear accumulated Aβ, whereas chronic SD and chronic inflammatory state are associated with abnormal activation of the M1 or M2 leading to sustained production of pro-inflammatory cytokines [335], and impaired phagocytosis of Aβ [336]. The imbalance between Aβ production and removal may increase Aβ deposition, triggering neuroinflammation, neurotoxicity and neuronal loss, ultimately impairing cognitive function [337, 338].

(3) Insomnia-Induced Cognitive Impairment Through GM Dysbiosis

Bidirectional communication system between the GM and the brain, known as the MGBA, is deemed to be essential in cognitive impairment induced by insomnia [339]. Wang et al. [340] discovered, for the first time, that SD leads to cognitive through the perspective of the "MGBA." Specifically, it was observed that the absence of GM in GF mice suppressed the peripheral and central inflammatory responses, gut barrier dysfunction and cognitive impairment induced by SD. Furthermore, transplantation of GM samples derived

from SD mice into GF mice resulted in activation of the TLR4/NF-κB signalling pathway, further disrupting cognitive function in the recipient mice [341]. Population-based research has shown a strong correlation between GM composition with both sleep and cognitive performance. For instance, in older adults with insomnia, variations in the composition of GM and the abundance of specific bacterial genera, such as *Lactobacillus crispatus* and *Streptococcus*, were linked to poor sleep quality and cognitive dysfunction [146]. Likewise, another study focusing on elderly individuals with chronic insomnia showed that those with higher sleep efficiency and better cognitive function exhibited higher relative abundance of *Lachnoclostridium* ASV207 and ASV027 [342]. These findings align with previous cross-sectional studies in older adults, where individuals with shorter sleep duration had lower *Lachnoclostridium* abundance [343], while those with cognitive impairment showed higher *Lachnoclostridium* abundance [344]. Meanwhile, changes in the abundance of *Blautia*—a member of the *Lachnospiraceae* family—have also been associated with cognitive ability in several studies, though the results remain inconsistent. Lower cognitive performance was linked to higher *Blautia* abundance [342], and its abundance was also elevated in insomniac adults who were less physically active [345]. However, in individuals with Parkinson's disease, reduced *Blautia* abundance correlated with cognitive decline [346], suggesting that further research is necessary to clarify the role of these microbiota in sleep and cognition. Additionally, this study identified novel microbiota associated with sleep (e.g., *Angelakisella* and *Sphingomonas*) and cognition (e.g., the *Ruminococcus gauvreauii group* and *Propionibacteriaceae*) [342],providing new directions for developing microecological interventions based on flora characterization. Animal studies also support this association. chronic SD rats exhibit lower levels of *Lactobacillus*, a genus shown to alleviate dextran sulphate sodium (DSS)-induced colitis and cognitive impairment [347]. Furthermore, typical SD-induced dysbiosis includes proliferation of pathogenic bacteria (e.g., *Ruminococcus*, *Prevotella*, *Escherichia*, and *Shigella*) alongside a decrease in SCFAs-producing bacteria. It is hypothesized that this process may lead to the disruption of the BBB, neuroinflammation, elevated ROS concentrations, reduced Aβ clearance, and Aβ plaque deposition [9].

(4) Insomnia-Induced Cognitive Impairment Through Neurotransmitter Disruption

Sleep disorders can exacerbate cognitive impairment by disrupting neurotransmitter metabolism and signalling pathways. In a mouse model of SD-induced cognitive impairment, significantly increased NE levels and reduced 5-HT and DA levels were observed in the hippocampus. These changes suggest that chronic SD may impair learning memory capacity by interfering with the normal function of the locus coeruleus-norepinephrine (LC-NE) system, resulting in abnormal NE release [348]. Cognitive studies indicate that learning and memory abilities depend on synaptic plasticity in the CNS and the modulation of various neurotransmitters, including NE, Glu, ACh, 5-HT, and DA [349]. Moderate NE levels enhance working memory via α-2A adrenergic receptors, whereas excessive levels stimulates α-1 receptors, leading to memory impairment [350]. DA plays a critical role in modulating hippocampal synaptic plasticity and cognitive memory through D1 receptors (D1R) [351]. Appropriate levels of DA and DA-D1R activity enhance cognitive function and synaptic transmission [352], while excessive or insufficient DA impairs cognition and memory [353].

Elevated 5-HT concentrations help maintain or improve memory capacity, whereas lower levels impair spatial memory [354]. Glu—a key neurotransmitter that regulating neural excitability and synaptic plasticity—is essential for learning, memory, and cognitive processes [355]. However, excessive Glu can cause neuronal excitotoxicity and contribute to neurodegenerative disease development [355]. The GM modulates Glu signalling pathways, influencing cognitive function in various neurological disorders [356, 357]. ACh, central neurotransmitter to cholinergic signalling, is vital for cognition, learning, attention, and sleep regulation [358]. Gut dysbiosis impairs cholinergic transmission and cognition ability by activating microglia, enhancing acetylcholinesterase activity, and promoting ACh degradation [359, 360]. Notably, neurotransmitter imbalances regulated by the MGBA regulation may be influenced by specific microbial metabolites, representing an additional potential mechanistic pathway by which insomnia mediates cognitive impairment through GM.

Research shows that GM alterations can promote oxidative stress, neuroinflammation, and neurotransmitter imbalance in insomnia-related cognitive decline. They can compromise the BBB integrity, and disturb neurotransmitter regulation, thereby initiate a self-perpetuating cycle that accelerates the transition from reversible functional disturbances to irreversible structural and cognitive damage.

5.2.2 Microbiota-Based Interventions Targeting SD-Induced Cognitive Impairment

Although the mechanisms underlying SD-induced cognitive dysfunction remain incompletely understood and effective clinical interventions are lacking, recent studies have identified gut probiotics as promising candidates for mitigating cognitive damage caused by SD. Specifically, *Akkermansia muciniphila* effectively alleviates cognitive deficits in SD mice by preserving hippocampal synapses and suppressing extensive microglial activation and synaptic phagocytosis within the hippocampus. Metabolomic analysis further revealed that *A. muciniphila* treatment increased serum acetate and butyrate levels in SD mice, which positively correlated with longer exploration times in the novel object recognition (NOR) test [119]. Butyrate, in particular, has been shown to regulate autophagy and upregulate α-synuclein RNA expression through activation of the PI3K/Akt/mTOR signalling pathway [361], thereby enhancing neurogenesis and synaptic plasticity, and promoting learning and memory [362]. Similarly, *Weizmannia coagulans* BC99 demonstrates potential in alleviating SD-related cognitive impairment. This probiotic increases sleep-related neurotransmitters such as 5-HT and DA while reducing CORT and NE levels. It also improves GM α-diversity and community structure similarity by increasing the abundance of beneficial bacteria like *Lactobacillus* and *Bifidobacterium*, suppressing potentially harmful bacteria such as *Olsenella*, and stimulating SCFA production. Importantly, *W. coagulans* BC99 indirectly reduces neuroinflammation by maintaining intestinal barrier integrity, inhibiting LPS translocation, and lowering peripheral inflammatory factors. The core of its anti-inflammatory effect involves inhibition of the NLRP3/ASC inflammasome pathway in both the jejunum and brain, creating a conducive environment for cognitive recovery [348]. Furthermore, Studies have shown that MT can restore circadian rhythms by upregulating BMAL1 expression or modulating the interaction between HDAC3 and Bmal1/Clock. MT also attenuates SD-induced oxidative stress and suppresses microglial activation and NF-κB pathway signalling, which collectively diminish secondary

neuroinflammation, hippocampal neuronal injury, and apoptosis. These combined effects ultimately improve cognitive function in rats subjected to prolonged REM sleep deprivation [363, 364].

5.3. Integrated Pathological Model of GBA Disorder

Insomnia patients are chronically exposed to stress, and colonic epithelial cells are receive central stress signals via the CRH-CRHR1-mitochondrial pathway, which interfere with the hypoxic environment in the intestinal lumen and shifts the dominant GM from obligate anaerobes (e.g., *Akkermansiaceae*) to facultative anaerobes (e.g., *Enterobacter*) [110]. *Akkermansiaceae* exert protective effects by maintaining intestinal barrier integrity and mitigating IR, adipose tissue inflammation, hepatic fat accumulation, and metabolic endotoxemia. The insomnia-associated reduction in *Akkermansiaceae* abundance has been linked to obesity, T2DM, and NAFLD [365]. Conversely, *Lachnospiraceae* is elevated in chronic insomnia mice, accompanied by visceral fat accumulation, adipose inflammation, and systemic IR. Research has reported that increased plasma LBP and NGAL levels negatively correlates with reduced insulin sensitivity (pAKT/AKT) in adipose tissue. Specific strains within *Lachnospiraceae* can disrupt the intestinal barrier, promoting the translocation of microbial products such as LPS into circulation, which triggers adipose tissue inflammation and metabolic disorders [300]. Colonization of *Lachnospiraceae* (strain AJ110941) in GF ob/ob mice reproduces these metabolic abnormalities. Its specific elevation under insomnia further supports its pathogenic potential in insomnia-associated metabolic impairments [366]. Notably, gut-derived LPS can reach the liver via the portal vein, activate TLR4 on KCs, thereby initiating NF-κB phosphorylation and enhancing NLRP3 inflammasome activity [304]. Persistent liver inflammation suppresses lipid metabolic regulators such as PPARα, disrupts β-oxidation, and promotes TG accumulation in the liver, thereby promoting NAFLD progression [367]. Peripherally, circulating LPS activates the NF-κB/MAPK pathway, triggering chronic low-grade inflammation that promotes JNK/IKK-mediated aberrant phosphorylation of insulin receptor substrate-1, thereby blocking downstream PI3K/AKT activation and ultimately disrupting insulin signaling to promote IR [368]. Insomnia-related GM dysbiosis also reduces SCFAs production, weakening their metabolic protective effects. In adipose tissue, SCFAs suppress lipogenesis by downregulating PPARγ or enhance fatty acid β-oxidation via activation of the AMPK–PGC-1α pathway, thereby reducing lipid accumulation [369]. In the liver, SCFAs upregulate FGF21 expression and activate the PI3K/AKT pathway to promote glucose and lipid homeostasis [314]. They also suppress SREBP-1c expression, reducing lipogenesis and alleviating NAFLD-related abnormalities [305]. Moreover, insomnia has been linked to a reduction in BSH-expressing beneficial microbes, including *Clostridium hylemonae*, *Bifidobacterium*, *Lactobacillus*, and *Ruminococcaceae*, which compromises the conversion of primary BAs to SBAs and attenuates the activation of BA receptors FXR and TGR5 [310]. In glucose metabolism, TGR5 activation promotes GLP-1 secretion and improves glucose tolerance [370]. FXR induces SHP expression, which inhibits the expression of key gluconeogenic enzymes, thereby reducing blood glucose levels [371]. In lipid metabolism, FXR inhibits lipid synthesis through the FXR-SHP-SREBP-1c pathway and promotes fatty acid oxidation through the FXR-PPARα-CPT1 pathway [372]. Therefore, decreased FXR/TGR5 activity under insomnia can disrupt

glucose and lipid metabolic homeostasis. Collectively, insomnia-induced GM dysbiosis can create disturbance in key microbial metabolites such as LPS, SCFAs, and BAs, forming a pathological network involving the gut–liver–adipose system characterized by intestinal barrier impairment, chronic systemic inflammation, and disruption of host–microbiota metabolic signaling, promoting peripheral metabolic dysfunction.

Metabolic abnormalities may increase the risk of cognitive impairment via multiple interrelated mechanisms, closely linked to insomnia-induced GM dysbiosis. Among them, GLP-1 not only promotes glucose-dependent insulin secretion but also reduces Aβ deposition and tau excessive phosphorylation, enhances neurogenesis and synaptic plasticity, alleviates oxidative stress and mitochondrial dysfunction, while inhibiting neuronal apoptosis and neurotoxicity [373]. Insomnia-induced disturbances in SCFAs and BAs metabolism can damage the rhythmic secretion of GLP-1, weakening its neuroprotective effects. Consequently, decreased GLP-1 expression may link the insomnia-related GM dysbiosis to peripheral metabolic dysfunction and central neurodegeneration. Peripheral metabolic abnormalities driven by GLP-1 deficiency—such as hyperinsulinemia—not only compete with Aβ for insulin-degrading enzyme, thereby reducing Aβ clearance [374], but also elevate toxic lipid metabolites that can cross the BBB and trigger neuroinflammation [375], collectively exacerbating cognitive decline. A previous study reported that insomnia-induced activation of proinflammatory cytokines and oxidative stress aggravate IR development in the brain [376]. IR in the brain impairs neuronal glucose uptake, energy metabolism, and synaptic plasticity, causing cognitive decline [377]. Moreover, IR stimulates GSK-3β activity, increases Aβ production and accelerates tau excessive phosphorylation, which further compromises normal brain function [378]. Collectively, these findings show that insomnia-induced GM dysbiosis disrupts key microbial metabolites and promotes inflammation, causing GLP-1 deficiency and IR, which converge to drive Aβ/tau pathology, neuroinflammation, and synaptic dysfunction. This integrated mechanism creates a direct pathogenic bridge between peripheral metabolic dysfunction and central cognitive decline within the GBA framework.

Besides metabolic-mediated effects, insomnia-induced GM dysbiosis may potentially promote cognitive impairment via inflammatory activation, abnormal microbial metabolites, and neurotransmitter imbalance. Circulating LPS activates inflammatory signaling in brain endothelial cells, inducing MMPs expression and disrupting BBB integrity [281]. This further activates glial cells and triggers NLRP3 inflammasome activation, thereby amplifying neuroinflammation [282, 379], and promotes the development of sleep disorders and induces neuronal damage and cognitive decline [380]. A preclinical study demonstrated that FMT from chronic SD mice, impaired cognition in recipient mice, accompanied by excessive phosphorylation and aggregation of tau protein in the hippocampus [379]. This suggests that the detrimental effects of chronic SD may be transmitted via GM, suggesting that GM dysbiosis is not merely a secondary consequence of SD but a direct pathogenic factor driving cognitive impairment. Further mechanistic analyses have indicated that chronic SD microbiota recipient mice show activated GSK-3β, autophagy-lysosomal system dysfunction, and NLRP3 activation in the hippocampus. GSK-3β, a tau kinase, was found to trigger abnormal tau phosphorylation and aggregation

[381] and to regulate NLRP3 [382]. Increased NLRP3 activity promotes neuroinflammation and blocks autophagy-mediated tau clearance [383]. Therefore, chronic SD-induced GM dysbiosis can activate the GSK-3β–NLRP3–autophagy dysfunction pathway, stimulating tau pathological accumulation and cognitive impairment. Microbial metabolites can also protect our deleterious roles. SCFAs alleviate neuroinflammation and improve cognitive by inhibiting aberrant microglial-mediated synaptic phagocytosis, suppressing inflammatory factors secretion, and modulating neurotransmitter and neurotrophic factor levels [119]. BAs metabolism also affects CNS function. BAs can activate intestinal FXR/TGR5 receptors to induce GLP-1 secretion, which can cross the BBB and exert anti-inflammatory and neuroprotective effects, thereby reducing Aβ aggregation and enhancing hippocampal plasticity [384, 385]. In line with this mechanism, supplementation with UDCA and TUDCA mitigates neuroinflammation, can improve mitochondrial function and protect against Aβ-induced neurotoxicity and synaptic damage [386]. Abnormal Trp metabolism also contributes to cognitive impairment, and its metabolites can affect cognition, sleep, and immune function [12]. In insomnia models, *Desulfovibrio* is enriched and negatively correlated with levels of 5-HT, GABA, and 5-hydroxyindoleacetic acid (5-HIAA) [387]. This genus produces hydrogen sulfide, which impairs intestinal barrier and induces systemic inflammation, thereby altering brain function via the GBA [388]. Conversely, decreased abundance of *Clostridia*_UCG-014 is linked to reduced levels of neuroprotective Trp metabolites such as kynurenic acid (KYNA) and indole-3-carboxylic acid (I3CA) [387]. Among them, KYNA counters the neurotoxicity of quinolinic acid (QA) and modulates neurotransmitter release, thereby promoting neuronal protection [389]. I3CA activates the aryl hydrocarbon receptor (AHR) to enhance gut barrier function and suppress inflammation [390]. In this context, insomnia-induced GM dysbiosis can stimulate the production of inflammatory cytokines (e.g., IL-6, TNF-α), activating rate-limiting enzymes such as IDO1 and KMO and promoting the shift of Trp metabolism toward the kynurenine (KYN) pathway [391, 392]. KYN crosses the BBB and is further metabolized into 3-hydroxykynurenine (3-HK) and QA in microglia , triggering neurotoxicity and neuroinflammation [12]. 3-HK has been shown to elevate hippocampal IL-6 and IL-1β expression and impair cognitive function [393]. Additionally, KYN and 3-HK levels are positively correlated with wake-promoting neurotransmitters (e.g., DA, NE) and inflammatory factors, while negatively correlated with 5-HT and GABA. In contrast, higher levels of 5-HT and 5-HIAA are associated with improved sleep and emotional status [387]. In summary, insomnia-induced GM dysbiosis shifts Trp metabolism toward neurotoxic branches, disrupting neuroimmune homeostasis through a combination of inflammatory activation and neurotransmitter imbalance. These effects, accompanied with impaired SCFAs and BAs metabolism, trigger central inflammation, synaptic and neuroplasticity damage, and tau pathology, inducing cognitive and emotional damage. Therefore, targeting the microbiota–metabolite–neuroinflammation pathway may be a novel therapeutic strategy for correcting insomnia-related cognitive impairment.

6. Contradictions and Gaps in Insomnia-Gut Microbiota Regulation

The relationship between insomnia and GM remains complex and at times inconsistent. Resolving these contradictions necessitate a comprehensive understanding of the various factors influencing GM, including

individual variability and circadian rhythms, alongside the integration of multi-omics approaches. This section examines the existing discrepancies in insomnia-GM research and outlines future directions to address these knowledge gaps.

6.1. Bridging Knowledge Gaps in GM and Insomnia Research

Studies have demonstrated a potential link between insomnia disorders and GM composition. Acute insomnia disorder (AID) and chronic insomnia disorder (CID) patients show reduced abundance of anaerobic bacteria producing SCFAs, but only CID patients present with increased pro-inflammatory taxa (e.g., *Blautia*) and inflammatory markers such as IL-1β [394]. This is likely because the insomnia period in AID patients is relatively short, and gut dysbiosis may not be sufficient to trigger inflammatory changes. Moreover, CID patients exhibit significant neuroendocrine dysregulation, which may further exacerbate sleep disturbance [395]. Notably, a recent study classified postmenopausal women with chronic insomnia into two groups—objective insomnia (O-IN) and paradoxical insomnia (P-IN)—based on International Classification of Sleep Disorders, Third Edition (ICSD-3) criteria. Despite similar self-reported symptoms, they presented significantly different GM profiles: *Collinsella* and *Clostridium* were enriched in O-IN patients, while *Bacteroides* predominated in P-IN patients [396]. This suggests that despite normal objective sleep in P-IN patients, the emotional stress or chronic low-grade inflammation resulting from long-term subjective distress may still influence GM composition via the GBA, reflecting heterogeneity in the biological pathways underlying insomnia subtypes.

Firmicutes and *Bacteroidetes* are the dominant phyla in the gastrointestinal tract of healthy adults, and their ratio is widely regarded as the key feature of GM homeostasis. However, studies related to insomnia have shown inconsistent variations in this ratio. For example, a significant reduction in F/B ratio has been observed in both chronic insomnia patients [397] and older adults (≥65 years) with chronic insomnia [342]. However, in short-term partial SD experiments conducted on healthy individuals, the F/B ratio increased [398], and in human studies involving sustained sleep restriction found no significant changes [399]. This discrepancy may be caused by the fundamental differences in the pathophysiological mechanisms underlying chronic insomnia and acute sleep loss. The former is generally associated with long-term neuroendocrine dysfunction, inflammation, and sustained activation of the HPA axis, which may influence the GM environment and composition via the GBA; the latter is more likely to reflect a short-term adaptive fluctuation rather than a stable pathological dysregulation.

Notably, a study involving young, healthy individuals observed that better self-reported sleep quality was associated with higher GM diversity and an increased F/B ratio. This was driven by the high relative abundance of *Blautia* and *Ruminococcus* (*Firmicutes*) and low *Prevotella* (*Bacteroidetes*), suggesting that good sleep may improve the gut microbiome structure [400]. These findings offer an important foundation for understanding the reduced F/B ratio in insomnia populations, supporting the association between sleep quality and GM health. However, increased *Blautia* observed in healthy sleepers appears contradictory to its role as a pro-inflammatory signature genus in CID patients [394]. In fact, *Blautia* represents a genus-level taxonomic

category that includes species and even strains with significant functional differences. This underscores the need for more detailed species- or strain-level analysis to resolve inconsistent findings regarding specific changes in bacterial composition in sleep studies.

Animal experiments have revealed a similar trend in F/B ratio. A decrease in F/B ratio was observed in PCPA-induced insomnia models involving male rats [401], male mice [402], and female mice [403]. Conversely, an increase in F/B ratio was detected in some mice [404] and rats [405] using SD models. This contrast may arise from differences in model mechanisms: The PCPA model simulates chronic insomnia by inhibiting serotonin synthesis, while SD models such as the modified multiple platform method (MMPM) primarily involve short-term acute stress, more akin to sleep loss states. Furthermore, differences in the microbial sequencing regions used (e.g., V1-V2, V3-V4), analytical tools (e.g., QIIME、DADA2、PICRUSt), sample sources (feces vs. colonic contents), and sampling timepoints across experiments may also influence F/B ratio. Furthermore, the F/B ratio varies across life stages and pathological conditions, with higher ratios commonly observed in adulthood, followed by a progressive decline with aging [406].

There are significant inconsistencies in current findings regarding the correlation between insomnia and GM composition, which potentially reflect the high degree of heterogeneity among insomnia disorders. Therefore, standardized classification of insomnia types and experimental models should be performed in future research. Clinically, insomnia disorders can be classified into short-term insomnia, chronic insomnia, and other insomnia based on ICSD-3 or Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [20], often supplemented by subjective assessment tools such as the Pittsburgh Sleep Quality Index (PSQI) and Insomnia Severity Index (ISI) [407]. Several biologically meaningful phenotypes of insomnia have been proposed, including O-IN, P-IN [396], insomnia with short sleep duration (ISSD), and insomnia with normal sleep duration (INSD) [408], which may help to reveal the heterogeneous pathophysiology of insomnia. In animal studies, commonly used models include the PCPA-induced model and the chronic unpredictable mild stress (CUMS) model to simulate chronic insomnia, as well as various forms of SD models—such as MMPM, REM-SD, and SF—to mimic acute sleep loss. These models differ significantly in terms of induction mechanisms, duration, and stress characteristics, which may lead to specific changes in GM. In microbiota analysis, it is crucial to move beyond traditional genus-level classification by employing multi-omics integration approaches to enable refined stratification at species, subspecies, strain, and genotype levels. This comprehensive methodology will elucidate the selective effects of specific sleep disorders on GM, ultimately providing a robust scientific foundation for personalized microbiota-based therapeutic interventions.

6.2. Addressing Individual Differences in GM Composition

Notably, GM undergoes dynamic changes throughout the human lifespan, and different periods of life (from birth to old age) present with distinct phenotypes of bacterial populations [409]. At birth, neonates experienced low diversity of microbiota and enhanced predominance of *phyla Proteobacteria* and *Actinobacteria* [410]. *Clostridia*, *Bacteroides* and *Bifidobacteria* gradually increase during the first months of life creating a complex adult-like GM after 1 year of age [411]. GM remains stable in healthy adults but exhibits

individual specificity influenced by genetic and environmental factors. However, individuals aged 65 years and older exhibit more pronounced alterations in GM composition compared to younger adults, primarily driven by age-related declines in intestinal function and nutrient absorption [412]. Gender also represents a critical factor influencing GM composition. Research has demonstrated significant differences in overall microbial community structure between males and females in both humans and rodent models, although the specific taxa implicated vary across studies [413]. Importantly, gender-related differences in microbial α-diversity fluctuate throughout the lifespan, peaking during adolescence to middle age before declining in later years, with females generally showing higher microbial diversity than males [414]. Hosts encode functional genes associated with immunity, metabolism, intestinal motility and bacterial adhesion that can shape the lifelong GM [415]. Although genetics plays a significant role, even twins exhibit different GM profiles and contribute to the development of chronic diseases [416]. He et al. [417] reported that host regional differences strongly impact gut microbiome composition. Environmental factors such as physical, psychological, exercise and dietary conditions also regulate and maintain GM and its metabolic products [418].

Consequently, individual differences in GM may explain the variability in insomnia phenotypes and treatment responses. Future research should investigate how genetics, diet, lifestyle and environmental factors interact to shape GM composition in insomnia patients, allowing for the implementation of personalized microbiota-based therapies.

6.3. Investigating Circadian Rhythms of the GM

The composition and function of GM are modulated by circadian rhythms. More than 20% of microbial genera show significant daily fluctuations, accompanied with specific taxonomic structures at different times [419]. For instance, the abundance of *Firmicutes* and *Bacteroidetes*, which dominate the mammalian GM, varies periodically from day to night, and is related not only to the timing of food intake and dietary structure [419-421], but influenced by the host's biological clock and gender [422]. In female mice, it was found that the abundance of GM and the number of *Bacteroides* exhibited pronounced circadian rhythmicity [422]. Circadian rhythm disorders (e.g., SD, jet lag, shift work and sleep disorders) influence the structure and ecological parameters of the microbiota community [423, 424], as well as the inflammatory state of the body [425], triggering dysbiosis [9, 419]. Exogenous administration of MT [426] or exposure to intermittent bright light enhanced counterclockwise shift workers' adaptation to circadian rhythms, thereby alleviating sleep disorders [427]. Timed MT supplementation at night may provide long-term benefits in insomnia patients, significantly improving sleep quality and life satisfaction [428].

In future, researchers should explore the optimal timing for dietary interventions (e.g., intermittent fasting and timed eating) to restore microbial circadian rhythms. Second, it is imperative to determine the dual regulatory effects of time therapy (e.g., MT supplementation) on the host's biological clock and the balance of GM. Third, the potential benefits of light interventions on microbiota composition in various individuals with circadian rhythm disorders need to be clarified. Finally, the impact of lifestyle adjustments (e.g., regular sleep

patterns, increased daylight light, reduced electronic screen exposure) on the microbial circadian rhythms deserved in-depth study to generate important ideas for promoting health.

7. Future Directions and Translational Opportunities for Clinical Applications

Integrating individual microbiota profiles with clinical data represents a critical step that facilitates the prediction, prevention and implementation of personalized medicine (PPPM). In clinical applications, GM and its metabolites, together with biomarkers and inflammatory indicators associated with the GBA may serve to promote the application of personalized treatment of insomnia. Therapeutic interventions, including probiotics, microbiota transplantation, and dietary modifications, hold significant potential for improving sleep quality and alleviating insomnia (Fig. 4). However, GM-based interventions are still limited by cost, safety, clinical knowledge and infrastructure.

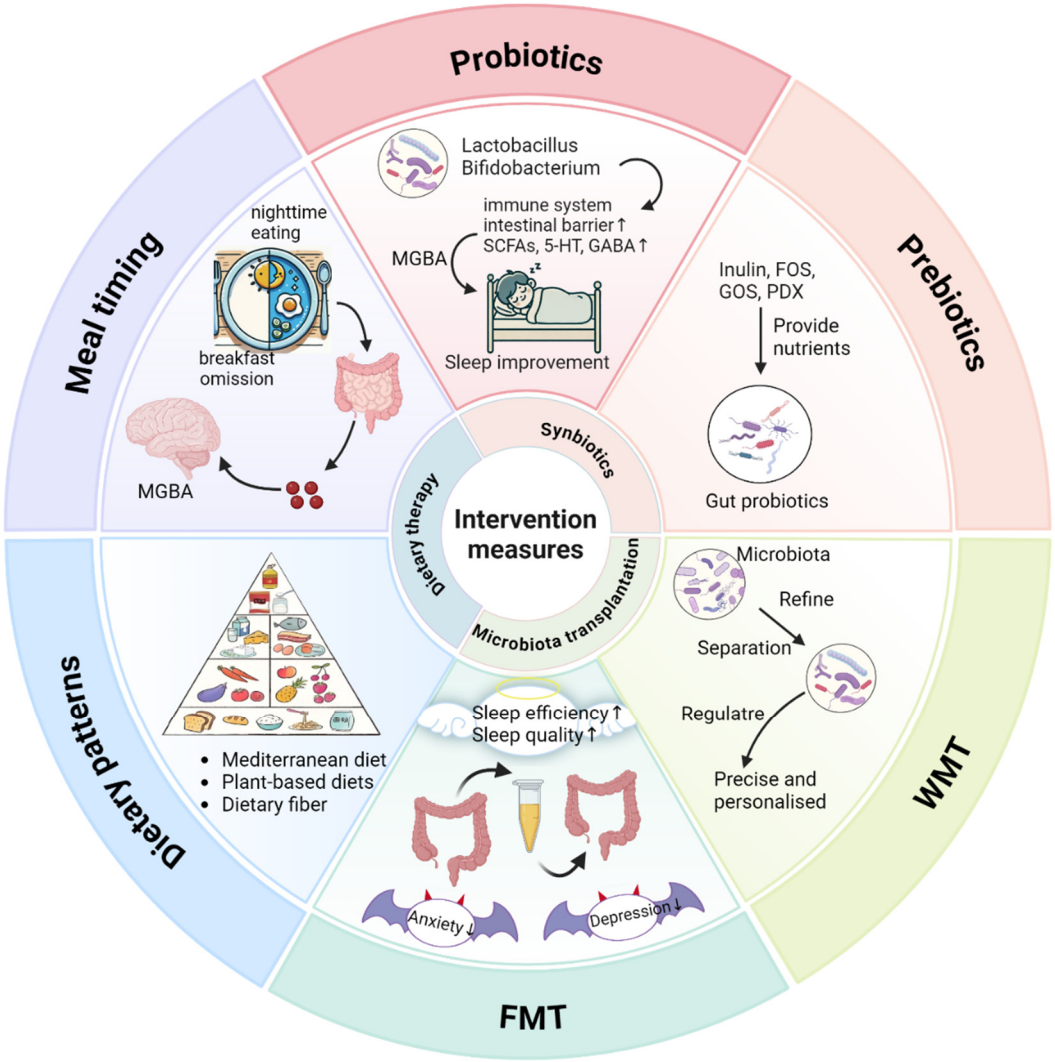

Fig. 4. Schematic diagram of the synthesis of gut health and sleep intervention measures. This circular diagram provides a comprehensive display of multiple intervention strategies related to gut health and their interrelationships. **Probiotics section:** Displays probiotics such as *Lactobacillus* and *Bifidobacterium*, which enhance the immune system, improve gut barrier function, and sleep via modulating the production of short-chain fatty acids (SCFAs), 5-hydroxytryptamine (5-HT) and gamma-aminobutyric acid (GABA). Arrows point to the effect of sleep improvement. **Prebiotics section:** Contains inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), polydextrose (PDX), etc., which can provide nutrients for gut

probiotics and promote gut microbiota balance. **FMT section:** Illustrates the process of fecal microbiota transplantation (FMT). Arrows indicate enhanced sleep efficiency and quality, reduced anxiety, and suppressed depression, indicating its positive effects on overall health. **WMT section:** Washed microbiota transplantation (WMT) involves microbial refinement and separation processes, facilitating precise and personalized treatments. Arrows reflect the GM, indicating its modulatory effects on the microbiota. **Dietary patterns section:** Includes the Mediterranean diet, plant-based diets, and dietary fiber intake, which maintain gut health and improve sleep quality. **Meal timing section:** Features factors such as nighttime eating and breakfast omission influence the microbiota-gut-brain axis (MGBA), affecting gut and sleep health, reflecting the interplay between meal timing, gut health and brain function.

7.1. Biomarker Discovery for Insomnia Diagnostics

Population-based studies have reported that GM dysfunction, such as increased *Bacteroidetes phylum* [429], *Bacteroides* and *Clostridiales* [430], may serve as biomarkers for identifying insomnia patients or differentiating between different insomnia types [431]. Specific gut bacteria, such as *Faecalibacterium* [117, 202, 432] and *Bifidobacterium* [433-435] have been associated with improved sleep quality. A previous study reported that *Prevotella* may be a biomarker of poor sleep quality [436]. SD elevates LPS levels, activates the TLR4/NF-κB pathway and reduces the abundance of SCFAs-producing bacteria [340], linking microbial metabolites like LPS and SCFAs to insomnia diagnosis and treatment evaluation. Changes in serum zonulin levels significantly contribute to the pathology of insomnia and may serve as a clinical biomarker for this condition [437]. Recent research has increasingly focused on emerging metabolites that act as critical mediators within the GBA, linking microbiota alterations to the systemic effects of insomnia. For instance, DCA has been shown to induce intestinal inflammation and dysbiosis by triggering oxidative stress in the intestinal epithelium and promoting the release of pro-inflammatory cytokines. These mechanisms closely mirror those observed in conditions of short sleep duration or SD highlighting DCA's potential as a biomarker for SD [408]. Similarly, hypoxanthine—a key intermediate in purine metabolism—was found to be significantly elevated in both the serum and hypothalamus of SD mice. hypoxanthine is strongly associated with oxidative stress and ROS accumulation SD-induced. Importantly, its levels can be reversed with appropriate intervention, demonstrating both sensitivity and reversibility to SD, and thus positioning hypoxanthine as a promising and reliable biomarker for SD [438].

As research into the relationship between GM and sleep health continues to advance, non-invasive diagnostic methods (e.g., fecal testing) are increasingly developed to monitor gut health of insomnia patients regularly. The application of bioinformatics techniques and 16S rRNA sequencing (e.g., scatter metagenomics and metabolomics) may help to identify key microbial species, changes in the abundance and metabolite levels in the gut. Utilizing novel machine learning algorithms (e.g., random forests and neural networks) may help to mine sleep-related data to train models and develop GM-based diagnostic and therapeutic models for insomnia disorders.

7.2. Medicine-food Intervention: Probiotics and Prebiotics

Conventional probiotics, primarily *Lactobacillus* and *Bifidobacterium* species, have been shown to modulate the host's immune system, protect against physiological stress, antagonize pathogens and improve

the intestinal epithelial barrier function [439], as well as regulate GM by secreting several beneficial metabolites (e.g., SCFAs, 5-HT, GABA) which enhance the sleep quality [440]. However, newly discovered probiotic strains offer significant potential for personalized interventions, underscoring the need to move beyond conventional strains and actively explore novel functional variants. Strain-level diversity is a critical consideration in probiotic selection, as different strains within the same species can exhibit distinct metabolic activities, immunomodulatory effects, and other functional properties. This emphasizes the importance of precise strain selection to achieve optimal health outcomes [441]. For example, *Lacticaseibacillus paracasei* K56, a novel probiotic strain isolated from the gastrointestinal tract of healthy infants in China, has been demonstrated to be safe for consumption [442]. A two-week intervention with L. *paracasei* K56 effectively alleviated stress and significantly improved symptoms of anxiety and insomnia. These benefits were likely mediated by an increased abundance of beneficial bacteria, including *Lacticaseibacillus* and L. *paracasei*, alongside elevated butyrate levels, while suppressing pathogenic bacteria such as *Shigella* and *Escherichia coli* [442]. Additionally, supplementation with *Bifidobacterium animalis subsp. lactis* BLa80 led to a notable reduction in the abundance of *phylum Proteobacteria* and an increase in *Bacteroidetes*, *Fusicatenibacter*, and *Parabacteroides*. Importantly, this intervention also enhanced the production of GABA, a key neurotransmitter associated with improved sleep quality [443]. A study by Zheng et al. [444] demonstrated that oral multi-strain probiotic preparations (SLAB51) suppressed oxidative damage, peripheral and brain inflammation caused by SD. *Lactobacillus brevis* DL1-11 is a strain that generates large amounts of GABA, and Yu et al. [445] demonstrated high doses of GABA-fermented milk extended sleep time, shorten sleep latency and improve sleep in mice by modulating the GM composition and increasing the relative abundance of SCFA-producing species. *Bifidobacterium breve* CCFM1025 may enhance sleep quality in individuals with insomnia by modulating HPA axis activity and regulating arousal behavior [446]. Of note, the efficacy of probiotics varies among individuals, influenced by factors such as health status, GM composition, dietary patterns, and lifestyle [439].

Prebiotics are indigestible compounds that selectively stimulate the growth or activity of specific GM with the aim of maintaining the host's health. Prevalent prebiotics comprise dietary fibers, inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS) and polydextrose (PDX) [447]. These prebiotics and their associated metabolites act on gut-associated epithelial cells and systemic immune cells, regulating immune responses and maintaining gut barrier function via G protein-coupled receptor-mediated pathways, HDAC inhibition, inflammasomes and Toll-like receptors [448]. Moreover, prebiotic diet was found to improve stress-induced dysregulation of neuroactive metabolites in the gut resulting in improved sleep quality by modulating various gut microbial metabolites (SCFAs, SBA, steroids, nucleotides) [449]. Colombo et al. [450] reported that infants consuming the formula containing prebiotics (PDX and GOS) regulated the sleep-wake patterns, improved sleep quality and sleep cycles, probably by increasing the production levels of butyrate-producing bacteria such as *Bifidobacterium* and *Lachnospiraceae*. Thompson et al. [451] fed GOS/PDX prebiotics to mice following stress or SD and found improvements in NREM and REM sleep

quality, stabilization of GM α-diversity and circadian rhythms. Moreover, Chung et al. [452] demonstrated that administration of a mixture of short-chain GOS and long-chain FOS (9:1) into SD mice improved the adverse effects of SD on gut physiology, neuropsychological function, inflammation, circadian rhythms and motor ability, while significantly modulating glucose tolerance to improve blood glucose homeostasis.

In conclusion, although probiotic and prebiotic supplementation can improve sleep via GM modulation, its efficacy is limited by the low colonization efficiency, poor survival rates, and high interindividual heterogeneity. A recent study proposed a novel precision medicine–food paradigm to overcome these challenges: (1) targeting key microbial metabolites, (2) enhancing beneficial microbe survival and colonization through advanced targeted delivery technologies, and (3) utilizing artificial intelligence (AI) and machine learning (ML) to integrate multi-omics data, thereby enabling microbiome functional analysis and guiding personalized interventions [453]. This innovative strategy holds significant clinical potential, particularly in managing and preventing chronic diseases such as insomnia, by offering personalized regimens based on an individual's GM function and metabolic capacity. Moreover, it has profound public health implications, as it could revolutionize the approach to chronic disease management through precision nutrition and functional foods. By addressing the limitations of traditional interventions, this paradigm lays the foundation for future therapeutic advancements, providing a critical step toward personalized health solutions and improving population health outcomes.

7.3. Microbiota Transplantation

Fecal Microbiota Transplantation (FMT) can restore the balance of GM in recipients and can potentially treat diseases associated with microbial dysbiosis [454]. A study by Fang et al. [433] suggested that FMT could treat adult chronic insomnia. By using the PSQI subscales, FMT markedly improves insomnia by diminishing sleep start latency, increasing sleep efficiency, and alleviating daytime fatigue symptoms. In non-insomniac patients administrated with FMT, it was observed that their sleep quality was significantly improved [433]. Evidence indicates that FMT can relieve anxiety and depression symptoms in CID patients which improves quality of life, and these effects are positively correlated with increased abundance of beneficial microbiota such as *Bifidobacterium*, *Lactobacillus*, *Turicibacter* and *Fusobacterium* [433]. Washed Microbiota Transplantation (WMT) is an advancement of FMT technology, which utilizes intelligent fecal bacterial separation system to isolate, wash and purify microbiota from healthy donor feces. This approach significantly reduces FMT-related adverse effects [455]. Li et al. [456] found that WMT improved sleep quality in patients with inflammatory bowel disease (IBD), achieving good effects in patients who had poor baseline PSQI scores. He et al. [457] observed that WMT could significantly enhance sleep quality and overall quality of life in SD patients, and the benefits improved with the duration of the treatment course. Furthermore, WMT modulated dysbiosis in SD patients by increasing the levels of *Bifidobacterium*, *Prevotella 7*, *[Ruminococcus] gnavus group* and *Faecalibacterium*, while reducing the relative abundance of *Escherichia-Shigella* and *Streptococcus*.

Currently, few studies have investigated the effect of microbiota transplantation on insomnia. Many of them focus on comorbid conditions rather than insomnia itself. Data indicate that microbiota transplantation can potentially treat sleep disorders. However, its clinical application is limited by procedural complexities and implementation barriers. The emergence of WMT technology has enabled researchers to employ microbiota transplantation, but additional studies are needed to enhance its effectiveness and safety. In addition, strategies for matching appropriate recipients and donors need to be further explored.

7.4. Functional Nutrition and Food-Based Strategies for Insomnia Management

7.4.1 Chrono-nutrition and Diet-Based Therapies

Nutritional pathways, shaped by dietary patterns and meal timing, regulate sleep through modulation of circadian rhythms, epigenetic mechanisms, and GM interactions [458]. It has been uncovered that the function and structure of GM are influenced by meal timing [419]. For instance, skipping breakfast and nighttime eating disrupt metabolic responses, energy balance and sleep cycles, suggesting that nutritional timing is crucial to the overall health and sleep regulation. Mediterranean diet [459] and plant-based diets (e.g., high fiber content, MT and its precursors, low dietary inflammation index) [460] have been associated with good sleep quality and reduced insomnia symptoms. Increased dietary fiber intake enhances the production of prebiotics and SCFAs, which mitigate sleep disorders associated with circadian rhythm disruption by strengthening the gut barrier, promoting sleep-related cytokine secretion, suppressing inflammatory pathways, and increasing serotonin levels [461]. Apart from general dietary patterns, specific functional foods and food-derived herbal medicines have shown good potential to improve sleep outcomes. The following section systematically categorizes and summarizes medicinal edible fungi, dietary micronutrients and natural supplements, edible plants, and traditional Chinese herbal medicines.

7.4.2 Medicinal Edible Fungi with Sleep-Promoting Effects

Multiple medicine food homology-derived fungi can improve sleep by regulating neurotransmitters, anti-inflammatory and antioxidant pathways, and GM homeostasis. *Cordyceps militaris* contains multiple bioactive compounds. For example, N6-(2-hydroxyethyl) adenosine upregulates GABAA α1 and 5-HT1A gene expression. *C. militaris* polysaccharides and total flavonoids regulate the balance of neurotransmitters in the brain, thereby prolonging sleep duration [462]. Cordycepin enhances θ-wave activity during NREM sleep via non-specific adenosine receptor activation, to promote sleep onset [463]. Triterpenes in *Ganoderma lucidum* (e.g., lucidenic acid D) downregulate COX-2 and iNOS expression, inhibit IL-6, TNF-α, and NO production, and consequently improve sleep quality [464]. *G. lucidum* polysaccharides may prolong NREM sleep by upregulating TNF-α expression [465] or enhancing GABAergic and serotonergic neurons [466]. In *Poria cocos*, the active compound pachymic acid increases intracellular chloride levels, GAD65/67 protein expression, and GABAA receptor subunit levels in hypothalamic neurons, which activates GABAergic pathways to regulate sleep architecture [467]. *P. cocos* acidic polysaccharides can improve GM dysbiosis and exert sedative effects by regulating metabolic pathways such as linoleic acid and α-linolenic acid. Furthermore, ergosterol in *P. cocos* promotes IL-1β and TNF-α secretion, enhancing the NREM sleep [13]. *Hericium erinaceus* contains *H.*

erinaceus mycelium extract and erinacines A/C, which exert sedative and neuroprotective effects by restoring DA levels [468] and increasing the pro-BDNF/BDNF ratio [469]. *Armillaria mellea* promotes sleep via inhibiting inflammation and oxidative stress. Specifically, it reduces MDA, TNF-α, IL-1β, and IL-6, while upregulating the GSH-Px and SOD expression level [13]. It also modulates the expression of GAD67 and 5-HT1A/2A receptors to maintain neurotransmitter homeostasis, while simultaneously restoring the gut microbial ecosystem in insomniac rats [470].

7.4.3 Natural Dietary Supplements and Micronutrients

Multiple natural dietary components have been shown to improve sleep quality and alleviate insomnia symptoms by regulating neurotransmitters, hormone levels, and the neuroendocrine system. Trp, an essential amino acid，serves as a precursor of 5-TH and MT, and participates in the regulation of the circadian rhythm by promoting MT synthesis. Foods rich in Trp include meat, dairy products, poultry, eggs, as well as plant-based foods like legumes and nuts [12]. Additionally, MT-rich foods, such as tart cherries, grapes, bananas, nuts, and oats, can induce natural sleep and maintain stable sleep-wake rhythms [471]. L-theanine, a non-proteinogenic amino acid found in the leaves of the tea plant (*Camellia sinensis*), is absorbed into the bloodstream and crosses the BBB, where it modulates the levels of various neurotransmitters—including DA, 5-TH, Glu, and GABA. It shortens sleep latency, alleviates daytime dysfunction, and improves overall sleep quality [472]. Vitamin D regulates sleep–wake rhythms by acting on sleep-related brain regions such as the hypothalamus. It also upregulates the expression of TPH-2, thereby promoting the conversion of Trp to serotonin and indirectly increasing MT levels [473]. Evidence indicates that vitamin D deficiency can increase the risk of sleep disorders [474]. Magnesium promotes the production and release of GABA and MT [475]. It also reduces cortisol levels by regulating the HPA axis, thereby alleviating stress and improving sleep [476]. Good dietary sources of magnesium include leafy green vegetables, almonds, dairy products, seeds, and whole grains. These natural supplements offer complementary strategies for improving sleep.

7.4.4 Edible Plants with Sleep-Promoting Phytochemicals

Various edible plants contain bioactive compounds that modulate neurotransmitter systems, receptor activity, and neurochemical signaling pathways to influence sleep. For instance, Daylily (*Hemerocallis citrina* Baroni, HC) contains flavonoids, phenolic acids, and amino acid derivatives, which improve sleep by regulating neuroactive ligand–receptor interaction pathways [477]. Lotus (*Nelumbo nucifera* Gaertn.) rhizomes, leaves, and seeds can promote sleep and may serve as functional foods for sleep enhancement. Active constituents such as quercetin-3-O-glucuronide and alkaloids from lotus leaves [478], and those in lotus seeds, including GABA, L-tryptophan, and alkaloids [479], can enhance central inhibitory signaling by binding to GABAA receptors. Lettuce (*Lactuca sativa* L.) contains dietary fiber, vitamins, and sleep-promoting phytochemicals. Its sedative effects are mainly caused by sesquiterpene lactones, such as lactucin and lactucopicrin, which act on GABAA receptors. A new lettuce variety rich in lactucin, Heukharang, upregulates the expression of GABAA receptor subunits and adenosine A1 receptors, demonstrating improved sleep quality in both animal models [480] and clinical trials [481]. Rosmarinic acid, the primary active

component of Rosemary (*Rosmarinus officinalis*), is a phenolic acid that modulates the GABAergic system [482]. It also functions as an adenosine A1R agonist, reducing neuronal activity in wake-promoting brain regions while enhancing sleep-promoting regions [483]. Chamomile (*Matricaria chamomilla* L.) contains flavonoids (e.g., apigenin, luteolin, quercetin) and terpenoids (e.g., chamazulene, bisabolol) with known effects on sleep, likely via GABAA receptor binding and antioxidant properties. Chamomile infusion is also rich in MT, which promotes natural sleep rhythms [484]. These edible plants exhibit natural and safe potential for sleep regulation through multi-target and multi-mechanism synergistic actions, highlighting their promising value as candidates for the development of sleep-promoting functional foods.

7.4.5 Chinese Herbal Medicines with Sleep-Promoting Effects

Numerous traditional Chinese herbal medicines and their active constituents possess strong sedative–hypnotic effects owing to their ability to modulate neurotransmitters, receptor expression, neuroendocrine signaling, and inflammatory pathways. Turmeric (*Curcuma longa*) contains curcuminoids (curcumin, demethoxycurcumin, and bisdemethoxycurcumin), which can shorten sleep latency and prolong NREM sleep duration by inhibiting histamine H1R [485]. The total saponins and purified saponins extracted from *Liriope spicata* Lour. exert sedative–hypnotic effects by increasing the expression of serotonergic and GABAergic neurons and modulating immune-inflammatory processes [486]. *Lilium davidii* (genus *Lilium*, family Liliaceae) improves insomnia symptoms by modulating GM, hypothalamic neurotransmitters, MT levels, and HPA axis homeostasis. Saponins, characteristic constituents of the *Lilium* genus, are considered the primary active components responsible for insomnia-relieving effects [487]. Studies have shown that total saponins extracted from *L. lancifolium* and *L. brownii* can prolong sleep duration in mice induced by pentobarbital sodium [488]. Tenuifolin, one of the major active saponins isolated from Yuan Zhi (*Radix Polygalae)*, exerts sedative–hypnotic effects by decreasing NE expression and increasing GABA and Ach production [489]. Suanzaoren (*Semen Ziziphus Spinosae*, ZSS) contains various bioactive compounds, including jujubosides A/B, flavonoids (e.g., spinosin), ZSS oil, and alkaloids (e.g., sanjoinine A), all of which exhibit sleep-enhancing pharmacological activities. These effects may be mediated through the modulation of both serotonergic and GABAergic systems, including receptor binding and upregulation of receptor subunit expression [490, 491]. *Schisandra chinensis* Fructus (Schisandra) is rich in phenolic lignans, including Schisantherin A (STA), Schisantherin B (SchB), and Gomisin N. Among them, STA and SchB promote the activity of GABAergic system in the cerebral cortex, hippocampus, and hypothalamus, thereby shortening sleep latency and prolonging sleep duration [492, 493]. Gomisin N appears to modulate both serotonergic and GABAergic systems and synergizes with 5-hydroxytryptophan [494]. Ginseng can regulate sleep owing to its ginsenosides. Ginsenoside Rg1(Rg1) regulates the noradrenergic system in the locus coeruleus and the serotonergic system in the dorsal nucleus of the midbrain, thereby prolonging total sleep time in rats [495].

Collectively, these data show that functional nutrition and food-based strategies offer promising, non-invasive alternatives for managing insomnia. Compared to pharmacological interventions, these approaches have few side effects and target multiple processes, including modulation of GM, neurotransmitter

systems, circadian rhythms, and inflammatory signaling. The synergistic action of multiple bioactive components—particularly in edible fungi, traditional herbal medicines, and plant-based foods—highlights the importance of dietary complexity and food matrix effects in sleep regulation. However, although several preclinical studies provide evidence to support their benefits, clinical translation needs to be clarified. Future research should conduct rigorously designed, placebo-controlled human studies, and adopt systems biology approaches to elucidate the host–microbiota–neuroendocrine interactions underlying sleep regulation.

8. Conclusions

In conclusion, this review comprehensively elucidates the intricate bidirectional relationship between insomnia and GM via the GBA, revealing multiple mechanisms through which insomnia disrupts GM composition and function, subsequently impairing CNS function. As a chronic stressor, insomnia primarily exerts its impact through hyperactivation of the HPA axis, immune dysregulation, neurotransmitter imbalance, and impaired anti-inflammatory signalling via the VN. These neuroendocrine and immune alterations directly affect the CNS while indirectly inducing GM dysbiosis through multiple pathways. Specifically, insomnia reduces the abundance of beneficial bacteria—such as *Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*, and *Akkermansia*—while promoting the proliferation of pathogenic taxa including *Proteobacteria*, *Klebsiella*, *Shigella*, and *Escherichia coli*. These microbial shifts disrupt metabolic and immune homeostasis within the gut microenvironment, leading to impaired intestinal barrier function, reduced mucus secretion, aberrant microbial metabolite profiles, and increased systemic inflammation. Consequently, these disturbances deteriorate gut health and perpetuate a vicious cycle of insomnia through ongoing neuroinflammatory feedback.

Recent evidence demonstrates that GM influences CNS function primarily through production of bioactive metabolites, neurotransmitter synthesis, BAs metabolism, and immune modulation, each contributing to regulation of sleep–wake cycles and cognitive processes. Among these, SCFAs cross the BBB to inhibit neuroinflammation, regulate synaptic plasticity, and maintain neuronal homeostasis, thereby exerting neuroprotective effects. GM is also essential for the formation of SBAs, which interact with bile acid receptors such as TGR5 and FXR to regulate intestinal and neuroinflammation, maintain BBB integrity, and modulate synaptic plasticity. Neurotransmitters influenced by GM metabolism directly regulate CNS neuronal activity via the VN, blood circulation, or receptor binding, thus impacting sleep and mood. The VN transmits gut signals—including chemical, immune, and endocrine cues—that modulate CNS function by reducing HPA axis activation and enhancing BDNF expression, ultimately improving sleep quality. Notably, this review further highlights how insomnia-induced GBA dysregulation exacerbates metabolic disorders and cognitive impairment. GM dysbiosis disrupts energy metabolism, contributing to insulin resistance, obesity, and chronic inflammation, while also impairing liver lipid metabolism and immune responses through gut-liver axis dysfunction. The alterations in microbial metabolites exacerbating hepatic fat accumulation, inflammation, and fibrosis. Concurrently, GM alterations trigger oxidative stress, neuroinflammation, and

neurotransmitter imbalances, impairing synaptic plasticity and cognitive function. Together, these processes form a self-reinforcing cycle linking insomnia, dysbiosis, metabolic dysfunction, and cognitive decline.

Despite these insights, significant contradictions persist in current research due to heterogeneity in study design, analytical methods, and populations studied. Conflicting findings regarding the F/B ratio and the abundance of specific bacterial taxa emphasize the urgent need for standardized, large-scale, multi-omics investigations. Advances in culture and sequencing technologies, coupled with a deeper understanding of human GM, have expanded the probiotic repertoire beyond conventional *Lactobacillus* and *Bifidobacterium* species to include next-generation probiotics such as *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis*, and *Bacteroides fragilis*. This review also highlights newly identified strains and metabolites—such as *Lacticaseibacillus paracasei* K56 and *Bifidobacterium animalis subsp. lactis* BLa80—which exhibit sleep-modulating effects and underscore the critical importance of strain-specific probiotic selection. Moreover, microbial-derived DCA and hypoxanthine have emerged as promising biomarkers for sleep disorders, offering novel targets for insomnia diagnosis and therapeutic intervention. These advancements lay the groundwork for more effective microbiota-targeted interventions in clinical practice.

The integration of microbiota-based therapies into clinical practice offers a promising approach for managing insomnia and related disorders. Current treatments for insomnia primarily rely on pharmacological options, which often come with significant side effects such as dependence and tolerance. In contrast, microbiota-based interventions, including probiotics, prebiotics, and microbiota transplantation, target the root cause of insomnia—dysbiosis—providing a potentially safer and more sustainable alternative. However, to ensure the effective application of these therapies in clinical practice, several challenges must be addressed. Standardized research protocols, rigorous clinical trials across diverse populations, and comprehensive long-term safety evaluations are essential steps in establishing these microbiota-based interventions as mainstream interventions. Recent research highlights the potential for profound clinical transformation through microbiota modulation, with significant public health implications. Insomnia is a global epidemic that contributes to the increasing risks of chronic metabolic diseases such as T2DM and obesity. Restoring microbiota balance through targeted therapies could reduce the prevalence and severity of these comorbidities, leading to better overall health outcomes. Moreover, improving sleep quality via microbiota modulation may enhance cognitive function and delay the onset of neurodegenerative diseases. Therefore, incorporating microbiota-targeted therapies into public health strategies could play a pivotal role in alleviating the growing burden of chronic diseases associated with insomnia.

The emerging paradigm of "Targeted Metabolites - Empowered Delivery - AI Navigation" represents the future of precision medicine-food interventions. This approach combines AI-driven microbiome profiling to create personalized treatment plans that dynamically adapt to the patient’s unique microbiome, circadian rhythms, and metabolic needs. By targeting key microbial metabolites and utilizing advanced delivery technologies, these therapies optimize the GBA, improving sleep quality. Additionally, these technologies

help overcome challenges such as poor colonization efficiency and interindividual variability of traditional probiotics and prebiotics, thereby enhancing the colonization competitiveness and functional expression of beneficial strains, ultimately improving the efficacy of microbiota-based interventions. AI and ML are central to this process, enabling personalized interventions by integrating multi-omics data to identify the specific microbial strains and metabolites that regulate CNS function and sleep, thereby optimizing microbiota modulation for each individual.

Food-based therapies, particularly functional foods and herbal medicines, represent another innovative approach for insomnia management. Chrono-nutrition strategies, such as timed dietary interventions and light therapies, aim to restore circadian rhythms and improve sleep quality. Additionally, certain medicinal edible fungi and dietary supplements, like Cordyceps militaris, Ganoderma lucidum, and L-theanine, have shown promising results in improving sleep by regulating neurotransmitters, exhibiting anti-inflammatory effects, and restoring GM homeostasis. These foods modulate the GABAergic and serotonergic systems, both essential for sleep regulation, providing an additional tool for managing insomnia.

Innovations such as intelligent delivery systems, multi-omics AI models, and personalized functional foods will improve the precision management of insomnia and related comorbidities while driving the modernization of traditional medicine and advancing precision nutrition. These therapies offer scalable solutions to address public health challenges by reducing reliance on traditional pharmacological treatments. Future clinical trials should focus on rigorous, placebo-controlled studies to validate the efficacy of these therapies and explore their potential for widespread clinical adoption. This integrated approach has the potential to revolutionize chronic disease management, providing sustainable solutions to improve population health and long-term wellness.

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Declaration of competing interest

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

Data availability statement

All other data is contained within the main manuscript and supplemental files.

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