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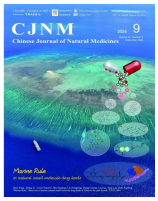
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Review

The therapeutic potential of saponins for neurological diseases *via* the gut-brain axis

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ABSTRACT

Neurological diseases (NDs) constitute a significant threat to global health and impose considerable economic burdens on society due to their complex etiology, poor prognosis, and chronic course. In recent years, significant research has highlighted the intricate connection between gut-brain axis (GBA) dysfunction and various NDs. The GBA facilitates bidirectional interactions linking the gastrointestinal (GI) tract and nervous system, preserving brain health through modulation of intestinal equilibrium, neural networks, and neuroendocrine, immune, and inflammatory pathways. Saponins, essential bioactive constituents in Traditional Chinese Medicine (TCM), have demonstrated substantial neuroprotective capabilities. Extensive studies indicate that saponins effectively prevent and manage NDs by influencing pivotal mediators within the GBA. Consequently, the GBA has emerged as a promising therapeutic target for saponins in neuroprotection. This review summarizes the interplay between the GBA and NDs and emphasizes recent findings on saponins as potential therapeutic agents targeting this axis, aiming to provide novel perspectives and therapeutic approaches for NDs.

1. Introduction

Neurological diseases (NDs) significantly affect human health and are characterized by symptoms such as impaired consciousness, cognitive decline, abnormal sensory functions, and motor dysfunction. These diseases have high mortality and disability rates, and studies have indicated an increasing annual incidence, with a notable trend toward younger populations [1], NDs include stroke, neurodegenerative disorders, depression, and peripheral neuropathy. Due to their complex etiology, pathogenesis, and diverse clinical manifestations, these diseases are challenging to diagnose and treat. Currently available treatments primarily include medication, surgery, and rehabilitation, which are costly, provide only limited symptom relief, rarely achieve complete recovery, and may cause severe adverse side effects [2]. Therefore, there is significant potential in developing drugs that are multi-targeted, highly effective, low in toxicity, and cost-effective.

Recently, increasing attention has been devoted to the intricate relationship between the gastrointestinal (GI) tract and the brain, particularly through the gut-brain axis (GBA). The GBA represents a complex bidirectional communication network linking the GI tract and the nervous system, primarily involving gut microbiota (GM) and their metabolites, the enteric nervous system (ENS), neuroimmune interactions, neuroendocrine responses, and the central nervous system (CNS) [3]. Substantial preclinical evidence indicates that preserving GBA integrity is essential for sustaining normal nervous system physiology. Notably, research highlights the frequent occurrence of GM dysbiosis in NDs such as multiple sclerosis (MS), Parkinson's disease (PD), and Alzheimer's disease (AD). Such dysbiosis typically induces prolonged inflammatory states, metabolic disturbances, accumulation of toxic compounds, and compromised intestinal barrier integrity [4-7]. Additional findings indicate that interactions between the intestinal ecosystem and the CNS *via* neural, endocrine, and immune routes significantly impact brain function and associated behaviors [8].

Traditional Chinese herbs, characterized by multiple therapeutic targets, minimal adverse effects, and low cost, have been extensively studied as neuroprotective agents. Based on their chemical structure and properties, active components of these herbs include alkaloids, glycosides, essential oils, polysaccharides, and organic acids [9]. Among these, saponins, crucial glycosidic compounds, are widely present in *Panax ginseng*, *Panax notoginseng*, *Glycyrrhiza uralensis*, Radix Bupleuri, *Astragalus membranaceus*, *Paris polyphylla*, and *Anemarrhena asphodeloides*. Based on their aglycone structures, saponins are classified into two primary types: triterpenoid and steroidal saponins. These compounds exhibit a wide range of pharmacological properties, including anti-inflammatory, antioxidant, anti-aging, and antiviral effects [10]. Due to their unique physiological functions, saponins have shown great potential in promoting neurological health [11]. Notably, saponins can cross the blood-brain barrier (BBB) and interact with CNS targets [12]. Specifically, ginsenosides, astragalos-

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ides, and notoginsenosides demonstrate multiple regulatory effects in neuroinflammation, oxidative stress, mitochondrial function, ferroptosis, endoplasmic reticulum stress, BBB integrity, neurogenesis, and angiogenesis. These factors are crucial in the pathophysiology of NDs [12-15].

Saponins are increasingly recognized as potential modulators of the GM. By reshaping the intestinal ecosystem, saponins indirectly affect the brain *via* immune-inflammatory pathways, neurotransmission, and endocrine regulation [16-18]. For example, ginsenosides, key bioactive compounds from *American ginseng,* enhance the diversity and balance of the GM, thus revitalizing the intestinal environment. This modulation helps maintain normal GBA functions, improving cognitive and motor impairments in aging individuals [19]. Similarly, studies have shown that Rb3 reduces cerebral infarct volume, decreases BBB permeability, and alleviates neurological deficits in rats with cerebral ischemia-reperfusion injury *via* GM-dependent mechanisms [20]. Therefore, targeted modulation of the GBA represents a promising therapeutic approach for NDs. However, comprehensive reviews detailing saponins' neuroprotective properties through GBA modulation remain scarce. Thus, this review synthesizes current knowledge regarding key components and regulatory mechanisms of the GBA and clarifies its role and implications in NDs. Additionally, we discuss how saponins enhance neurological health through their impact on the GBA, aiming to provide a comprehensive scientific foundation for future treatments and facilitate broader clinical applications.

2. Methods

Databases searched included PubMed, Google Scholar, Web of Science, and CNKI (up to September 2025). The following keywords were used: "saponins", "triterpenoid saponins", "steroidal saponins", "gut-brain axis", "gut microbiota", "intestinal flora", "microbiota-gut-brain axis", "neurological disorders", "nervous system diseases", "neurodegenerative diseases", "neuroprotection", "short-chain fatty acids", "ginsenosides", "astragaloside IV" and "panaxosides". Articles retrieved were screened according to specific inclusion and exclusion criteria to ensure relevance. Inclusion criteria included: (1) scholarly articles addressing saponins, the GBA, and neuroprotective effects; (2) experimental studies (*in vivo* or *in vitro*) involving saponins and the nervous system. Exclusion criteria included: (1) publications in languages other than English or Chinese; (2) non-peer-reviewed articles; (3) studies on Chinese herbal formulas containing saponins without clearly defined mechanisms of saponin action.

3. Communication mechanisms of the GBA

Communication between the GM and the brain occurs primarily through three interlinked pathways: neural, immune, and endocrine routes. The neural route primarily involves the CNS, vagus nerve (VN), and ENS, establishing a direct and critical connection between the gut and brain. The immune pathway facilitates bidirectional communication between the gut and the nervous system, effectively linking functional changes across these systems [21]. This pathway is particularly crucial, as it mediates the GM's regulation of nervous system functionality and behavioral outcomes [22], immune interactions involve GM engagement with immune cells, altering cytokine profiles that subsequently influence brain physiology [23, 24]. Additionally, the hypothalamic-pituitary-adrenal (HPA) axis, a central neuroendocrine pathway, also facilitates bidirectional gut-brain communication, crucially maintaining systemic homeostasis [25]. Communication between the GM and the HPA axis is intricately linked with the immune system, intestinal barrier, BBB, and both sensory and autonomic nervous systems (ANS) [26] (Fig. 1).

3.1. Neural pathway

The GI tract is unique compared to other peripheral systems because of its extensive intrinsic nervous system. The ENS, a distinct division of the ANS, is distributed throughout the GI tract. It consists of the submucosal and myenteric plexuses, forming a complete neural network within the intestinal wall. Sensory neurons respond to chemical signals released by the GM or intestinal cells. These neurons subsequently regulate neural signaling or directly activate afferent axons. The ENS maintains a long-term bidirectional interaction with the GM [27]. Changes in GM composition can affect ENS development, activity, and function, including neuronal density and proportions [28]. Additionally, the ENS regulates GI motility patterns, secretion, nutrient absorption, and maintains GM homeostasis [29].

The VN is a critical component linking the ENS and serves as the most direct communication route between the gut and the brain [30]. It rapidly transmits signals bidirectionally between these two regions. Both food ingestion and changes in GM composition can be detected by afferent VN fibers, influencing perceptions such as appetite and mood. Conversely, efferent VN fibers transmit commands from the brain, regulating digestive and absorptive functions in the GI tract [31]. Research using a rat model of *Salmonella*-induced emotional disorders demonstrated that VN transection blocked neural signals transmitted to the brain by *Salmonella*. This significantly reduced neuronal activation in the amygdala and solitary nucleus, alleviated inflammation in both the gut and brain, and reduced anxiety-like behavior [32]. Moreover, VN signals can alter cholinergic tone, modulate GI mucosal inflammation, and activate immune responses, facilitating the interaction between immune and nervous systems [33].

Effective communication between the gut and brain *via* the ENS relies on the close relationship between the ENS and GM. Neurotransmitters or neuromodulators produced by GM act as essential signaling molecules for the ENS, playing a crucial role in gut-brain communication [34]. Short-chain fatty acids (SCFAs), which are extensively studied GM metabolites, influence gut-brain communication through both direct and indirect pathways. On one hand, SCFAs regulate the secretion of neurotransmitters such as 5-Hydroxytryptamine (5-HT) and glucagon-like peptide-1 (GLP-1), indirectly stimulating VN or ENS neurons [35]. On the other hand, SCFAs bind directly to FFAR2/3 receptors on VN cells, influencing neural signaling along the VN [36]. These mechanisms provide pathways through which microbial metabolites can affect brain activity.

3.2. Immune pathway

Stable functioning of the CNS relies on immune cell regulation. Resident immune cells, including microglia, innate immune cells, and adaptive immune cells, defend against brain infections and damage through phagocytosis, antigen presentation, cytokine production, and inflammatory responses, while also promoting neuronal plasticity [22]. Peripheral immune cells also significantly regulate CNS immunity. The CNS, which has limited circulation of blood-derived immune cells, is particularly susceptible to cytokine network dysregulation. Such dysregulation critically impacts the differentiation of neurons, oligodendrocytes, and astrocytes, and is essential for maintaining CNS homeostasis [37]. The GM regulates the maturation and function of CNS-resident immune cells and peripheral immune cell activation, thereby modulating neuroinflammation, neurological injury, autoimmunity, and neurogenesis [22].

In germ-free (GF) mice, studies showed alterations in microglial activation-related genes, with impaired maturity and morphology. Further experiments demonstrated that GF mice exposed to the toll-like receptor 4 (TLR4) agonist lipopolysacchar-

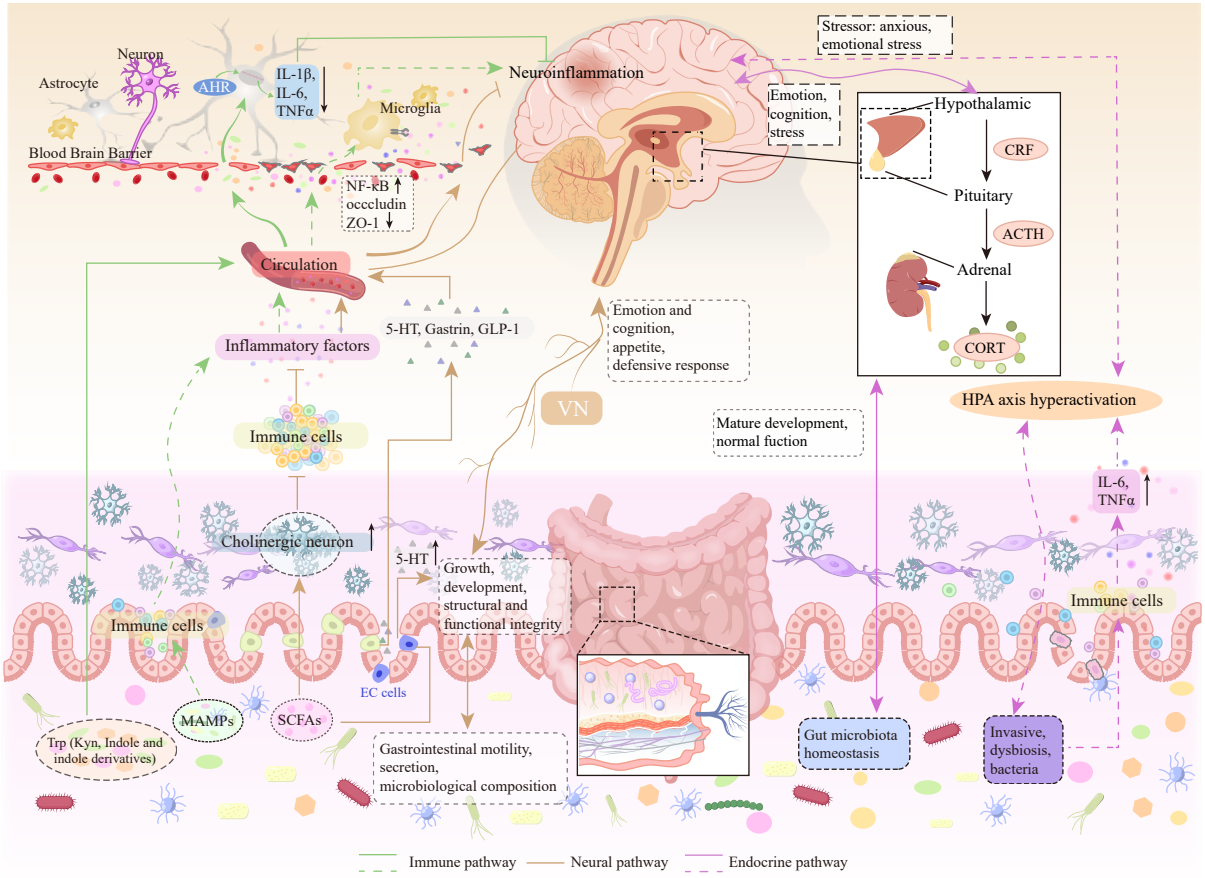


Fig. 1 The bidirectional communication pathways of the GBA. The gut communicates with the brain through three parallel and interacting pathways. Specifically, the neural pathways, primarily composed of the CNS, VN, and ENS, serve as the primary direct connection between the brain and the gut. On one hand, GM homeostasis supports the development, structure, and functional integrity of the ENS. On the other hand, the CNS transmits signals *via* the VN to regulate the ENS, thereby exerting remote influence on the GM. Similarly, the ENS perceives signals transmitted from the gut and conveys them *via* the VN or humoral pathways to the CNS. Additionally, neural pathways can interact with immune pathways, transmitting the metabolic state of the GM to the CNS *via* the bloodstream. Immune pathways: GM and its metabolites can regulate immune responses. For example, intestinal tryptophan metabolites regulate astrocyte activity by activating the AHR to limit inflammation in the CNS. Meanwhile, MAMPs, which are extensively present within the intestine, initiate host immune responses, resulting in the secretion of abundant pro-inflammatory cytokines. These cytokines enter systemic circulation, traverse the BBB, and stimulate microglia to adopt an M1 polarization state, thereby exacerbating neuroinflammation. In the neuroendocrine context, the HPA axis serves as the primary neuroendocrine regulatory system. Upon perceiving stress, the brain activates the HPA axis, prompting secretion and systemic release of hormones such as CRF, ACTH, and CORT. These hormones subsequently modulate GI functionality. Simultaneously, intestinal microbiota equilibrium is essential for proper HPA axis functioning, preventing its excessive activation and providing feedback to the brain *via* the axis's negative regulatory mechanisms. Disruption of intestinal homeostasis through increased permeability, inflammatory responses, or microbial toxins can overstimulate the HPA axis, resulting in emotional stress and anxiety mediated by cerebral mechanisms. Furthermore, the excessive release of cortisol (CORT) from the HPA axis can further damage the intestinal barrier and exacerbate dysbiosis, creating a vicious cycle. Abbreviations: AHR, aryl hydrocarbon receptor; ZO-1, zonula occludens-1; 5-HT, 5-hydroxytryptamine (serotonin); GLP-1, glucagon-like peptide-1; VN, vagus nerve; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; CORT, cortisol; HPA axis, hypothalamic-pituitary-adrenal axis; EC cells, enterochromaffin cells; SCFAs, short-chain fatty acids; MAMPs, microbe-associated molecular patterns; Trp, tryptophan; Kyn, kynurenine.

ide (LPS) displayed disrupted cytokine and chemokine pathways in microglia, resulting in defective innate immune responses [38]. Additionally, tryptophan, a microbiota-derived metabolite, regulates astrocyte activity by activating the aryl hydrocarbon receptor (AHR) to limit CNS inflammation. In an experimental autoimmune encephalomyelitis (EAE) mouse model, antibiotic ampicillin treatment reduced AHR agonist levels and increased EAE severity, whereas supplementation with tryptophan metabolites or tryptophanase (both natural AHR ligands) reduced CNS inflammation and improved EAE outcomes [39]. TH17 cells represent key pathogenic cells in MS. Animal studies revealed that brain autoimmunity-triggering effector TH17 cells originate from the gut, findings validated also in humans. Further studies showed that gut TH17 responses negatively correlated with *Prevotella* abundance in the human small intestine, suggesting that *Prevotella* may be a critical regulator of neuroinflammation in MS [40]. Microbe-associated molecular patterns (MAMPs), evolutionarily conserved microbial structures from bacteria, viruses, fungi, and parasites, are recognized by the host innate immune system, initiating immune responses characterized by extensive pro-inflammatory cytokine release. These cytokines cross the BBB through dedicated transport systems, activating glial populations, notably microglia. Such activations alter normal cellular functions and potentially precipitate neurological damage [41].

3.3. Endocrine pathway

The HPA axis is a critical neuroendocrine system that responds to stress *via* endocrine neurons located in the paraventricular nucleus (PVN). These neurons secrete corticotropin-releasing factor (CRF) and vasopressin (VP), which stimulate adrenocorticotropic hormone (ACTH) release from the pituitary, thereby driving glucocorticoid (primarily cortisol) production from the adrenal cortex. Glucocorticoids complete a negative feedback circuit to regulate the stress response and modulate essential functions, including digestion, immunity, and energy metabolism [42]. The GM significantly influences HPA axis regulation, with microbial colonization during early life profoundly affecting HPA axis development and maturation [43]. Studies have shown that supplementation with *Bifidobacterium* probiotics alleviates HPA axis dysfunction in obese mouse models induced by high-fat diets, normalizing corticosterone (CORT) levels and reversing the decrease in hippocampal glucocorticoid receptor (GR) levels [44]. The absence of GM results in HPA axis hyperactivity in

stressed rats, characterized by elevated serum CORT, increased hypothalamic CRF mRNA expression, and reduced hippocampal GR mRNA levels [45]. Elevated CORT levels have been demonstrated to impair hippocampal structural integrity, promote oxidative stress, and aggravate anxiety-depressive behaviors in animal studies [46, 47]. A notable inverse relationship exists between CORT and 5-HT concentrations, although the specific regulatory mechanisms involved remain poorly understood [48]. Primarily synthesized by intestinal enterochromaffin cells and GM from dietary tryptophan, 5-HT significantly influences immune regulation, inflammatory responses, GI sensory-motor functions, behavioral patterns, and sleep cycles. Disruptions in 5-HT homeostasis contribute notably to anxiety and depressive disorders [49, 50]. Consequently, gut-derived signals modulate hormonal secretion through the HPA axis, forming a comprehensive regulatory loop termed the "gut–HPA–brain axis". This axis maintains physiological balance and is implicated in NDs pathogenesis.

Furthermore, research increasingly emphasizes interactions among the GM, immune system, and neuroendocrine mechanisms. Microbial-derived pro-inflammatory substances, such as LPS, activate TLR4, triggering peripheral and central immune responses, and excessively stimulating the HPA axis, thereby adversely affecting BBB integrity and emotional behaviors [51]. Additionally, the tryptophan metabolic pathway intricately interacts with the neuroendocrine system [52]. The GM converts dietary tryptophan into neuroactive metabolites through three primary pathways: the 5-HT, kynurenine, and microbial indole pathways. Within the 5-HT pathway, tryptophan is sequentially converted to 5-HTP and then to 5-HT. This neurotransmitter communicates gut-derived signals to the CNS through systemic circulation or the VN, indirectly modulating HPA axis activities and adaptive responses within the CNS [53]. Concurrently, the kynurenine pathway begins with the metabolism of tryptophan to kynurenine by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO), generating downstream neuroactive metabolites. Among these, kynurenic acid (KA) serves as an antagonist of both N-methyl-D-aspartate (NMDA) receptors and α7 nicotinic acetylcholine receptors, balancing neuronal excitation and providing neuroprotection. In contrast, quinolinic acid (QA) acts as an excitotoxic agonist at NMDA receptors, causing neuronal damage and apoptosis [54]. Additionally, KA and QA directly affect neurons in the PVN, modulating CRF secretion and influencing HPA axis activation [55]. In the indole pathway, the GM metabolizes tryptophan into indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and other indole derivatives, activating the AHR pathway in astrocytes, increasing tight junction protein expression, enhancing intestinal barrier function, reducing systemic LPS entry, and thus suppressing neuroinflammation and excessive HPA axis activation [39]. Additionally, the GM directly produces neurotransmitters such as gamma-aminobutyric acid (GABA), norepinephrine, and dopamine, which cross the BBB, reaching the CNS and modulating sensory behavior [56]. Overall, these studies demonstrate that communication among GM, the neuroendocrine system, and the brain occurs through diverse direct and indirect mechanisms.

4. GBA in neurological diseases

Previous studies indicate that the GM participates in the pathological processes of most NDs through the GBA, including anxiety and depression, autism spectrum disorder (ASD), schizophrenia, epilepsy, PD, AD, amyotrophic lateral sclerosis (ALS), and MS. Therefore, it is reasonable to consider its role in the progression of various NDs. The following discussion examines the mechanisms underlying the GBA, highlights associated communication mediators involved in the pathophysiology of NDs, and briefly summarizes potential therapeutic approaches targeting the GBA.

4.1. Depression and anxiety

Depression, characterized by persistent low mood, cognitive impairment, and reduced activity, is one of the most common psychiatric disorders worldwide. Nearly 85% of individuals with depression also experience anxiety symptoms, reflecting the frequent co-occurrence of these conditions due to shared genetic and neurobiological factors [57]. Nonetheless, the precise etiology remains unclear. Increasing evidence shows a strong link between GM dysbiosis and the development of depression and anxiety. The underlying mechanisms involve altered metabolism, HPA axis dysregulation, and chronic inflammation [58-60]. Abnormal production and metabolism of SCFAs are closely associated with depression. Reduced SCFA levels result in decreased synthesis and release of monoamine neurotransmitters, including 5-HT and dopamine, which are essential for mood regulation. This reduction represents a key pathogenic pathway in depression [61]. Furthermore, butyrate functions as a potent histone deacetylase inhibitor and exerts antidepressant effects by upregulating neurotrophic factor expression, promoting neurogenesis, and enhancing synaptic plasticity [62]. Acetyl-CoA synthase short-chain family member 2 (ACSS2) has emerged as a novel target for sustained antidepressant responses. Studies indicate that SCFAs markedly increase both cellular and nuclear ACSS2 levels. The ACSS2–peroxisome proliferator-activated receptor gamma (PPARγ)–tryptophan hydroxylase 2 (TPH2) axis may represent a potential mechanism of action [63]. HPA axis dysfunction is also common in depression. Overactivation of the HPA axis elevates cortisol and corticotropin-releasing hormone levels, resulting in excessive glucocorticoid production. This disrupts the function of the medial prefrontal cortex, hippocampus, and amygdala, impairing emotional regulation, learning, and memory, ultimately contributing to depressive symptoms [64]. Furthermore, extensive evidence indicates that inflammation plays a crucial role in the pathogenesis of depression [65, 66]. Inflammatory depression has been identified as a treatment-resistant subtype. GM dysbiosis can lead to the accumulation of pro-inflammatory metabolites and damage to the intestinal mucosal barrier, which intensifies neuroinflammation through immune pathways and drives the pathophysiological processes underlying depression [67].

Currently, medication remains the cornerstone of depression treatment. Selective serotonin reuptake inhibitors represent first-line drugs, while serotonin-norepinephrine reuptake inhibitors are also widely used. However, the clinical efficacy of these medications remains debated. Patients often develop resistance during advanced depression stages, leading to suboptimal outcomes [68]. Nevertheless, microbiome-targeted therapies hold significant potential advantages for depression treatment. Increasing evidence supports microbiome-based therapeutic approaches, including probiotics, dietary interventions, and fecal microbiota transplantation (FMT) [67]. Probiotic supplementation, commonly used clinically, involves strains such as *Lactobacillus* [69], *Bifidobacterium* [70], and *Bacillus* [71]. These probiotics alleviate depressive and anxiety symptoms through mechanisms including improving GM composition, regulating gut SCFAs and neurotransmitter levels, and reducing serum cortisol concentrations. Prebiotics are substrates supporting beneficial gut microorganisms [72], dietary fructooligosaccharides (FOS) and galactooligosaccharides (GOS), serving as prebiotics for beneficial bacteria such as *Bacillus longisporus*, effectively reduce stress-induced CORT release and pro-inflammatory cytokines levels, elevate SCFA concentrations, mitigate stress-induced HPA axis responses, and ultimately improve anxiety and depression-like behaviors in mice [73]. Synthetic biotics produced by combining FOS, GOS, inulin, and probiotics also effectively alleviate depressive and anxiety symptoms in patients with depression, exhibiting greater efficacy than probiotics alone [74]. Postbiotics, non-living microorganisms that

are directly or indirectly beneficial to host health [75], result from microbial fermentation of prebiotics. Thus, postbiotics exhibit effects similar to probiotics, including protecting intestinal barrier integrity, promoting GM homeostasis, inhibiting inflammation, and regulating GBA signaling to alleviate anxiety and depression-like behaviors [76]. However, unlike probiotics, postbiotics avoid issues related to virulence factor absorption and antibiotic resistance gene production [77]. Diet significantly influences GM composition and function. Feeding mice a high-cholesterol diet markedly reduces GM diversity, leading to lipid metabolism disorders, impaired glucose tolerance, increased inflammatory responses in the CNS, and abnormal 5-HT signaling, exacerbating anxiety and depression-like behaviors [78]. Conversely, adherence to healthy dietary patterns, such as the Mediterranean or ketogenic diet (KD), significantly reduces depression risk [79, 80]. Finally, FMT transfers functional microbiota from donors to recipients' GI tracts, rapidly modulating GM [81]. Studies indicate that FMT can alleviate constipation, depressive, and anxiety symptoms by reshaping GM and regulating 5-HT levels [82]. Therefore, regulating GM composition and enhancing GBA function are crucial for preventing and treating depression and anxiety.

4.2. Autism spectrum disorder

ASD is a neurodevelopmental condition characterized by impaired social interactions, communication deficits, and repetitive behaviors. ASD etiology encompasses multifaceted interactions involving epigenetic regulation, immune dysregulation, and environmental chemical exposure [83, 84]. Disruptions or dysfunctions in GM composition have been identified consistently in animal models and clinical ASD populations, signifying frequent comorbidity [85, 86]. Current research strongly supports the hypothesis that altered social behaviors in ASD may be mediated through the GBA. Proposed mechanisms include alterations in GM composition, GM metabolite levels, and VN-dependent pathways, which may influence social deficits in genetic, environmental, or idiopathic ASD models [87]. For instance, in animal experiments, transplanting GM from ASD human donors into GF mice induces characteristic autistic behaviors. Metabolomics analyses further indicated that amino acid metabolism might represent a critical mechanism through which GM regulates behavior. In an idiopathic mouse model of autism, supplementation with taurine and 5-aminovaleric acid (5AV) from conception to adulthood significantly reduced repetitive behaviors and alleviated anxiety symptoms, demonstrating the positive effects of GM metabolites on social behavior [88].

Similar findings have been reported in human studies, where patients with ASD exhibited GM dysbiosis, characterized by higher abundances of pathogenic bacteria, such as *Clostridium* and *Ruminococcus*, and significantly lower abundances of beneficial bacteria, such as *Bifidobacterium* and *Bacillus longisporus*. Furthermore, plasma neurotransmitter levels, particularly 5-HT, and microbial metabolites, primarily SCFAs, were significantly imbalanced [35, 89]. After probiotic treatment, SCFA levels in affected children significantly increased, ameliorating 5-HT hyperactivity and dopamine metabolism disorders [90]. Recently, immune dysregulation in ASD has received extensive attention. Dysregulated cytokine, chemokine, microglial, and immune activation-related molecular signaling pathways are frequently reported in ASD patients and animal models [91]. Numerous immune phenotypes are closely associated with the GM, indicating that immune regulation may represent a critical intersection linking GM and ASD [92]. Additionally, studies have demonstrated that *Lactobacillus reuteri* independently regulates oxytocin release *via* VN-dependent mechanisms, thus reversing social behavioral deficits [93]. These findings collectively highlight the significant role of the GBA in ASD pathogenesis and management.

4.3. Schizophrenia

Schizophrenia represents a severe, chronic psychiatric condition characterized by disturbances in cognitive processes, emotional regulation, and behavioral patterns. Its etiology is complex, incorporating genetic predispositions and environmental influences. The GM, as a critical internal environmental factor, significantly influences schizophrenia onset and progression [94]. Research indicates that maternal immune activation (MIA) during pregnancy is a strong risk factor for NDs. MIA disrupts maternal microbiota composition, transmitting adverse effects to offspring and potentially elevating the risk of schizophrenia [95]. Nucleotide-binding oligomerization domain-containing protein 2 (NOD2), serves as a pattern recognition receptor crucial for microbial recognition, host defense, and immune regulation. A dual-action model combining MIA exposure with NOD2 deficiency has been established. By analyzing maternal and offspring GM composition, offspring immune responses, neurodevelopmental status, and behavioral outcomes, the study validated the interaction between genetic and environmental factors, highlighting the significant impact of GM dysbiosis on schizophrenia [96]. However, the specific mechanisms through which the GM influences schizophrenia remain unclear.

Recent comparative studies revealed that patients with schizophrenia have lower GM richness (Chao index) and diversity (Shannon index) compared with healthy controls, indicating severe dysbiosis [97]. Furthermore, schizophrenia patients exhibit decreased levels of SCFA-producing bacteria and abnormal glycolipid metabolism in their GM [98]. These alterations may represent a critical connection between GM and schizophrenia pathogenesis. Metabolomic and metagenomic experiments found that animal models transplanted with GM from schizophrenia patients exhibited behaviors consistent with low glutamate animal models. These findings suggest that disruptions in glutamate pathways might underlie GM-mediated effects [97]. Additionally, immune regulation represents an important pathway through which the GM influence schizophrenia progression [99]. Studies indicate that dietary inulin ameliorates functional abnormalities in schizophrenia mouse models, including motor and cognitive impairments. This beneficial effect appears closely related to the immunomodulation along the GBA, whereby inulin alleviates neuroinflammation by regulating the GM, enhancing intestinal barrier integrity, and preventing systemic LPS translocation [100]. In summary, the aforementioned studies clarify potential mechanisms by which the GM influences schizophrenia etiology. Thus, microbial interventions targeting schizophrenia hold significant implications for disease prevention and treatment.

4.4. Epilepsy

Epilepsy, a prevalent chronic neurological condition, is characterized by recurrent, transient seizures. The fundamental pathophysiological feature involves abnormal and excessive synchronization of neuronal activity within the brain, often resulting in impairments in consciousness, behavior, and memory functions [101, 102]. Epilepsy has a complex etiology and is classified into six categories: structural, genetic, infectious, metabolic, immune, and unknown factors [103]. Growing evidence suggests a close association between epilepsy and the GM. Dysbiosis of the GM significantly elevates epilepsy susceptibility [104]. Comparative studies between epilepsy patients and healthy individuals revealed significantly increased relative abundances of specific GM genera, such as *Verrucomicrobium* and *Akkermansia*, and significantly decreased abundance of *Lactobacillus* in epilepsy patients [105]. Additionally, SCFAs may influence seizure duration by reinforcing the structural integrity of the GI tract and BBB, inhibiting histone deacetylases activity, increasing astrocytic glutamine synthase

activity, and preserving the equilibrium between excitatory and inhibitory neurotransmission [106]. Microglial cells also significantly mediate SCFA interactions in epilepsy. SCFAs transmit signals *via* the VN to inhibit microglial-driven neuroinflammation, consequently demonstrating antiepileptic properties [107, 108].

Studies indicate that antibiotic treatment can influence seizure control and increase epilepsy susceptibility, especially in individuals with a history of epilepsy. For instance, administration of the fluoroquinolone antibiotic ciprofloxacin in zebrafish models enhanced seizure-like behavior and reduced latency [109], similar findings were obtained in Sprague-Dawle rats, where ciprofloxacin significantly increased seizure susceptibility, intensity, duration, and related mortality. Microbial community analysis after ciprofloxacin treatment showed reduced relative abundances of *Lactobacillus*, *Ruminococcus*, *Parabacteroides*, and *Butyricicoccus,* whereas abundances of *Bacteroides*, *Akkermansia*, and *Eisenbergiella* increased. Additionally, endogenous indole metabolite levels, involved in regulating inflammation and autoimmune responses, were significantly decreased. However, these alterations normalized following FMT, reversing epilepsy susceptibility in model organisms [110].

Various interventions for epilepsy involve the GBA, including KD, probiotics, FMT, antibiotic therapy, and combined antiepileptic drug-microbiota strategies. KD has emerged as a promising non-pharmacological epilepsy treatment, characterized by high fat, restricted carbohydrates, and controlled protein intake. Its mechanism involves altering neuronal metabolic states, stabilizing synaptic activity, and regulating neurotransmitters *via* ketone bodies produced during ketosis, thus exerting antiepileptic effects [111, 112]. Studies indicate that KD can partially restore microbial ecological balance in refractory epilepsy patients. Specifically, the abundances of *g-Eubacterium* and *g-Dialister* significantly normalized following KD treatment, accompanied by increased SCFA concentrations. These findings suggest GM alterations and SCFA production may underlie improved epilepsy outcomes with KD [113]. Additionally, treatments using prebiotics, probiotics, and synbiotics in kainic acid-induced epileptic rats effectively alleviated spontaneous seizures and cognitive deficits. These interventions effectively restored intestinal microbiota homeostasis, inhibited neuroinflammation by reducing inflammatory factor production, and positively affected oxidative stress and neurotransmitter regulation [114]. Brivaracetam, a third-generation broad-spectrum antiepileptic drug, when combined with probiotics (*Lactobacillus* and *Bifidobacterium*), significantly inhibited epileptic brain activity by delaying generalized myoclonic and tonic-clonic seizure onset. Combined therapy demonstrated superiority over monotherapy. Potential mechanisms involve *Lactobacillus* and *Bifidobacterium* as major producers of glutamate and GABA, regulating neurotransmitter balance, restoring neuronal synchronization, and reducing excessive excitation, thus modulating seizure thresholds [115, 116].

4.5. Parkinson's disease

PD is the second most common neurodegenerative disorder after AD. Its principal neuropathological features include the abnormal aggregation of α-synuclein protein and the progressive loss of dopaminergic neurons in the substantia nigra [117]. The primary clinical manifestations of PD are predominantly motor deficits, including bradykinesia, tremor, rigidity, and gait impairment [118, 119]. Constipation is particularly common in PD patients, occurring in approximately 50%–80% of cases [120, 121]. Exploring the mechanisms underlying GBA interactions may provide deeper insights into PD pathology. Studies have reported reduced populations of SCFA-producing bacteria in PD patients, adversely impacting intestinal barrier integrity and immune homeostasis [122]. Additionally, PD-associated metagenomic analyses have identified multiple microbial pathways responsible for degrading environmental pollutants, such as toluene, nitrotoluene, xylene, α-hexachlorocyclohexane, and trichloroethylene. Exposure to these pollutants substantially increases the risk of developing PD [123-125]. PD model mice under GF conditions, as well as those with antibiotic-induced microbiota depletion, showed enhanced microglial activation, increased α-synuclein pathology, and aggravated motor deficits compared to conventionally colonized controls. Furthermore, mice transplanted with microbiota from PD patients displayed significantly worse motor symptoms, underscoring the significant contribution of GM to PD pathogenesis [126]. Additional studies demonstrate that α-synuclein aggregates can undergo retrograde transport from the intestine to the brain *via* the VN, facilitated by microtubule-associated mechanisms, enabling neuronal uptake [127].

Enteric neuropeptides regulate GBA communication by modulating immune responses to pathogens and environmental toxins and maintaining intestinal barrier integrity. Dysregulation of enteric neuropeptides is closely associated with classic CNS pathology in PD [128]. Vasoactive intestinal peptide (VIP) is a bioactive peptide isolated from the intestine. Existing research suggests VIP alleviates PD progression by regulating glial cell activation, enhancing antioxidant defenses, and promoting neuronal protection and repair [129]. GLP-1, produced by intestinal L-cells, has attracted attention for its role in PD. Oral administration of *Lactococcus lactis* engineered to carry a GLP-1 gene plasmid significantly improved motor dysfunction in 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD transgenic mouse models. Mechanistically, this engineered bacterium inhibits dopaminergic neuron death, reduces abnormal α-syn aggregation, suppresses neuroinflammation, and promotes neuronal survival through the GLP-1 receptor/PI3K/Akt pathway in the substantia nigra [130]. Furthermore, the intestinal barrier plays a critical role in the pathogenesis and progression of PD. Studies indicate that intestinal inflammation, intestinal barrier dysfunction, and altered GM metabolites collectively represent early events in α-synuclein pathology. These changes occur prior to CNS disease manifestation. Activation of inflammatory signaling pathways may constitute a critical link between intestinal α-syn accumulation and intestinal barrier damage [131]. Therefore, assessing intestinal barrier integrity may serve as a biomarker for early PD diagnosis and management [132]. Recent findings also indicate that microbial metabolites, such as functional bacterial amyloid proteins, may promote α-syn aggregation and contribute to PD pathogenesis. Conversely, certain gut-derived vitamins exhibit neuroprotective effects *via* anti-amyloid, antioxidant, and anti-inflammatory properties [133]. Furthermore, research indicates that IPA can specifically inhibit the abnormal activation of enteric glial cells, a process implicated in PD pathogenesis. Consequently, IPA alleviates PD-related pathology by reducing neuroinflammation, improving gut-brain barrier function, and restoring dopaminergic neuronal activity [134]. In summary, targeting GM composition and metabolites presents novel and effective therapeutic strategies for PD.

4.6. Alzheimer's disease

AD is a progressive neurodegenerative condition. The pathological hallmarks of AD include amyloid-β (Aβ) plaque formation, neurofibrillary tangles resulting from hyperphosphorylated tau protein, and significant neuronal loss. Patients typically experience progressive cognitive decline, notably impairing memory, learning, and daily functioning [135]. Although AD etiology is complex and not fully understood, recent findings suggest a significant role for GBA interactions. Current mechanistic hypotheses primarily focus on two aspects. First, the composition and functional integrity of the GM are critical for maintaining intestinal

barrier health, host metabolic regulation, mitochondrial function, and systemic inflammation modulation [136-138]. Compared to healthy individuals, patients with cognitive impairment exhibit significantly altered GM composition, abundance, and function. Fifty-nine key microorganisms associated with risk factors for neurodegenerative diseases, including Aβ plaque formation, tau protein phosphorylation, and the APOE-4 allele, have been identified [51]. Recently, gut fungal communities have received considerable attention. In AD patients and AD mouse models, the gut fungal profile undergoes significant changes. Intestinal fungi activate microglia, induce neuroinflammation, and promote Aβ deposition. Fungal prion-like proteins accelerate the aggregation of Aβ and phosphorylated tau proteins *in vitro*. Conversely, probiotic fungi, such as the yeast strain *Saccharomyces*, can reduce AD-related pathology and improve cognitive function [139].

Second, GM metabolites include neuroactive substances such as neurotransmitters and their precursors, SCFAs, tryptophan, IPA, and neuropeptides. These metabolites are involved in AD-related pathophysiological processes, including immune inflammation, epigenetic modifications, BBB function, and energy metabolism [140-142]. Elevated colonic VIP levels significantly ameliorate cognitive impairments in animal models with compromised neurological function. Enhanced VIP expression restores cognition-related protein levels, inhibits microglial polarization toward pro-inflammatory phenotypes, and supports repair of intestinal mucosa and the BBB [143]. Bacterial extracellular vesicles (BEVs), nanoscale membrane-bound vesicles secreted by bacteria, traverse intestinal and BBB, delivering bioactive molecules and facilitating host-microbial communication. Depending on their bacterial origin, BEVs can exert dual immunomodulatory effects, anti-inflammatory or pro-inflammatory, *via* GBA immune signaling pathways [144, 145]. Based on these mechanisms, increasing evidence supports interventions targeting the GBA as innovative therapeutic approaches for AD prevention and management. Supplementation with probiotics, prebiotics, butyrate, and associated dietary interventions [146, 147], represent non-invasive, beneficial approaches to mitigate neurodegeneration and improve cognitive function.

4.7. Others

In addition to the aforementioned conditions, the GBA demonstrates significant potential in the treatment of other NDs, including stroke, MS, and ALS [148-151]. GM dysbiosis can exacerbate inflammatory reactions, activate host immune responses, and alter neurotransmitter levels, thereby aggravating brain damage and hindering recovery after stroke [152]. Tryptophan metabolism is considered a key mechanism for GBA function, generating metabolites and enzymes with dual roles in its metabolic pathway. The balance between neurotoxic and neuroprotective substances, such as neuroprotective KA and neurotoxic QA, is critical in ischemic stroke (IS) progression [153].

MS is an autoimmune, inflammatory, demyelinating, and neurodegenerative disease of the CNS [154]. Compared to healthy individuals, MS patients exhibit notable shifts in GM composition. Alterations in carbohydrate and lipid metabolism, SCFA pathways, and bile acid synthesis have also been observed, supporting associations between GM and MS progression [155]. Furthermore, MS patients commonly experience intestinal epithelial and mucus barrier disruptions, which are closely correlated with GM dysbiosis. This impairment underscores the pivotal role of intestinal barrier integrity in regulating exogenous stimuli and pathogen entry, thereby influencing inflammatory diseases such as MS [156]. Recent studies also highlight GM dysbiosis-induced pyroptosis as a contributor to heightened inflammatory factor release and neuroinflammation in MS [157]. Accumulating evidence suggests that GM dysbiosis significantly impacts ALS progression by compromising intestinal barrier integrity, elevating endotoxemia, and exacerbating systemic inflammation. Consequently, interventions targeting GBA interactions, such as probiotics, prebiotics, antibiotics, or bacteriophages, have been proposed as complementary therapeutic strategies for ALS [158].

5. The therapeutic effects of saponins on neurological diseases *via* the GBA

Saponins, recognized for their multiple pharmacological targets and low toxicity, have received considerable attention as potential neuroprotective agents. Prominent examples include ginsenosides, astragalosides, *Panax notoginseng* saponins (PNS), Dioscin, Escin, Saikosaponins, Xanthoceraside, Quinoa saponin, Radix Polygalae saponins (RPS), and Anemoside B4. Emerging evidence suggests significant therapeutic potential of saponins in CNS disorders, including depression, AD, PD, stroke, and epilepsy [159].

Given the increasing recognition of GBA involvement in NDs, saponins have attracted substantial interest. They demonstrate therapeutic effects on NDs primarily through bidirectional modulation between the gut and brain *via* neural, immune, and endocrine pathways. In neural regulation, saponins influence the synthesis and release of intestinal neurotransmitters and directly interact with the VN. Intestinal signals reach the CNS through the circulatory system or vagal afferents, thus enabling neural modulation [160, 161]. Immunological regulation mediated by saponins is also critically important. They modulate GM composition by enhancing beneficial bacteria and suppressing harmful populations, thus alleviating intestinal inflammation [162]. Moreover, saponins reduce pro-inflammatory cytokine production by inhibiting excessive activation of intestinal immune cells, thereby improving local inflammatory responses. Consequently, peripheral inflammatory cytokine levels decrease, limiting their infiltration into the CNS and alleviating neuroinflammation [163]. Furthermore, studies indicate saponins influence endocrine pathways through regulation of intestinal hormone secretion and modulation of HPA axis activation, thereby facilitating gut-brain communication [164, 165]. Overall, unlike traditional targeted therapies, saponins achieve brain protection through peripheral mechanisms mediated by the GBA. Their multi-target and multi-pathway interactions provide novel therapeutic avenues for treating NDs. The following sections discuss the neuroprotective effects of various saponins and their primary GBA-related mechanisms, aiming to provide insights into their clinical application and underlying protective mechanisms.

5.1. Ginsenosides

Ginsenosides, the primary bioactive constituents derived from *Panax ginseng*, belong to the triterpenoid saponins family. Their structure typically comprises a steroidal backbone, though their glycoside structures vary considerably [166]. Ginsenosides display numerous pharmacological properties, such as antitumor, anti-inflammatory, antioxidant, antidiabetic, immunoregulatory, and neuroprotective activities [167, 168]. Ginsenosides are generally categorized based on differences in their aglycone structure into panaxadiol-type (Rb1, Rb2, Rb3, Rc, Rg3), panaxatriol-type (Re, Rg1, Rg2, Rh2), oleanane-type (RO), and octillol-type (F11) saponins [166]. The intestine is the primary metabolic site for ginsenosides, where deglycosylation occurs *via* enzymes secreted by intestinal microorganisms. For example, ginsenosides Rh4 and Rk3 are produced by the deglycosylation of Rg1 [169, 170]. Significant impacts of GM composition changes on the pharmacokinetics and biological activity of ginsenosides have been confirmed. Studies have demonstrated that metabolites produced by ginsenoside deglycosylation exhibit higher bioavailability compared to their par-

ent compounds [171]. Increasing evidence indicates that bidirectional communication of the GBA is closely associated with the pharmacological effects of ginsenosides, particularly their neuroprotective properties (Table 1).

Through network pharmacology and preclinical research, ginsenosides have been implicated in modulating key mechanisms relevant to NDs, including oxidative stress, apoptosis, inflammation, cholinergic function, mitochondrial homeostasis, synaptic plasticity, and neurogenesis [172, 173], These activities involve critical signaling pathways such as PI3K/Akt, CREB/BDNF, Keap1/Nrf2, SIRT1/NF-κB, BDNF-TrkB, and NF-κB/NLRP3 [174-176]. Research indicates that ginsenosides promote brain plasticity through peripheral pathways including GM, cytokines, and vagal afferents, confirming that the GBA is a crucial pathway for translating cellular and molecular changes into improvements in higher-order brain functions [177]. Specifically, Rg1 modulates glucocorticoid and androgen receptor expression in the prefrontal cortex and hippocampus, alongside serum CORT and testosterone levels, enhancing the functions of both the HPA and hypothalamic-pituitary-gonadal axes, thereby alleviating depression-like behaviors in animal models induced by chronic unpredictable mild stress (CUMS) and gonadectomy [178]. Moreover, metabolomic studies in depressive mouse models revealed that Rg1 treatment increases serum and cerebral concentrations of IAA. Changes in GM composition, particularly *Lactobacillus* enrichment, appear responsible for these effects. Rg1 also elevates oxytocin levels in mouse brains, activating the hypothalamic-hippocampal-oxytocin signaling pathway [179]. Morphine dependence, a destructive neuropsychiatric disorder resulting from chronic morphine use, was recently shown to be regulated by Rg1. Rg1 modulates GM composition, increases *Bacteroides* abundance, and affects the tryptophan metabolic pathway, thereby effectively reducing morphine dependence [160]. Rg3 alleviates brain damage induced by organophosphorus pesticide poisoning *via* the GBA. Its mechanisms include reversing GM dysbiosis, improving intestinal barrier function, inhibiting NLRP3/caspase-1/IL-1β-mediated macrophage M1/M2 polarization to reduce inflammation, and suppressing HPA axis hyperactivation by increasing GR protein expression, thereby improving cognitive dysfunction [180]. Similar effects were observed with Rh4 and Rk3. Rh4 inhibits NLRP3 inflammasome activation, increases intestinal probiotics, and alleviates intestinal barrier damage, HPA axis overactivation, and synaptic damage. Rk3 targets tryptophan hydroxylase to regulate tryptophan metabolism, exerting antidepressant effects [181, 182].

Additionally, Rb1 mediates the normalization of GM metabolites, inhibits HPA axis overactivation, and reduces inflammatory responses, restoring social behavior deficits induced by social isolation [183]. In an MPTP-induced PD mouse model, Re treatment improved GM diversity and abundance, promoted intestinal mucosal repair, inhibited inflammation, delayed dopaminergic neuronal degeneration, and synergistically regulated arachidonic acid metabolism, thereby improving motor dysfunction [184]. Studies report that Rd, the primary active component in *red ginseng* and *Bifidobacteria-fermented red ginseng*, regulates intestinal ecosystems, inhibits nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and NF-κB + /Iba1 + cell populations in the hippocampus, reduces serum CORT and IL-6 induced by *Escherichia coli*, and significantly alleviates behavioral abnormalities in anxiety and depression mouse models [185]. Notably, ginsenoside CK (CK), an intestinal metabolite of natural diol ginsenosides, delays progression of mild cognitive impairment, PD, and other NDs *via* microbiota-dependent mechanisms. CK increases GM diversity, enriches beneficial bacteria, reduces pathogenic bacteria, maintains intestinal barrier and BBB integrity, and inhibits oxidative stress and neuroinflammation, producing significant therapeutic benefits [186, 187]. *Rhizoma Panacis Japonicin*, also belonging to the *Panax* genus of the Araliaceae family, contains various saponin components. Research indicates that total saponins of *Rhizoma Panacis Japonicin* effectively treat EAE through GBA communication. Specific mechanisms include inhibiting the TLR4-MyD88-NF-κB signaling pathway, modulating GM composition and suppressing neuroinflammation [188].

5.2. Astragalosides

Astragalosides are a class of triterpenoid saponins derived from *Astragalus membranaceus* (*Fisch.*) and constitute the primary active components of the TCM *Astragalus*. Astragalosides exhibit multiple biological properties, encompassing anti-inflammatory, antioxidant, anti-apoptotic, immunomodulatory, hypoglycemic, and antiviral activities [189]. Among astragalosides, Astragaloside IV is particularly prominent and extensively investigated. Numerous studies, both *in vitro* and *in vivo*, have demonstrated the therapeutic potential of Astragaloside IV in treating NDs such as AD, PD, depression, stroke, traumatic spinal cord injury, and MS [190].

Its neuroprotective mechanisms include attenuating ferroptosis-related lipid peroxidation in AD [191], reducing macrophage infiltration and inflammation by inhibiting mitochondrial citrate transport [13], regulating glial cell polarization to decrease neuroinflammation [192], maintaining BBB integrity to alleviate cognitive deficits and inflammatory responses following sepsis [193], suppressing oxidative stress and microglial activation to protect dopaminergic neurons [194], preventing apoptosis [195], limiting HPA axis hyperactivation to improve peripheral immune function [165], and enhancing angiogenesis through the SIRT7/VEGFA signaling axis to ameliorate cerebral infarction outcomes [196]. However, pharmacokinetic analyses reveal the limited oral bioavailability and poor membrane permeability of Astragaloside IV, resulting in low systemic and cerebral concentrations [197]. Hence, recent studies suggest that Astragaloside IV might exert indirect neuroprotective effects through modulation of GM and related metabolites [198] (Table 2). Studies have demonstrated that Astragaloside IV inhibits neuroinflammation, repairs intestinal barrier dysfunction, and alleviates cognitive impairment induced by CUMS, effects that depend on maintaining GM homeostasis and metabolic activity [199]. Astragaloside IV regulates GM composition, increasing beneficial bacteria (e.g., *Lactobacillus* and *Oscillospira*) and normalizing microbial metabolites such as SCFAs and amino acids. Furthermore, Astragaloside IV regulates the Th17/Treg cell balance and controls inflammatory cytokine secretion, thereby reducing neuroinflammation and depressive symptoms [200].

Alterations in GM composition represent important risk factors for IS. Transferring fecal supernatant from IS mice into GF mice induces oxidative stress and abnormal autophagy. Astragaloside IV treatment normalizes GM composition, thereby alleviating oxidative stress and autophagic dysfunction [201]. In intracerebral hemorrhage (ICH) mouse models, Astragaloside IV reduces immunoglobulin G leakage, brain edema, neuronal loss, apoptosis, and inflammatory responses. These therapeutic effects appear to be mediated by regulating GM composition and serum metabolism, reducing pathogenic bacteria populations [198]. A recent study suggested that the intestinal microbial metabolite of Astragaloside IV, 3-epicycloheptenol, exhibits superior bioavailability and BBB permeability compared to Astragaloside IV itself. This metabolite stably binds to therapeutic targets (CSF1R, PTK2, and CDC42) in ICH treatment, reducing neuroinflammation and providing neuroprotection [202].

5.3. Panax notoginseng saponins

PNS, the main bioactive components of *Panax notoginseng*, primarily comprise five major ginsenosides including the distinctive marker compound notoginsenoside R1 (NG-R1). This

Table 1 Summary of neuroprotective mechanisms of ginsenosides *via* the GBA.

Saponins	Primary source	Experimental model	Dosage regimen	The changed GM and GM metabolites	The improved ND hallmarks	Ref.
Ginsenoside Rg 1	*P. ginseng*	UMS-induced depression mice	20 and 40 mg·kg^{-1} i.g. for 14 d	*Allobaculum* and Muribaculaceae↑, *Bifidobacterium*↓, *L. murinus*↑	IAA levels in serum and brain tissue↑, oxytocin signaling↑	179
		Conditioned place preference (CPP)-induced morphine dependent mice	100 and 200 mg·kg^{-1} i.g. for 7 d	*B. vulgatus*↑, Bacteroidetes↑,	BDNF/TrkB↓, Hippocampal and serum 5-HT↓	160
Ginsenoside Rg 3	*P. ginseng*	Chlorpyrifos-induced organophosphorus pesticide	80 and 160 mg·kg^{-1} i.g. for 21 d	The abundance and homogeneity↑ (Chao, ACE and Pielou index), *Mycobacterium*↑, norank-f-Muribaculaceae, *Lactobacillus* and *Dubosiella* decreased↑, SCFAs↑	HPA axis overactivation↓, neuroinflammatory responses↓, BDNF, SYP, and PSD-95↑, phosphorylated cAMP response element binding protein (p-CREB) and phosphorylated extracellular signal-regulated kinase (p-ERK) ↑, hippocampal CD86↓, CD206↑, NLRP3, ASC, and caspase-1↓	180
Ginsenoside Rh4	*P. ginseng*	CUMS-induced depression mice	20 and 40 mg·kg^{-1} i.g. for 14 d	*Lactobacillus*↑, *Allobaculum*, *Helicobacter*, and *Mucispirillum*↓, SCFAs↑	surviving hippocampal neurons↑, HPA axis overactivation↓, neuroinflammatory responses↓, oxidative stress↓, apoptosis↓, BDNF, SYP, and DCX↑, p-CREB, p-ERK↑, Dendritic spine density↑, inflammatory factors↓, NLRP3, ASC, and caspase-1↓	181
Ginsenoside Rk3	*P. ginseng*	CUMS-induced depression mice	20 and 40 mg·kg^{-1} i.g. for 14 d	5-HT↑, *Lactobacillus*, *Prevotella*, *Oscillospira*, *Allobaculum*, and *Parabacteroides*↑, *Clostridium* and *Adlercreutzia*↓, SCFAs↑	neuronal damage ↓, HPA axis overactivation↓, neuroinflammatory responses↓, the integrity of the BBB↑, Oxidative stress and apoptosis↓	182
Ginsenoside Rb 1	*P. ginseng*	Post-weaning social isolation-induced mice	0.1 mg·kg^{-1} i.g. for 14 d	methylpentadecanoic acid↓, O6-benzyl-8-oxoguanine↑	myelin-associated glycoprotein (MAG)↑, DNA repair protein↑	183
Ginsenoside Re	*P. ginseng*	MPTP-induced PD mice	10 and 40 mg·kg^{-1} i.g. for 4 weeks	The diversity and richness ↑ (Chao1 and Shannon indices), *Allobaculum*, *Sutterella*, *Akkermansia*↓, *Bifidobacterium*, *Odoribacter*, *Prevotella*↑	neuronal damage↓, TH-positive neurons↑, α-Syn accumulation↓, oxidative stress↓, neuroinflammatory marker↓, apoptosis↓	184
Ginsenoside Rd	*P. ginseng*	immobilization stress or *Escherichia coli*-induced anxiety/depression mice	5 mg·kg^{-1} i.g. for 5 d	Proteobacteria↓, gut dysbiosis↓	NF-κB activation and NF-κB + /CD11c + cell population↓, inflammation↓	185
Ginsenoside compound K	*P. ginseng*	D-galactose-inducedmice	80 mg·kg^{-1} i.g. for 5 weeks	Bacteroidetes and Firmicutes↑, *Bacteroides*, *Akkermansia*, *Prevotella*, and *Roseburia*↑, propionate↑	neuroinflammation↓, BBB impairment↓ (ZO-1 and Occludin↑), Serum LPS↓	186
		MPTP-induced PD mice	10 and 40 mg·kg^{-1} i.g. for 48 d	The diversity and richness ↑, Bacteroidetes↑, Verrucomicrobia, Actinobacteria and Proteobacteria↓, *Lactobacillus*, *Akkermansia*↓	the expression of α-Syn↓, inflammatory factors↓, oxidative stress↓	187
Total saponin of Rhizomes of *P. japonicus*	Rhizomes of *P. japonicus*	EAE mice induced by myelin oligodendrocyte glycoprotein (MOG) 35-55	36.5 and 73 mg·kg^{-1} i.g. for 28 d	Firmicutes to Bacteroidetes (F/B) ratio↓, Muribaculaceae-unclassified, *Enterorhabdus* and *Prevotella*↑	Demyelination↓, Th17/Treg, Th1/Th2 cell ratios↓, neuroinflammation↓, TLR4-MyD88-NF-κB↓	188

unique dammarane-type saponin serves as a key identifier for quality control and exhibits a broad spectrum of pharmacological activities, such as anti-inflammatory, antioxidant, antitumor, and cardiovascular protective effects [203]. Notably, NG-R1 exhibits pronounced protective effects on cerebrovascular diseases [204]. For example, NG-R1, identified as a phytoestrogen, mitigates endoplasmic reticulum stress by targeting estrogen receptors, modulates the PI3K/Akt signaling pathway, inhibits apoptosis of neurons, and provides neuroprotection against hypoxic-ischemic brain injury [205]. Nicotinamide phosphoribosyltransferase (NAMPT) boosts energy metabolism, sustains mitochondrial integrity, and reduces ischemic injury. Experimental findings indicate that NG-R1 promotes post-stroke angiogenesis by directly interacting with NAMPT, enhancing vascular endothelial growth factor (VEGF) expression, and modulating the NAMPT-NAD + -SIRT1 pathway and Notch/VEGFR-2 signaling, indicating the potential of NG-R1 as a therapeutic candidate for IS [206].

Given the increasing attention given to GM, research increasingly highlights the GBA as a critical mediator for NG-R1's neuroprotective properties (Table 3). In animal models of middle cerebral artery occlusion/reperfusion (MCAO/R) injury, NG-R1 alleviates GM dysbiosis through inhibition of TLR4/MyD88/NF-κB signaling and reduces intestinal inflammation and barrier disruption. These actions subsequently decrease systemic inflammation, ameliorating neurological deficits [17]. Reduced *Lactobacillus* abundance occurs in ischemia/reperfusion (I/R) models, PNS treatment significantly reverses this reduction, promoting histidine synthesis in serum, gut, and brain, and enhancing neuroprotection [164]. Histidine, a bioactive amino acid and histamine precursor, exerts anti-inflammatory and antioxidant effects, which are crucial for improving cognitive dysfunction [207]. The protective effects of NG-R1 on blood vessels, including lipid improvement, inhibition of plaque formation, vascular inflammation reduction, and insulin resistance control, likely involve the GBA. NG-R1 enhances GM diversity, increases *Akkermansia* abundance, alleviates metabolic disturbances, and improves gut barrier function. Vascular plaques, inflammation, and insulin resistance, known risk factors, contribute to neurological damage [208]. In addition to NG-R1, total saponins derived from *Panax notoginseng* leaves restore GM equilibrium and intestinal mucosal integrity, modulate the BDNF-TrkB-PI3K/Akt pathway *via* regulation of the HPA axis, suppress neuronal apoptosis, and enhance cognitive functions in chronic cerebral hypoperfusion-induced vascular dementia rat models [209].

5.4. Dioscin

Dioscin is a natural steroidal saponin, abundant in natural products such as *Trigonella* and *Dioscorea*, exhibiting significant neuroprotective effects. Studies indicate that dioscin reduces

Table 2 Summary of neuroprotective mechanisms of astragaloside IV *via* the GBA.

Saponins	Primary source	Experimental model	Dosage regimen	The changed GM and GM metabolites	The improved ND hallmarks	Ref.
Astragaloside IV	*Astragalus membranaceus*	collagenase type Ⅶ injection-induced intracerebral hemorrhage (ICH) model	25, 50 and 100 mg·kg^{-1} i.g. for 14 d	Clostridiales vadinBB60 group, *Klebsiella*↑, *Ruminiclostridium 6*, *Faecalibaculum*, *Tyzzerella 3*, Ktedonobacterales, *Anaerovorax*, *Jatrophihabitans*, Frankiaceae, Defluviitaleaceae and Atopobiaceae↓	survival neurons↑, brain edema↓, neuroinflammation↓, LPS↓	198
		CUMS-induced depression mice	40 and 80 mg·kg^{-1} i.g. for 6 weeks	α diversity↓ (Chao1 index), *Lactobacillus reuteri* and *Bacteroides acidifaciens*↑, *Ruminococcus flavefaciens* and *Bacteroides caecigallinarum*↓, purine metabolism, ABC transporters, and carbohydrate digestion and absorption↑	inflammatory response↓	199
		CUMS-induced depression rats	40 mg·kg^{-1} i.g. for 28 d	*Lactobacillus*, *Oscillospira*, and *Ruminococcus*↑, isoleucine, SCFAs, ethanol↑	Th 17/Treg↓, anti-inflammatory cytokines↑ (IL-10 and TGF-β)	200
		Fecal supernatants of IS-induced mice	50 mg·kg^{-1} i.g. for 12 weeks	*Bifidobacterium*, *Blautia*, *Escherichia-Shigella*↑, *Megamonas*, *Holdemanella*, *Clostridium*↓	oxidative stress↓ (T-AOC, SOD and GSH), autophagy markers↓ (Beclin-1, Atg12 and LC3 II)	201

acute inflammatory responses and oxidative damage following subarachnoid hemorrhage by inhibiting NLRP3 inflammasome signaling and enhancing SIRT1-dependent pathways, thus reducing neuronal damage [210]. In I/R models, dioscin exerts neuroprotective effects by inhibiting oxidative stress and apoptosis through downregulation of the HMGB-1/HMG pathway, reducing inflammatory responses [211]. Recent studies also report neuroprotective effects mediated by dioscin *via* the GBA (Table 4). Dioscin reverses MPTP-induced GM dysbiosis. In a GM-dependent manner, it targets the GLP-1 signaling pathway, mediates bile acid metabolism, and inhibits oxidative stress and neuroinflammation, thereby alleviating PD symptoms [212].

Diosgenin, a common derivative of dioscin, has emerged as a multi-target candidate for NDs including stroke, AD, PD, MS, epilepsy, and peripheral neuropathy [213, 214]. Recent evidence suggests that Diosgenin exerts neuroprotective effects by modulating the GM and subsequent cascades. For example, Diosgenin treatment significantly restored *Bacteroides* and *Parabacteroides* abundance in a mouse epilepsy model induced by pentylenetetrazole, inhibited enteric glial cell activation and TLR4-My88 signaling, improved intestinal barrier integrity, and alleviated inflammatory injury [213]. In mouse models of depression, Diosgenin restored HPA axis function and activated hippocampal BDNF/TrkB/ERK/CREB signaling, enhancing neurotrophic function. These effects appear dependent on GM modulation [16]. Additionally, Diosgenin reversed GM alterations induced by oxaliplatin (an anticancer drug), increased microbiota richness and diversity, enhanced abundances of *Erysipelotrichaceae* and *Lachnospiraceae*, elevated the *Firmicutes*/*Bacteroidetes* ratio, and inhibited LPS-TLR4 inflammatory signaling, thereby exerting analgesic effects [214].

5.5. Others

In addition to the aforementioned saponins, compounds such as Escin, Saikosaponins, Xanthoceraside, Quinoa saponin, RPS, and Anemoside B4 regulate GM homeostasis and exert therapeutic effects on NDs *via* the GBA (Table 4). Although Escin does not penetrate the BBB to directly improve brain damage after IS, studies have shown that Escin acts directly on the gut. It targets the GR/p38 MAPK/NF-κB signaling pathway, regulating immune responses, reducing intestinal inflammation, and decreasing intestinal permeability. Subsequently, Escin modulates the LPS/TLR4/NF-κB signaling pathway *via* systemic circulation, inhibiting neuroinflammation and alleviating ischemic brain injury [18]. Saikosaponin A treatment increases GM abundance and diversity, elevates *Verrucomicrobia* abundance, enhances monoamine neurotransmitter levels, suppresses hippocampal inflammation and oxidative stress, reduces hippocampal injury, and significantly improves reserpine-induced depressive-like behaviors [215]. Total saikosaponins inhibit β-secretase 1 (BACE1) expression *via* Nuclear factor erythroid 2-related factor 2 (Nrf2) pathway activation, reducing Aβ production and deposition, alleviating neuroinflammation and oxidative stress, and helping to reverse dysbiosis to improve cognitive dysfunction in AD mice [216].

Xanthoceraside, a triterpenoid saponin from *Xanthoceras sorbifolia Bunge* fruit shells, demonstrates prominent anti-AD effects. Research indicates that Xanthoceraside ameliorates memory and learning deficits in AD animal models by modulating the relative abundance of specific microbial communities and inducing beneficial shifts in GM composition. Additionally, Xanthoceraside notably affects the production of microbial metabolites, including neurotransmitters, amino acids, and bile acids [217, 218]. Quinoa saponin similarly stabilizes GM composition, enhancing probiotic abundance and SCFA production, inhibiting TLR4/MyD88/NF-κB signaling, and thereby reducing inflammation in intestinal and nervous systems. These effects significantly relieve anxiety- and depression-like behaviors induced by LPS in mouse models [162]. RPS beneficially modulates GM by increasing beneficial bacterial abundances (*Actinobacteria*, *Pasteurella*, *Lactobacillus*, and *Clostridium*), promoting butyrate production, and reducing inflammatory cytokines. Additionally, RPS decreases the level of complement system component C3, negatively associated with cognitive function, thus exerting anti-aging effects [219]. Anemoside B4 suppresses inflammatory responses, controls inflammatory cytokine release, and regulates GM, exerting protective effects

Table 3 Summary of neuroprotective mechanisms of PNS through the GBA.

Saponins	Primary source	Experimental model	Dosage regimen	The changed GM and GM metabolites	The improved ND hallmarks	Ref.
Notoginsenoside R1	*P. noto ginseng*	MCAO/R-induced I/R rats	20, 40 and 80 mg·kg^{-1} i.g. for 7 d	The diversity and richness ↑ (Shannon and Simpson indices), Bacteroidota↑, Proteobacteria↓, Enterobacterales↓	neurological damage↓, neuroinflammation↓ (IL1β, Tnfα, and Il6), the integrity of the BBB↑ (ZO-1, Occludin), TLR 4/MyD 88/NF-κB↓	17
P. notoginseng saponins	*P. notoginseng*	MCAO/R-induced I/R rats	100 mg·kg^{-1} i.g. for 7 d	Proteobacteria↓, Firmicutes↑, *Lactobacillus*↑, *Lactobacillus reuteri*↑, glutamine, alanine, and valine↓	neurological damage↓, Serum histidine↑	164
The total saponins of *P. notoginseng* leaves	*P. notoginseng* leaves	bilateral common carotid artery occlusion (BCCAO)-induced rats	100 and 200 mg·kg^{-1} i.g. for 28 d	*Ligilactobacillus*↑, Clostridia UCG-014 unclassified↓	neurological damage↓, BDNF and TrKB↑, PI3K/Akt↑, HPA axis overactivation↓	209

Table 4 Summary of neuroprotective mechanisms of Dioscin and other saponins through the GBA.

Saponins	Primary source	Experimental model	Dosage regimen	The changed GM and GM metabolites	The improved ND hallmarks	Ref.
Dioscin	*Dioscorea*	MPTP-induced PD mice	20, 40 and 80 mg·kg^{-1} i.g. for 21 d	Microbial diversity↑ (Chao1 index,OTU numbers), Firmicutes and Proteobacteria↑, Bacteroidia, Bifidobacteriales and Lactobacillales↓, BSH activity↓	neuron viability↑, oxidative stress↓	205
Escin	*Aesculus hippocastanum*	MCAO/R-induced I/R rats	0.225, 0.45 and 0.9 mg·kg^{-1} i.v. at 30 min post-reperfusion	the integrity of intestinal barrier↑ (Claudin-1, Occludin and ZO-1)	Garcia test scores↑, cerebral infarct volume↓, Cort↓, inflammation↓, LPS/TLR4/NF-κB↓	18
Saikosaponin A	*Radix bupleuri*	reserpine-induced depression mice	50 mg·kg^{-1} i.g. for 16 d	Firmicutes↓, Verrucomicrobia↑	Serum dopamine↑, degeneration of neurons↓, Oxidative stress↓ (LPO and ROS), pro-inflammatory factors↓, TNFR1/NF-κB↓	215
Total saikosaponins	*Radix bupleuri*	APP/PS1 transgenic mice	20, 40 and 80 mg·kg^{-1} i.g. for 30 d	*Desuflovibrio*, *Helicobacter*, *Mucispirillum*, *Roseburia*, and *Clostridium*↓	Aβ level and senile plaque↓, Nrf2 signaling↑, autophagy↑ (LC3-II and Beclin-1), p-tau protein↓, oxidative stress and inflammation↓	216
Xanthoceraside	*Xanthoceras sorbifolia*	$Aβ_{1-42}$-induced AD rats	0.18 and 0.36 mg·kg^{-1} i.g. for 21 d	Firmicutes to Bacteroidetes (F/B)↓, *Escherichia Shigella*↓, Prevotellaceae and *Lactobacillus*↑, SCFAs↑, 5-HT level↑, ratios of bile acids↑	the levels of Arg, Glu, Pro-and 5-HT in plasma↑, hippocampal neuronal loss↓	217
		$Aβ_{1-42}$-induced AD rats	0.056, 0.112 and 0.224 mg·kg^{-1} i.g. for 18 d	Firmicutes to Bacteroidetes (F/B)↓, *Clostridium IV*, *Enterorhabdus*, *Coriobacterium*, *Corynebacterium*, *Desulfovibrio*, and *Defluviitalea*↓, *Acetobacteroides* and *Alloprevotella*↑	hippocampal neuronal loss↓	218
Quinoa saponin	*Quinoa*	LPS-induced anxiety/depression mice	100 mg·kg^{-1} i.g. for 30 d	α diversity↑, *Faecalibaculum*, *Dubosiella*↑, SCFAs↑,	neurotrophic proteins, key synaptic proteins (PSD-95, SYP), and neurotransmitters↑, TLR4/MyD88/NF-κB↓, Neuroinflammation↓	162
Radix polygalae saponins	*Radix polygalae*	108 weeks old mice as aging model H_2O_2 induced-neuro 2a cell *Caenorhabditis elegans*	0.05, 0.1 and 0.2 mg·kg^{-1} i.g. for 78 weeks 25, 50 and 100 μg·mL^{-1} in NGM plates for 15 d	Actinobacteria, Bacteroidetes, and Firmicutes↑, Proteobacteria and Verrucomicrobia↓, *Brucella*, *Desulfovibrio*, *Akkermansia*↓	aging-related genes↓ (C3, Fcgr1 and Fcgr3), BDNF, PSD 95, p-AKT and p-ERK↓ Oxidative damage↓(ROS) aging-related phenotypes↓, lipofuscin↓	219
Anemoside B4	*Pulsatilla*	EAE mice induced by myelin oligodendrocyte glycoprotein residues 35–55 (MOG_{35-55})	100 and 200 mg·kg^{-1} i.g. for 18 d	Firmicutes↓, *Akkermansia*↓	inflammation and demyelination of the spinal cord↓ (TNF-α, IL-6 and IL-17)	220

against EAE [220]. In summary, these studies collectively confirm the potential of saponin-based natural compounds in combating neurodegeneration and neuroinflammation through modulation of the GBA. The mechanism of saponins is shown in Fig. 2.

5.6. Drug toxicity and side effects

Saponins hold significant therapeutic potential, primarily through their synergistic effects on multiple targets regulating the GBA in NDs. However, like other therapeutic agents, they carry potential risks of toxicity and side effects, which are frequently overlooked. The reported toxicity of saponins predominantly affects the GI tract, liver, kidneys, and reproductive system [221]. Hepatic and renal toxicities are the most common side effects associated with PNS [222]. At inappropriate doses, cardiac toxicity can also occur. A study investigating the cardiac toxicity of PNS in rats using hemodynamic methods demonstrated significant cardiotoxicity at higher doses (≥150 mg·kg^{-1}) [223]. Clinical studies evaluating the safety of PNS have reported adverse reactions mainly characterized by drug-related rashes [224]. Additionally, Ginseng and Ophiopogon injection is a widely used herbal preparation in clinical practice, primarily containing Rb1, Rb2, Re, and Rg1, for adjunctive therapy in coronary heart disease, heart failure, and arrhythmias. A six-month toxicokinetic study in Beagle dogs showed increased exposure to panaxadiol-type ginsenosides, posing potential toxicity risks and possible drug-drug interactions during administration [225]. Studies report toxic side effects of saikosaponins, including hepatotoxicity, neurotoxicity, hemolytic toxicity, and cardiotoxicity [226], exhibiting dose-dependent toxicological characteristics [227]. Notably, saikosaponins are pharmacologically active in hepatoprotection but simultaneously responsible for hepatotoxicity. In zebrafish toxicological studies, low concentrations of Saikosaponin A (1.77–5.30 μmol·L^{-1}) demonstrated protective effects without toxicity, whereas concentrations above 5.30 μmol·L^{-1} exhibited significant hepatotoxicity [228]. Clinical reports have also described liver injury associated with Dioscorea saponin tablets [229]. Currently, the coexistence of pharmacological activity and toxicity limits the clinical application of saponins. Improving pharmacotoxicological research, elucidating mechanisms of liver and kidney toxicities, and strictly defining safe dosage ranges are essential to balance efficacy and safety, thus maximizing the therapeutic value of saponins.

5.7. Drug delivery systems of saponins

Saponins generally display low oral bioavailability, primarily attributed to their considerable molecular weight, limited membrane permeability, extensive first-pass metabolic degradation in both hepatic and intestinal environments, competitive reactions in the GI tract, and susceptibility to modification by intestinal microbiota [230]. These characteristics markedly restrict their clinical utility. Consequently, considerable research effort has been dedicated to developing innovative formulations aimed at improving their bioavailability. Approaches include encapsulation techniques such as liposomes, nanoparticles, emulsions, micelles, solid dispersions, cyclodextrin complexes, and microspheres, as well as advanced drug delivery technologies like electrospun nanofiber membranes, hydrogels, and microneedle arrays [231].

For example, studies have reported that ginseng polysaccharide-Re complexes enhance Re absorption by inhibiting efflux pro-

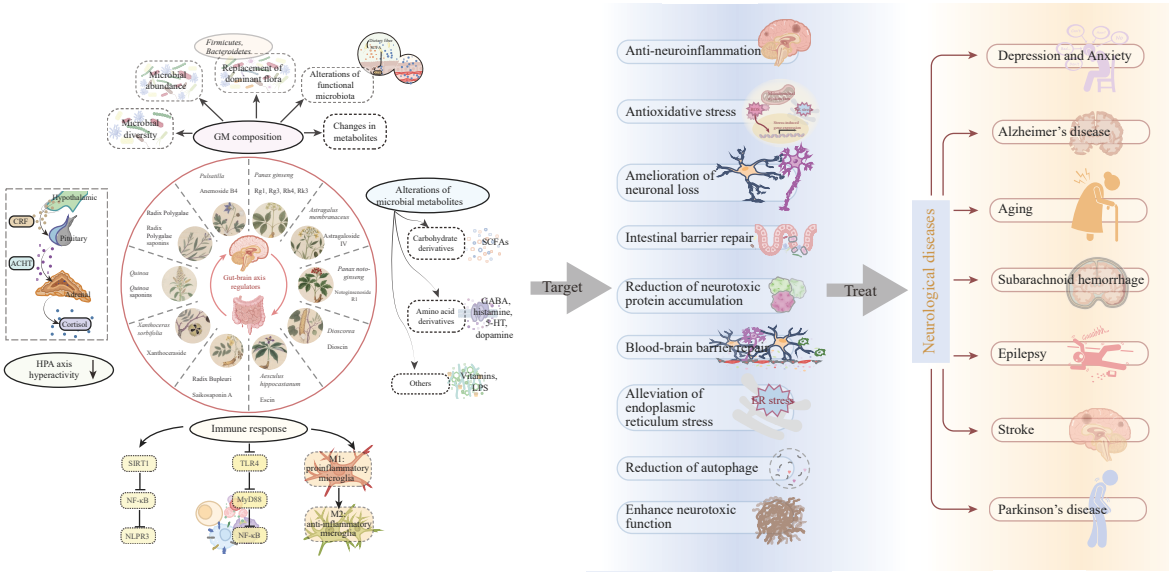


Fig. 2 Saponins improve NDs by regulating the GBA. Saponins can modulate the composition of the GM, regulate microbial metabolism and the levels of metabolites, reduce inflammatory responses, and prevent excessive activation of the HPA axis. Saponins treat NDs by acting on multiple targets. Abbreviations: GM: gut microbiota; GABA: gamma-aminobutyric acid; LPS: lipopolysaccharide.

tein expression and increasing intestinal permeability, resulting in stronger hepatoprotective effects [232]. In another study, biomimetic liposomes (MM-Lip-Rg3/PNS), encapsulating Rg3 and PNS within macrophage-membrane-coated microspheres, delivered *via* intranasal administration, specifically targeted ischemic brain injury sites. MM-Lip-Rg3/PNS selectively accumulated in ischemic areas, including microglia, improving brain inflammation and reducing infarct size, thereby enhancing therapeutic efficacy. Pharmacokinetic analyses indicated MM-Lip-Rg3/PNS exhibited stronger lesion-targeting and prolonged half-life [233]. Another study utilized hyaluronic acid-modified ZIF-8 as a carrier for Saikosaponin A and doxorubicin, forming a highly stable nanodrug delivery system with increased drug loading capacity. This approach enhanced tumor targeting efficacy and mitigated cardiotoxicity through dual-drug interactions [234]. DPPC-glucoside-diosgenin (P-SG-Dio), a novel multifunctional nanoliposome, showed high cellular uptake and trans-epithelial transport efficiency, significantly improving anti-hyperuricemic and anti-inflammatory effects upon oral administration [235]. Cyclodextrins, widely used carriers due to their hydrophilic exterior and hydrophobic interior, form inclusion complexes with hydrophobic drugs, enhancing solubility and stability. A recent study designed folate-targeted, polyethylene glyco-modified amphiphilic cyclodextrin nanoparticles encapsulating Rg3 and quercetin. Pharmacokinetic studies indicated that these cyclodextrin nanoparticles significantly improved drug delivery barriers, prolonged Rg3 circulation in plasma, increased tumor targeting, and enhanced the anticancer efficacy of Rg3 [236]. In summary, drug delivery systems markedly improve saponin bioavailability by optimizing their physicochemical properties, promoting targeted drug release, and enhancing therapeutic efficacy.

6. Summary and prospects

Despite saponins' promising therapeutic potential for NDs *via* the GBA, the current research progress still faces certain limitations. First, the GBA comprises complex components, with GM forming a highly intricate ecosystem. Most studies confirm the efficacy of saponins for treating NDs and their association with the GBA but fail to clarify precise mechanisms of action [215]. Therefore, further studies, including gene sequencing [237], genome-wide association studies [238], multi-omics analyses [239], and FMT [240] are necessary. Second, certain GM communities or metabolites have dual probiotic and pathogenic roles, and current studies have not fully elucidated their mechanisms. For example, *Sutterella*, a bile-tolerant Gram-negative bacterium, has demonstrated both protective and pathogenic effects through immune regulation, microbial metabolism, and gut barrier modulation in NDs. Similarly, *Akkermansia* usually beneficially modulates metabolism and immunity but shows increased abundance in some epilepsy and PD patients, potentially disrupting mucus layers, exacerbating gut inflammation, and impairing barrier function [187]. Such dual functions depend on host genetics, microbial ecology, disease stages, environmental factors, and methodological variability [241]. Additionally, the microbial metabolite IAA, derived from tryptophan, increases intestinal microbial diversity, strengthens gut barriers, and supports gut health. Conversely, impaired clearance of IAA leads to its accumulation as a uremic toxin, which exacerbates oxidative stress and inflammation, thereby adversely affecting health [242]. Clarifying these seemingly contradictory findings requires developing standardized protocols to elucidate causal relationships.

Third, the extraction and separation processes for saponins remain challenging. Selecting suitable extraction methods is crucial to enhance their utilization. Techniques such as ultrasonic extraction, microwave-assisted extraction, and supercritical fluid extraction significantly improve the efficiency of saponin extraction [190]. Fourth, limited bioavailability and potential toxicity restrict their commercial applications. Currently, most research investigating the neuroprotective effects of saponins remains at the preclinical stage, although some studies have advanced into early clinical trials. For instance, Xuesaitong Soft Capsules, formulated from PNS, were approved by China's State Drug Administration in 1999 to treat IS. A recent double-blind, placebo-controlled, multicenter study reaffirmed the efficacy and safety of Xuesaitong Soft Capsules as adjunctive therapy for IS patients [243]. Similarly, multiple clinical studies have demonstrated the efficacy and safety of ginsenosides in treating acute IS and improving cognitive impairment in patients with moderate AD [244, 245]. Furthermore, clinical studies involving oral administration of Astragaloside IV indicate potential benefits, such as reducing anxiety, producing neurosedative effects, supporting neural health, promoting functional recovery, and protecting against attention deficit disorder and cognitive decline [246]. However, due to small sample sizes, short follow-up periods, and complex mechanisms associated with multi-component formulations, additional large-scale clinical tri-

als are urgently needed to establish the clinical applicability of saponins.

It is well known that transitioning from preclinical studies to clinical research poses significant challenges. Primarily, research into the pathophysiological processes of NDs has long relied on mouse models and postmortem human brain tissue samples. However, species differences, the complexity of the human genome, prolonged developmental timelines, and unique brain architecture limit accurate replication of human conditions in rodent models [247]. To overcome these limitations, brain organoid models, derived from human embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) using three-dimensional technology, offer promising avenues for translational research and deepening insights into human brain development and disease mechanisms [248]. Secondly, plant extracts containing saponins often exhibit complex compositions and widespread isomerism [249]. Extraction under specific conditions may induce structural transformations. For instance, gastric acid exposure or vinegar-roasting processes can convert saikosaponins, primarily transforming SSa into SSb1 and SSd into SSb2. These transformations may influence the pharmacological activities of saikosaponins, particularly antiviral and hepatoprotective effects [250]. Similarly, the low bioavailability of saponins necessitates various routes of administration and diverse dosage formulations, resulting in multiple metabolic pathways and numerous saponin derivatives with varying pharmacological effects and toxicities [251]. Nevertheless, these characteristics create significant challenges for studies on pharmacodynamics, toxicology, drug quality, and standardization. Establishing clear correlations among pharmacological activity, standardized quality control, and clinical efficacy is critical for precision medicine. Thus, future research must utilize techniques such as UPLC-Q-TOF-MS, mass spectrometry imaging, metabolomics, and network pharmacology. These methods enable quantitative analysis and rigorous quality control of bioactive saponin components [252], providing the foundation for precision saponin therapy. Finally, in clinical drug application, evaluating and ensuring safety remains fundamental. Dose-related and idiosyncratic toxicities highlight the necessity for clinical trials to rigorously consider individual variability and drug interactions concerning efficacy and toxicity. This requires integrating toxicity assessments, pharmacokinetic analyses, and pharmacodynamic studies, while leveraging advanced tools like artificial intelligence to establish comprehensive drug databases. Such resources will guide the development of scientifically robust and rational dosage standards.

Overall, saponins demonstrate promising therapeutic effects on NDs *via* the GBA. By modulating multiple targets, including GM and their metabolites, immune cells, cytokines, and neurotransmitters, saponins restore intestinal microbial balance, alleviate neuroinflammation and oxidative stress, repair damage to the intestinal barrier and BBB, inhibit excessive HPA axis activation, and improve neuronal function and synaptic plasticity. These effects collectively offer additional therapeutic options for NDs. The modulation of GM by saponins appears to be the initial step in remotely influencing brain function. This modulation particularly involves interactions with SCFA-producing bacterial genera such as *Bacteroides*, *Prevotella*, *Bifidobacterium*, and *Lactobacillus*. By regulating SCFA synthesis, saponins influence intestinal barrier integrity, immune-inflammatory responses, HPA axis activation, and neurotransmitter synthesis and release. Additionally, the regulatory effects of saponins on pro-inflammatory pathogens, such as *Vibrio vulnificus* and *Escherichia coli,* should also receive attention. By reducing inflammatory factor production, saponins mitigate both local and systemic inflammation. From a pharmacological standpoint, saponins exert their beneficial effects by intricately regulating critical signaling pathways involved in the progression of NDs, including NF-κB, PI3K/Akt, Nrf2, and BDNF-TrkB. However, as an important class of natural compounds, saponins frequently face challenges due to their complex chemical composition, intricate extraction methods, metabolic pathways, and mechanisms of action, as well as limited bioavailability and potential toxicity. This paper highlights evidence supporting the therapeutic potential of saponins, summarizes the possible mechanisms underlying their neuroprotective effects *via* the GBA, and briefly reviews current studies on saponin toxicology and targeted drug-delivery systems. Collectively, these efforts aim to accelerate the clinical translation of saponins, thereby providing novel therapeutic strategies for NDs.

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Declaration of competing interest

These authors have no conflict of interest to declare.

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