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Review Article

Ginseng as a therapeutic target to alleviate gut and brain diseases via microbiome regulation

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ABSTRACT

The human gut, which contains a diverse microbiome, plays an important role in maintaining physiological balance and preserving the immune system. The complex interplay between the central nervous system (CNS) and the gut microbiome has gained significant attention due to its profound implications for overall health, particularly for gut and brain disorders. There is emerging evidence that the gut-brain axis (GBA) represents a bidirectional communication system between the CNS and the gastrointestinal tract and plays a pivotal role in regulating many aspects of human health. Ginseng has shown potential to ameliorate conditions associated with dysbiosis, such as gut and CNS disorders by restoring microbial balance and enhancing gut barrier function. This comprehensive review provides valuable insights into the potential of ginseng as a herbal modulator of GBA as a therapeutic intervention for preventing and treating gut and neurological diseases via microbiota regulation to ultimately enhance overall health. Furthermore, we emphasize the therapeutic benefits of ginseng, its ability to enhance beneficial probiotics, such as Firmicutes, *Bacteroides*, *Lactobacillus, Bifidobacterium*, and *Akkermansia* while reducing pathogenic bacteria prevalence, such as *Helicobacter, Clostridium*, and Proteobacteria. Although the connection between ginseng regulation of microbial communities in response to the gut and neuropsychiatric disorders is lacking, additional investigations are warranted to elucidate the underlying mechanisms, optimize dosages, and explore the clinical relevance of ginseng in promoting GBA balance and ultimately overall health.

1. Introduction

The gut microbiome is dynamic and critical to human health. The human microbiome constitutes a complex ecosystem, with the intestinal microbiota being the most extensive in terms of scale and species diversity [1]. The gut microbiome is a vast ecosystem of commensal bacteria residing and comprises $> 10^{12}$ microorganisms per gram of content. Additionally, the human gut microbiome is approximately 1 kg, which is about the same weight as the brain [2]. At approximately 2.5 years of age, there are 10^{10} to 10^{12} gut bacteria per gram in the gut [3]. The gut microbiome is primarily characterized by two dominant bacterial phylotypes: Firmicutes and Bacteroidetes. These constitute approximately 90 % of the intestinal bacteria in healthy individuals, with the remaining 10 % comprises Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteria (among others) [1]. The gut-brain axis (GBA) is crucial for homeostasis and plays a critical role in regulating various aspects of the intestine, including mucus layer production, permeability, and immune functions [4,5]. The gut microbiome also

Abbreviations: AD, Alzheimer disease; AOM, azoxymethane; CNS, central nervous system; CRC, colorectal cancer; DSS, Dextran sulfate sodium; FRG, fermented red ginseng; GBA, Gut-brain axis; GC-K, ginsenoside compound K; HPA, hypothalamic-pituitary-adrenal; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; NF-κB, nuclear factor kappaB; PD, Parkinson's disease; SCFAs, short-chain fatty acids; TNBS, trinitro-benzene-sulfonic acid; TNF, tumor necrosis factor; TLR, Toll-like receptor; WGP, Water soluble ginseng polysaccharides; WGPA, Water soluble ginseng polysaccharides acidic fraction; WQP, Polysaccharides of *P. quinquefolius*.

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controls basic aspects of the central nervous system (CNS), and health behaviors. Gut microbiome composition abnormalities are linked to immune, endocrine, and nervous system disorders, including intestinal motility, mood changes, depression, and increased susceptibility to stress factors, resulting in gut and neurodegenerative diseases via interactions with GBA [2,4,5]. This complex interaction of GBA via gut microbiota regulation is often underemphasized, leading to diagnostic and management delays in treating underlying disorders.

Ginseng is a traditional medicinal herb derived from the root of the *Panax* sp. [Araliaceae] plant and is widely recognized throughout the world [6]. Ginseng possesses immunomodulatory activities and has been used for centuries to treat physical and mental illnesses including gut and CNS abnormalities [6–8].

This overview introduces the comprehensive GBA concept and highlights its potential to treat a variety of intestinal and CNS abnormalities through gut microbiome modulation.

2. Gut-brain axis (GBA): a bidirectional communication system

The GBA is a complex and dynamic network of bidirectional communication system that coordinate the emotional and cognitive centers of the brain with the peripheral functions of the intestine to ensure gut homeostasis [4,5]. GBA interactions are mediated by several neuroimmune-endocrine pathways that involve multiple essential components, such as the enteric nervous system, CNS, circulatory system, immune system, brain, blood-brain barrier, and hypothalamic–pituitary–adrenal (HPA) axis, which can penetrate the mucus and epithelial layers, thereby affecting intestinal and neuronal functions [4,7]. The communication network of these biological pathways includes multiple direct and indirect signaling through hormones, neurotransmitters (neuropeptides), chemical transmitters, metabolic products, and microbial and tryptophan metabolites [4,5]. GBA facilitates the gut and brain connection, allowing these biological networks to monitor gut functions, including intestinal motility, enteric reflex, mental health, enteroendocrine signaling, and metabolic pathways [4,5].

2.1. Microbiota-GBA

Emerging evidence indicates that the gut microbiome, including its diverse microbiome-derived metabolites and products, contributes to the pathogenesis and/or progression of many gut and CNS abnormalities, including neurodevelopmental, neuropsychiatric, and neurological disorders, and participates in bidirectional communication between the brain and gut [2,4,5]. A detailed description of these pathogenic microbiota as the hub of the gut and CNS disorders are shown in Fig. 1. Brain structure and function can be gut-modulated; in turn, the brain regulates the gut microenvironment and microbiota composition [9]. Numerous studies have explored the impact of microbiota-targeted interventions on patients with CNS diseases [5,6]. For instance, in healthy females, probiotic consumption (4 weeks) resulted in changes in the functional connectivity of the brain's emotion recognition network [10]. In another study in healthy subjects, probiotics enhanced emotional decision-making and caused concurrent changes in certain microbial taxa [9].

The gut microbiota communicates with the gut and CNS through regulation of the tryptophan metabolism pathway to induce serotonin

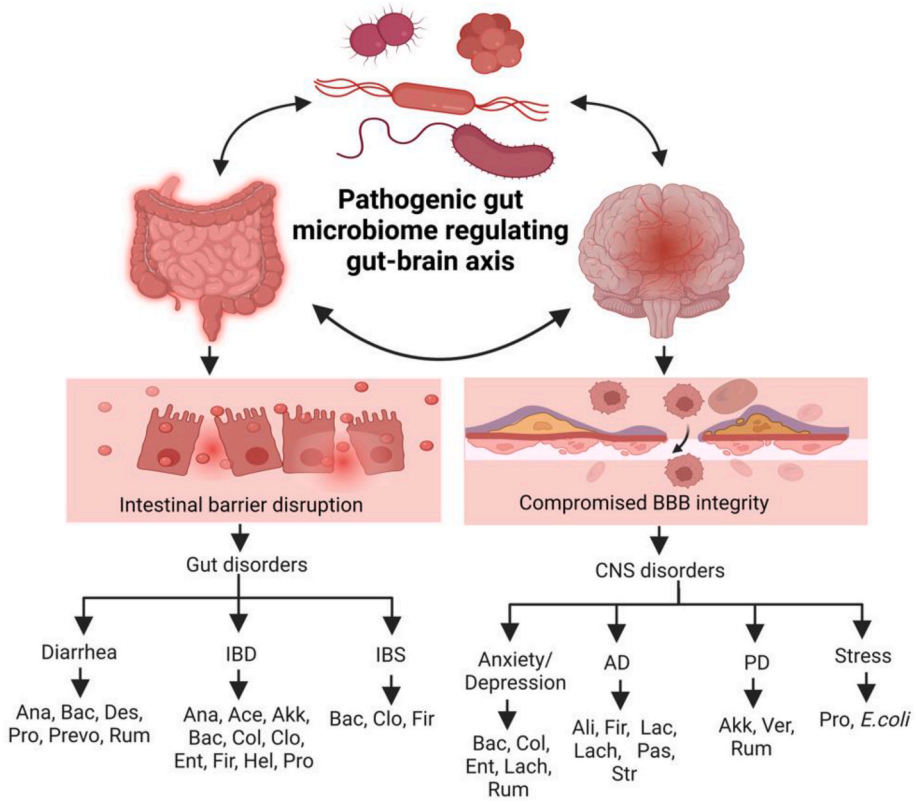

Fig. 1. Schematic representation highlighting the tripartite microbiota-gut-brain relationship and cross-talk between pathogenic microbiota as the hub of the gut and CNS disorders. In pathological conditions, microbial dysbiosis induces gut microbiota alterations which lead to increased intestine epithelial barrier permeability and blood-brain barrier disruption, in turn leading to increased risks of potential pathogenic disorders. Consequentially, gut microbiota composition is affected by risk factors underlying these disorders that may induce chronic inflammatory reactions in the gut and the brain. Abbreviations: Ace, *Acetatifactor*; Ali, *Alistipes*; Akk, *Akkermansia*; Ana, *Anaerotruncus*; Bac, Bacteroidetes; Clo, *Clostridium*; Col, Colibacillus; Des, *Desulfovibrio*; Ent, *Enterococcus*; *E. coli*, *Escherichia coli*; Fir, Firmicutes; Hel, *Helicobacter*; Lach, Lachnospiraceae; Pas, Pasteurellaceae; Prevo, Prevotae; Pro, Proteobacteria; Rum, *Ruminococcus*; Str, *Streptococcus*; Ver, Verrucomicrobia.

and short-chain fatty acid (SCFA) release. This is progressively linked to a range of complex host behaviors, including intestinal disorders, mood states, stress-induced anxiety or depression, and cognitive behaviors (either direct or indirect) signaling [9,11]. These pathways not only interact directly with endocrine and enterocyte cells and the mucosal immune system, but can also cross the gut barrier or the blood-brain barrier to enter the systemic circulation. Alternatively, microbial signals can communicate via the vagus nerve or spinal cord central pathways [12]. Collectively, these pathways are referred to as the microbiota-gut-brain axis (microbiota-GBA), which represents a comprehensive concept of biochemical signaling and interactions between the brain, gut bacteria, and the gastrointestinal tract [4]. Among them, SCFAs, which are gut bacterial metabolites, are mainly represented by saturated fatty acids such as acetate, butyrate, lactate, propionate, and succinate, which are mainly produced by bacteria (e.g., *Bacteroides, Prevotella Roseburia, Ruminococcus*) through fermentation of fiber-rich substrates to modulate regulators to maintain homeostasis and immune cells in the human body [13]. Increased luminal butyrate production promotes mucosal healing and encourages the production of protective mucus along the intestinal epithelium [14].

3. Ginseng

Ginseng has been known for centuries to treat physical and mental ailments, promote longevity, and have immunomodulatory activity [6]. There are several ginseng species, but *Panax ginseng* Meyer (Asian ginseng, Korean ginseng or Korean red ginseng), *Panax notoginseng* (Chinese ginseng or Sanchi), and *Panax quinquefolius* L. (American ginseng) have received considerable attention worldwide for their use in health care products and food additives to alleviate disease symptoms and improve health status [6].

Recently, ginseng has been found to contain approximately 200 active compounds, including ginsenosides, oils, polyacetylenes, and polysaccharides [15]. Ginseng owes its pharmacologic properties to the ginsenosides (referred to as steroidal saponins) found in ginseng extracts [16]. The pharmacological actions of ginseng include a variety of biological activities against cancer, immunology, inflammation, and psychiatric disorders such as depression and metabolic syndrome [6,15].

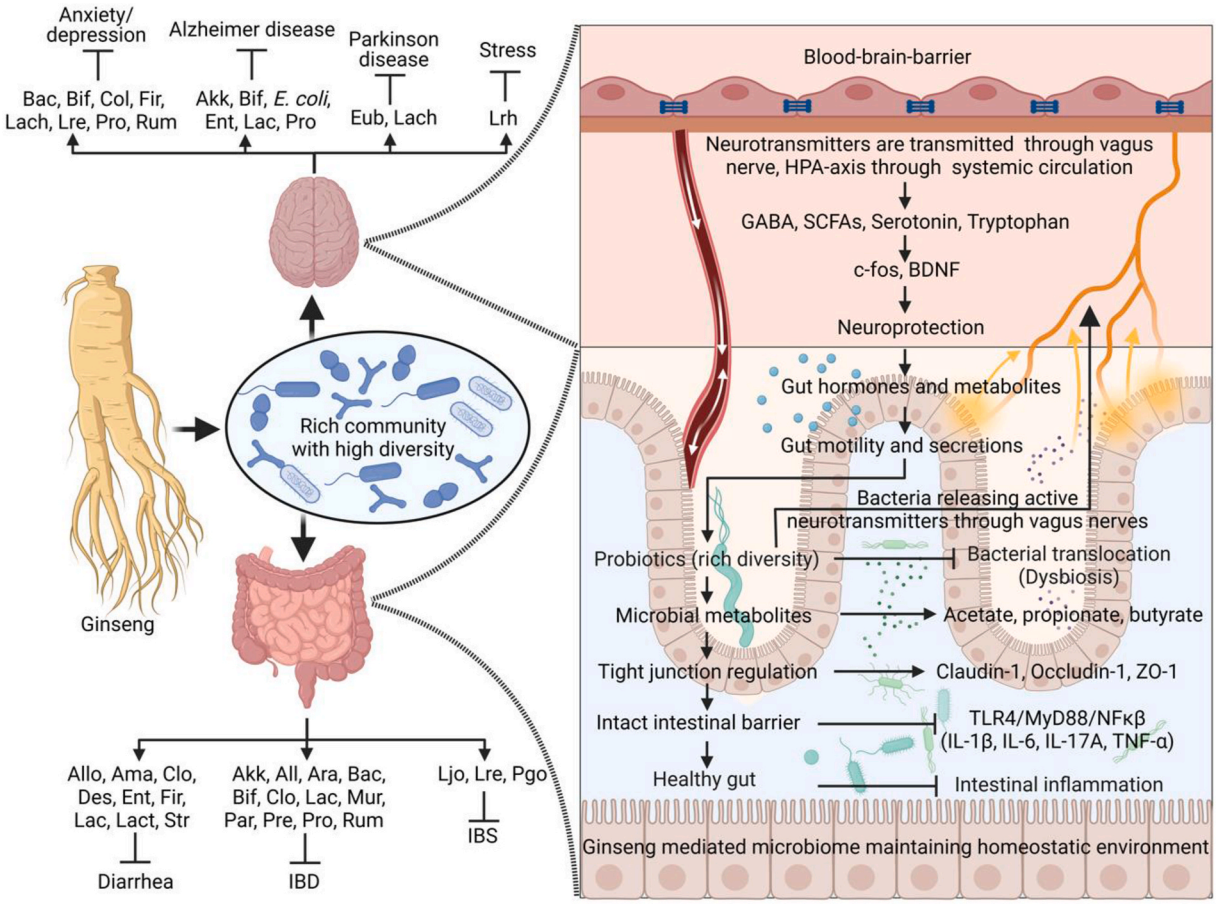

Fig. 2. Ginseng regulation of the microbiome via the gut-brain axis. The gut microbiome modulates pathophysiological mechanisms underlying gut and CNS disorders via multiple direct and indirect signaling pathways. Ginseng exerts its preventive/therapeutic effect via gut microbiome modulation leading to gut blockage and CNS disorders. These effects include endocrine (cortisol), immune (cytokines), and neural (vagus, enteric nervous system and spinal nerves) pathways. Ginseng and its components regulate the microbial effect via systemic circulation in the gut, communicating by synthesizing bioactive molecules (cytokines, hormones, microbial metabolites and neurotransmitters) and is mediated by the vagus nerve and HPA axis that cross the blood-brain barrier and modulates immune-response, neurogenesis, and neuroprotection. These effects modulate epithelial cells to target enteroendocrine and enterochromaffin cells, which regulate gastrointestinal secretions through abundant community diversification. This can lead to SCFA activation, which release several beneficial components and regulate intestinal barrier function via the TLR4/MyD88/Nfkβ pathway. Otherwise, bidirectional communication between the brain and the gut microbiome is mediated by the vagus nerve, which transmits neuronal, endocrine, and immune signals from the gastrointestinal tract to the brain via the autonomic nervous system and ENS, which influence brain health (image created using the BioRender application). Abbreviations: Akk, *Akkermansia*; All, *Allobaculum*; Allo, *Alloprevotella*; Ama, *Atractylodes macrocephala*; Ara, *Arabidopsis*; Bac, Bacteroidetes; Bif, *Bifidobacterium*; Clo, *Clostridium*; Col, Colibacillus; Des, *Desulfovibrio*; Ent, *Enterococcus*; Eub, *Eubacterium*; Esc, *Escherichia*; Fir, Firmicutes; Lac, *Lactobacillus*; Lach, Lachnospiraceae; Lact, *Lactococcus*; Ljo, *Lactobacillus johnsonii*; Lre, *Lactobacillus reuteri*; Lrh, *Lactobacillus rhamnosus*; Mur, Muribaculaceae; Par, *Parasutterella*; Pgo, *Parabacteroides goldsteinii*; Pre, Prevotellaceae; Pro, Proteobacteria; Rum, *Ruminococcus*; Str, *Streptococcus*.

4. Ginseng and gut microbiome

The pharmacological effects of ginseng are closely linked to the gut microbiome, which acts as the primary mechanism of ginsenoside conversion [8,17–19]. Gut microbiota can play a very important role in the bioavailability of nonpolar ginsenosides as it can biotransform them. Currently, ginseng has many poorly understood ginsenosides with poor biological activity. However, through processing and modification by gut microorganisms, a total of 289 ginsenosides, including free ginsenosides, have been identified and their biological activity is expected to be greatly improved [20]. Furthermore, SCFA production was consistently boosted by supplementation with extracted ginsenosides, suggesting that saponins preferentially support SCFA-producing bacterial growth [21,22]. SCFAs are pivotal in mediating gut-brain interactions by exhibiting neuroactive effects on gut-brain signaling pathways, including the immune and endocrine systems [13,14]. After oral administration, ginseng or red ginseng ginsenoside is exposed to stomach acid, digestive and bacterial enzymes to be broken down or metabolized by intestinal microbiota and eventually absorbed from the intestine and enter the bloodstream [23]. Treatment with ginseng has been shown to increase levels of several probiotics, including *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *Verrucomicrobia*, while concurrently reducing levels of pathogenic bacteria such as *Deferribacters*, *Helicobacter*, *Lactobacillus* for several intestinal and neurological conditions. A detailed description of the therapeutic effect of ginseng via modulation of microbiome to attenuate gut and CNS disorders is shown in Fig. 2 and Tables 1 and 2. *Bacteroides*, *Eubacterium*, and *Bifidobacterium* are important bacteria involved in ginsenoside conversion *in vivo* [24]. Additionally, ginseng extract intake for 34 weeks in rats decreased the Bifidobacteriaceae and *Lactobacillus* abundance and increased Proteobacteria, Methylobacteriaceae, *Parasutterella,* and *Sutterella* abundance, suggesting that it regulates host gut metabolism. The increased *Bifidobacterium* and *Lactobacillus* abundance demonstrated that ginseng extract contributed to probiotic amplification [25]. *Bifidobacterium* and *Lactobacillus* are known to be associated with positive effects of increasing barrier function [26], which highlights its metabolic benefits [27]. After long-term ginseng extract administration in rats, probiotics such as *Bifidobacterium, Clostridium, Lactobacillus,* and *Allobaculum* significantly increased in the intestinal microbiota, suggesting that long-term ginseng extract intake could facilitate probiotic growth. Meanwhile, some pathogenic bacteria, such as *Butyricimonas*, *Helicobacter*, *Parabacteroides*, and *Alistipes* were significantly downregulated, further indicating that long-term ginseng extract intake may have a positive effect on inhibiting pathogenic bacteria colonization [28].

Table 1
Ginseng regulation of the microbiome to inhibit gut disorders.

Disease	Increase	Ginseng compounds/ extracts	Decrease	General mechanism
Diarrhea	Ana, Bac, Des, Pro, Prevo, Rum	Fermented ginseng, Ginseng polysaccharide, Shenzhu capsule (contains ginseng)	Allo, Ama, Clo, Des, Ent, Fir, Lac, Lact, Str	Reduces diarrhea index, inhibits pro-inflammatory cytokines through NF-kB blockade.
IBD	Ana, Ace, Akk, Bac, Col, Clo, Ent, Fir, Hel, Pro	Ginseng polysaccharide, Ginsenoside Rk3	Akk, All, Ara, Bac, Bif, Clo, Lac, Mur, Par, Pre, Pro, Rum	Decrease MPO, disease activity index, malondialdehyde levels and serum pro-inflammatory cytokines. Enhance mTOR dependent autophagy. Increase tight junction proteins, and inhibit NF-kB inflammatory pathway.
IBS	Bac, Clo, Fir	KRG	Ljo, Lre, Pgo	Reduces the anxiety-like behavior, frequency of visceral pain, and mitigated abdominal pain-related behaviors leading to normalization of healthy gut function.

The various pharmacological benefits associated with ginseng are due to the presence of natural antioxidant compounds extracted from its berries, leaves, roots, and stems [17–19]. Additionally, these pharmacologically active ingredients support neurogenesis, neuronal growth, neurotransmission, and synaptogenesis thereby protecting the CNS from unexpected events [7]. Upon treatment with KRG, responders were relatively enriched in the Lachnospiraceae (family) and the Clostridiales (order) compared to non-responders [29]. Moreover, the prebiotic effects of ginseng on beneficial bacteria in the genera *Akkermansia, Lactobacillus,* and *Bifidobacterium* have remained consistent across multiple studies [30]. In terms of beneficial aspects related to gut barrier function, *Akkermansia*, specifically *Akkermansia muciniphila, Bifidobacterium* and *Lactobacillus* [31]. Ginseng polysaccharides promote the growth of *Bacteroides* spp. and *Lactobacillus* spp. which are major ginsenoside-metabolizing bacteria, restore gut microbiome, and enhance intestinal metabolism as well as absorption of specific ginsenosides [32]. Notably, the composition of gut microbiota varies significantly among individuals and changes at different life stages [1].

4.1. Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a chronic inflammatory disorder characterized by recurrent episodes of inflammation in the intestines. People with IBD are at a higher risk of developing CNS complications than people without IBD. Clinical studies highlight the important link between IBD and mental illness, particularly depression and anxiety; Individuals with a history of depression are more prone to be diagnosed with IBD, and certain antidepressants have a protective effect against IBD [19,33]. The prevalence of depression and anxiety in IBD patients is 22–25 % and 32–35 %, respectively [33,34]. Mice exposed to immobilization stress results in the colitis and gut dysbiosis leading to the outbreak of anxiety/depression with neuroinflammation by imbalanced activation of the microbiome-gut-brain axis [18]. Gut microbiota dysregulation associated with depression give rise to gastrointestinal symptoms such as IBD, with irritable bowel syndrome (IBS) being the most common. These conditions are often characterized by abundant changes in the two main phyla, Bacteroidetes and Firmicutes [35]. The gut microbiome modulates behavior, influences neurodevelopment, and contributes to neurological disorders [18]. Furthermore, studies are increasingly recognizing that alterations in the diversity and proportions of the microbiome and microbial metabolites are associated with a wide range of neurological and psychiatric diseases [4]. Oral L. *reuteri* administration alleviates ampicillin-induced anxiety and colitis [37]. Fermented red ginseng (FRG), a common tonic and herbal medicine alleviated anxiety/depression and colitis and depression-exposed mice by regulating microbiota-GBA and immobilized stress-exposed mice through the regulation of HPA [18]. Similarly, FRG administration promoted health as it improved stool consistency and increased the frequency of bowel movements in elderly Korean women [23].

Gut dysbiosis, characterized by an imbalance in the composition and metabolic activity of the microbial population, is the driving force behind gut inflammation and permeability disruption [35]. American ginseng increases the composition of beneficial bacteria, including *Lactobacillus, Bifidobacterium, Parasutterella, Clostridiales*, and Lachnospiraceae families, thus effectively restoring intestinal immune disorders, mucosal integrity impairment, and gut microbiome dysregulation [38]. Ginseng can restore gut microbiota dysfunction in colitis models [39]. Administration of ginseng polysaccharides to DSS-treated rats

Table 2
Ginseng regulation of the microbiome to inhibit neurological disorders.

Disease	Increase	Ginseng	Decrease	General mechanism
Anxiety/ Depression	Bac, Col, Ent, Lach, Rum	Bifidobacterium fermented red ginseng and ginsenoside Rd	Bac, Bif, Col, Fir, Lach, Lre, Pro, Rum	Reduces IL-6, TNF-α, and depressive behavior by inhibiting brain-derived neurotrophic factor and MPO through the NF-kB pathway
AD	Ali, Fir, Lach, Pas, Str	Qishen Wan formula (contains ginseng), Ginsenoside Rg1	Akk, Bif, E. Coli, Ent, Lac, Pro	Improves learning and memory by reducing pathological damage and Aβ concentration in the hippocampus and reducing levels of pro-inflammatory cytokines through the NF-kB pathway.
PD	Akk, Rum, Ver	KRG	Eub, Lach,	KRG extract prevents MPTP-induced dopaminergic neuronal death, activation of microglia and astrocytes, accumulation of α-synuclein in the substantia nigra, and regulation of inflammation-related factors in the colon.
Stress	Pro, *E. coli*,	KRG	Lrh	KRG ameliorates inflammation and effectively regulates stress-induced hormonal changes to maintain homeostasis.

Ace, Acetatifactor; Ali, Alistipes; Akk, Akkermansia; All, Allobaculum; Allo, Alloprevotella; Ama, Atractylodes macrocephala; Ana, Anaerotruncus; Ara, Arabidopsis; Bac, Bacteroidetes; Bif, Bifidobacterium; Clo, Clostridium; Col, Colibacillus; Des, Desulfovibrio; Ent, Enterococcus; *E. coli*, *Escherichia coli*; Eub, Eubacterium; Fir, Firmicutes; Hel, Helicobacter; KRG, Korean red ginseng; Lach, Lachnospiraceae; Lac, Lactobacillus; Lach, Lachnospiraceae; Lact, Lactococcus; Ljo, Lactobacillus johnsonii., Lre, Lactobacillus reuteri., Lrh, Lactobacillus rhamnosus; Mur, Muribaculaceae; MPO, Myeloperoxidase; Par, Parasutterella; Pas, Pasteurellaceae; Pgo, Parabacteroides goldsteinii Pre, Prevotellaceae., Prevo, Prevotae; Pro, Proteobacteria; Rum, Ruminococcus; Str, Streptococcus; Ver, Verrucomicrobia.

significantly increased the relative abundance of probiotics, decreased the relative abundance of pathogenic bacteria, and inhibited various inflammatory signaling pathways [40]. *Panax ginseng* significantly increased the relative abundance of beneficial bacteria (*Akkermansia,* Muribaculaceae norank, and Lachnospiraceae NK4A136), but markedly decreased the abundance of pathogenic bacteria (*Bacteroides, Desulfovibrio,* and *Parabacteroides*) [41].

Administration of FRG to a DSS-induced colitis model prevented the loss of tight junction protein (Zonula Occludens-1) while inhibiting the NF-κB inflammatory pathway [42]. Consistently, clinical trials have also shown improved stool consistency and bowel function in patients with IBD taking FRG for three weeks [23]. Treatment with KRG, FRG, Rd, or protopanaxatriol mitigated colitis by modulating gut dysbiosis and NF-κB-mediated expression [43]. The gut microbiome maintains a balance between beneficial and pathogenic bacteria to help defend the gut [11]. Similarly, bifidobacteria-FRG can reduce Th2 type cytokines (IL-4, IL-5, and IL-13) levels in the colon and restore gut microbiota populations such as Actinobacteria, Bacteroidetes, and Firmicutes phyla [44]. FRG mitigates trinitrobenzene sulfonic acid (TNBS)- and *Escherichia coli*-induced colitis [45]. Administration of red ginseng to rats with TNBS-induced colitis showed therapeutic effects by increasing the abundance of probiotics and decreasing the abundance of pathogenic bacteria [46]. Dysbiosis is also a common occurrence in IBD, which is strongly correlated with mood disorders and GBA disruptions [35].

Overall, ginseng and its extracts increase the Bacteroidetes population and decrease the Proteobacteria population. This indicates that ginseng has remarkable potential as a therapeutic product to preserve intestinal barrier function and favorably modulate tight junction protein expression [47], and may help alleviate anxiety/depression through improvements in gut microbiota and hippocampal inflammation [43]. Similarly, 15 and 30 mg/kg/day of American ginseng significantly repressed AOM/DSS-induced colitis and colon cancer development by suppressing pro-inflammatory cytokines and restoring the microbiota profiles [48]. In another study, American ginseng contributed significantly to the restoration of a disrupted microbial community resulting from AOM/DSS-induced dysbiosis [39]. Administration of 60 mg/kg of ginsenoside compound K (GC-K) suppressed AOM/DSS-induced colitis-associated colorectal cancer (CRC) growth and restored *A. muciniphila* abundance [47], contributing to intestinal barrier function improvement [31]. Furthermore, GC-K treatment significantly decreased *Bacteroides* spp., an indicator of ulcerative colitis. Moreover, fecal microbiota transplantation experiments confirmed that restoration of the gut microbiota by GC-K could significantly alleviate DSS-induced colitis [49]. Additionally, American ginseng markedly decreased AOM/DSS-induced colon inflammation as well as tumorigenesis by restoring gut microbiome balance [39]. Synergistically, American ginseng polysaccharide and ginseng ginsenoside enhanced various beneficial mucosa-associated bacteria such as *Bifidobacterium*, *Clostridiales*, and *Lachnospiraceae*, while decreasing pathogenic bacteria *Escherichia, Shigella* and Peptococcaceae suggesting enhanced mucosal immunity and gut barrier protection [38]. Changes in abundance were observed at the family level, with increases in the Bacteroidaceae and Porphyromonadaceae families linked to the beneficial effects of American ginseng in countering colitis and inhibiting tumor growth [38]. Furthermore, in a non-small cell lung cancer model, the administration of ginseng polysaccharides at a dose of 200 mg/kg enhanced recovery from bacterial imbalance by modulating the relative abundance of bacteria such as *Bacteroides vulgatus, Escherichia, Rikenella* and *Parabacteroides distasonis* [50]. Water-soluble ginseng polysaccharides (WGP) and their purified acidic fraction (WGPA) enhanced the relative abundance of *Ruminococcus* and SCFA production, suggesting that ginseng polysaccharides are a potential intervention strategy for colitis prevention [51]. In particular, treatment with American ginseng polysaccharides and ginsenosides has been shown to prevent side effects induced by the anticancer drug cyclophosphamide treatment in cancer patients (immune dysfunction and intestinal barrier dysfunction), suggesting that it could be used as an immunostimulant targeting the gut microbiome-metabolites axis to prevent cyclophosphamide-induced intestinal barrier dysfunction [38]. Administration of ginsenoside Rb1 to AOM/DSS-induced CRC model mice restored gut microbiota composition [52] and significantly decreased levels of pro-inflammatory cytokines, including IL-1β, IL-6, IL-17A, IL-22, IL-33, and TNF-α, suggesting that ginsenoside Rb1 can be used as an effective therapeutic target to prevent inflammation-associated CRC development [52]. Ginsenoside Rk3 significantly reduced Firmicute/Bacteroidetes phylum ratios, effectively improving the metabolic imbalance of the gut microbiota and inhibiting the inflammatory cascade through inhibition of the TLR4/NF-κB signaling pathway, indicating its potential use as a natural anti-inflammatory agent to reduce obesity-induced colitis [53]. Similarly, ginseng improves gut barrier integrity and immune function by regulating tight junction molecules (ZO-1) through inhibition of the TLR4/NF-kB pathway [21,22]. Both WGP and WGPA alleviated the colitis symptoms in Wistar rats via inhibition of TLR4/MyD88/NF-κB--signaling pathway [51]. Ginsenoside Rk3 intake enriched the genera *Alloprevotella*, *Bacteroides* and *Blautia* and effectively improved gut microbiota imbalance, significantly reducing the Firmicutes/Bacteroidetes ratio, indicating that Rk3 can help restore the gut microbiota, causing beneficial changes, thereby alleviating gut inflammation [21, 22]. When ginseng-derived exosome-like nanoparticles were administered to DSS-induced colitis mice, NF-κB was inhibited, effectively suppressing inflammatory cytokines such as TNF-α and IL-6 [54]. Furthermore, ginseng-derived exosome-like nanoparticles reduced the Firmicutes/Bacteroidota ratio of the gut microbiome, suggesting that it has therapeutic effects against IBD [54]. Administration of *Panax quinquefolius* at a dosage of 200 mg/kg to the DSS-treated mice decreased the abundance of Firmicutes and increased the abundance of Bacteroidetes,

resulting in an increase in the total SCFA content, including acetic acid, butyric acid, propionic acid, and tight junction proteins, in colitis mice compared to DSS alone [55]. Ginsenoside Rk3 increases the abundance of probiotic bacteria such as Lactobacillaceae and *Bacteroides*, but decreases the abundance of pathogens that promote the production of inflammatory factors such as Proteobacteria and Helicobacteraceae [53].

Collectively, ginseng and its extracts increased the Firmicutes/Bacteroidetes phylum ratio and exhibited microbiome modulating effects that were beneficial in alleviating IBD [26,27] (Fig. 2). *Lactobacillus johnsonii* attenuated TNBS-induced gastrointestinal inflammation and memory impairment in mice [56]. In summary, ginseng demonstrates the potential to inhibit inflammation and improve colitis by helping to prevent and treat gut and neurological diseases by increasing the relative abundance of probiotics including *Bacteroides* and *Lactobacillus* and reducing the relative abundance of pathogenic bacteria such as *Helicobacter*, thereby restoring the gut microbiome [36].

4.2. Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder involving gut-brain interactions, characterized by altered bowel habits and chronic recurrent abdominal pain, and occurs in up to 4.8 % of the global population [8,57]. IBS patients (>50 %) have comorbid depression or anxiety [58]. IBS patients have higher levels of anxiety and depression compared to controls; Between 30 % and 40 % of IBS patients have a comorbid anxiety or depression disorder [59]. Notably, the diagnosis of IBS precedes mood disorders, which means that in some patients, primary intestinal dysfunction may contribute to mood disorders [58,60]. Furthermore, individuals with higher baseline levels of anxiety and depression were significantly more likely to develop IBS [58,60]. Dysregulation of the gut microbiome due to depression can manifest as gastrointestinal symptoms, with IBS being the most common, but often accompanied by an increase in *Bacteroides* and Firmicutes [35] as shown in Fig. 1. When the gut microbiota of IBS mice was compared to that of control mice at the genus level, increased levels of *Prevotella* species but decreased levels of *Bacteroides* and *Parabacteroides* were observed [61]. In another study, KRG significantly reduced the anxiety-like behavior, frequency of visceral pain, and macroscopic score in IBS mice [8]. Stool consistency improved and bowel frequency increased in older women treated with FRG [43]. Moreover, KRG remarkably increased the beneficial gut microbes comprising *Lactobacillus (L.) reuteri*, *Lactobacillus johnsonii*, and *Parabacteroides goldsteinii* in IBS mice [8]. *L. reuteri* reportedly reduces inflammatory cytokine levels and strengthens the intestinal barrier [62]. *L. johnsonii* consumption also stimulates mucin secretion, which improves the intestinal barrier [63]. In mice injected with zymosan to induce symptoms similar to human IBS, 100 mg/kg of red ginseng (RG) increased levels of the beneficial bacteria *L. johnsonii, L. reuteri* and *P. goldsteinii* levels were all increased. However, the levels of *P. goldsteinii*, unlike *L. johnsonii* and *L. reuteri,* recovered to normal control levels, suggesting that normalization of healthy gut function is associated with the presence of *P. goldsteinii* [8]. RG significantly inhibited the expression of IL-1β in the gut and c-fos in the prefrontal cortex [8]. Moreover, treatment with RG mitigated abdominal pain-related behaviors, potentially due to a reduction in visceral hypersensitivity. Visceral pain in IBS has been linked to activation of IL-1β and TNF-α in the intestinal wall [64], suggesting that gastrointestinal symptoms are integral to conditions involving gut-brain interactions, such as IBS, which often co-occur with psychiatric diagnoses and psychological symptoms [8,65]. These findings are further supported by the evidence of high correlations between patients with IBS and those with depression and anxiety, and comorbidities found among these patients [65].

4.3. Diarrhea

Diarrhea is the leading cause of abdominal disorders with high morbidity and mortality rates worldwide. Pathogenic microbiota contribute substantially to diarrhea [66,67]. Ginseng and its extracts can help restore intestinal homeostasis by improving water and salt metabolism to relieve diarrhea [24]. There are three probiotic bacteria that are well known for relieving abdominal pain and pediatric diarrhea, including *L. reuteri, L. johnsonii,* and *P. goldsteinii* [8]. Changes in microbiota due to increased Bacteroidetes and decreased Firmicutes are indicative of intestinal barrier disruption and diarrhea in patients with IBS [68]. WGP significantly increased Firmicutes and relatively reduced Actinobacteria, Bacteroidetes, and Proteobacteria [66]. Polysaccharides of *Panax quinquefolius* (WQP) was observed to alleviate antibiotic-associated side effects such as dysbiosis and diarrhea induced by lincomycin [67]. Moreover, WQP reduced TNF-*α,* IL-1β, IL-6, and IL-17A levels, increased IL-10 and IL-4 levels, and promoted gut microbial diversity and composition in colon tissue [55]. At the bacterial genus level, WGP caused a relative increase in *Lactococcus, Lactobacillus*, and *Streptococcus* counts and a relative decrease in *Bacteroides*. In particular, an important strain of beneficial bacteria in the gut microbiota that responds to WGP has been found to be *Lactobacillus* [66]. *L. johnsonii* is similar in function to *L. reuteri* and has anti-inflammatory effects by preventing the proliferation of pathogens, thus relieving abdominal pain and pediatric diarrhea [69]. WQP increased SCFA levels, including acetate and propionate production, with relative increases in *Bacteroides* and *Lactobacillus* and relative decreases in *Coprococcus* and *Blautia* [67]. KRG administration showed a consistent tendency to normalize enteric microbiota [8]. FRG alleviated antibiotic-associated diarrhea and colonic inflammation at a dosage of 0.5 g/kg/d and suppressed the expression of colonic TLR4 and NF-κB [70]. Both FRG and ginseng polysaccharides have shown therapeutic effects on diarrhea by increasing the relative abundance of *Lactobacillus* and Firmicutes bacteria and inhibiting Bacteroidetes and Proteobacteria [70,71]. Similarly, WGP alters gut microbiota composition and diversity, restores gut microbiota, balances metabolic processes, and promotes mucosal repair in mice with antibiotic-associated diarrhea [66]. In the chemotherapy-induced diarrhea mice model, the combination of volatilized oil from *Atractylodes macrocephala* and ginseng polysaccharides significantly reduced the diarrhea index and improved colon lesions by restoring the gut microbiota structure [72].

4.4. Alzheimer disease

Alzheimer's disease (AD) is a progressive, multifactorial neurodegenerative disorder characterized by progressive cognitive impairment, memory, and motor deficits, resulting in a decline in behavioral, mental, and functional activity that impairs quality of living [17,73]. Behavioral, psychiatric, and neurodegenerative disorders often display the hallmarks of AD [17,73]. KRG (30 and 100 mg/kg/day) is effective in preventing disorders responsible for the progression of AD and improving the cognitive behavior of mice [17]. Consistently, continuous administration of *Panax ginseng* powder (4.5 g) to AD patients for 12 weeks has shown clinical efficacy in improving cognition [73]. The gut microbiome influences neurodevelopment, regulates behavior, and contributes to the resolution of neurological disorders [8]. Ginseng extract, ginsenosides, or preparations containing ginseng may exert neuroprotective effects and improve memory disorders by modulating the gut microbiome [74]. *P. quinquefolius* supplementation may elicit cognitive enhancement and improve short-term memory, potentially via gut microbiome modulation and neurotransmitter upregulation [75]. Furthermore, microbial diversity, which affects several metabolic pathways, was altered and reduced in AD mice compared to wild-type control, resulting in reduced levels of SCFAs compared to normal controls, leading to amyloid deposition, cognitive deficits, and intestinal abnormalities [76]. Gut microbiota species differ in patients with AD,

which is a major risk factor for disease progression [77]. Furthermore, disruption of the gut microbiota plays an important role in the development of AD-related pathogenicity [76]. The microbial profile of AD patients in feces exhibited increased number of Bacteroidetes and decreased numbers of Actinobacteria and Firmicutes compared to controls. In particular, the Clostridiaceae, Ruminococcaceae, and Turicibacteraceae lineages within the Firmicutes were reduced in AD patients [78]. Supplementation with *P. quinquefolius* significantly increased acetate, butyrate, and propionate levels in AD patients, which was associated with increased *Lactobacillus* and *Akkermansia muciniphila* [75]

The Qisheng Wan formula, which contains ginseng and ginsenoside Rg1, restores disordered gut microbiota and reduces inflammatory factor levels to reduce AD symptoms [79,80]. Administration of KRG (30 mg/kg/day) to a rat AD model resulted in a *Lactobacillus* dominance of the gut microbiome, restoration of blood-brain barrier integrity, reduced microglial activation, and improved memory and cognition, indicating that KRG improves AD pathology via GBA [17]. Altogether, these results strongly support the involvement of the microbiota in AD development in AD-susceptible animal models.

4.5. Anxiety/depression

Anxiety/depression is a neuropsychiatric disabling mental disorder characterized by persistent feelings of sadness, mental and behavioral disorders, and even suicidal tendencies [7]. Depression is more often associated with GBA dysfunction such as appetite loss, metabolic abnormalities, gut pathologies, and microbiome composition abnormalities [4].

Gastrointestinal inflammation is triggered by gut dysbiosis, which leads to the migration of gut microbial byproducts, such as endotoxins, into the bloodstream, progressing to depression/anxiety with neuroinflammation [8,11]. When the gut microbiome is disrupted by depression, it can lead to gastrointestinal symptoms such as IBS and IBD. More than 50 % of patients with IBS have anxiety or depression [58]. Anxiolytic treatment with KRG significantly diminished anxiety-like behavior, frequency of visceral pain, and macroscopic score in IBS mice [8].

Anxiety/depression is often associated with a relative increase in the abundance of Bacteroidetes, whereas in animals and patients, the abundance of *Lactobacillus* is reduced, as well as levels of Firmicutes [27,35]. FRG has demonstrated its ability alleviates anxiety, depression, and UC in mice via gut microbiome regulation [33]. *L. johnsonii* treatment alleviated anxiety by ameliorating gastrointestinal inflammation [81]. KRG significantly reduces the frequency of anxiety-like behavior and visceral pain in mice with IBS by promoting beneficial microbes such as *L. reuteri* and *L. johnsonii* [8]. Furthermore, treatment with KRG and FRG, Rd, or protopanaxatriol has been shown to improve gut microbial imbalance (Bacteroidetes and Proteobacteria abundances), thereby reducing anxiety and depression [43]. The role of the gut microbiome in physiological conditions that are normally psychologically regulated has been reported, emphasizing that depressive symptoms may be transferred from person to person. For example, when feces from depressed patients were transplanted into germ-free mice, they had higher levels of anxiety and depressive symptoms, and their microbiota profiles were different from the feces of control mice [11,82,83]. Microbiota associated with depression, such as *Anaerostipes, Blautia, Clostridium, Klebsiella, Lachnospiraceae incertae sedis, Parabacteroides, Parasutterella, Phascolarctobacterium*, and *Streptococcus*, significantly induce abnormalities in the HPA axis, emphasizing the importance of the gut microbiome on neurodegenerative disorders [83,84]. Notably, *Bifidobacterium* and *Lactobacillus* exerted antidepressant effects [85,86]. Additionally, *Bifidobacterium* and *Lactobacillus* are associated with increased barrier function in the gut [26], which likely contributes to various metabolic benefits [27].

4.6. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder and the second most common disease affecting movement [87]. Symptoms such as difficulties in walking, slowing of movements, and tremors are often accompanied by behavioral and cognitive defects [87]. These data suggest that patients with PD have a different gut microbiome composition than that of healthy controls or patients with other neurological disorders [88]. Animal models have demonstrated a fundamental role for the microbiome in the pathogenesis of PD. The microbiome in germ-free mice transplanted with the microbiota of PD patients showed physical impairment compared to the microbiome in germ-free mice transplanted with the microbiota of healthy human donors [89]. In some cases, such as in PD, gastrointestinal dysfunction may precede the onset of central neurological symptoms [88,90]. Surprisingly, PD patients had gut microbiota depleted of SCFAs (primarily butyrate)-producing bacteria, such as the Lachnospiraceae family of taxa [91]. American ginseng effectively attenuated the intestinal microbiota, including Lachnospiraceae, contributing to barrier integrity [38]. The microbiome of PD patients was altered compared to controls and was dominated by the phylum Verrucomicrobia and genera *Mucispirillum*, *Lactobacillus*, *Parabacteroides*, and *Porphyromonas*. In contrast, in controls, *Prevotella* was more abundant suggesting that an abnormal immune response may contribute to the inflammatory process in PD [92]. Verrucomicrobia, which is highly found in increased amounts in PD patients, contributes to neurodegeneration and is significantly reduced by red ginseng consumption. The relative increase in *Eubacterium* and relative decrease in *Ruminococcus* and Verrucomicrobia with KRG extract administration may improve PD symptoms and neurologic function [90].

4.7. Stress

Excessive and frequent exposure to stressor factors results in the release of adrenaline and cortisol from the adrenal glands, which may activate the HPA axis, leading to the release of inflammation-related cytokines from immune cells [7]. Stress has been linked to psychological disorders such as anxiety and depression and has detrimental health effects, including gut disease [37,81]. For example, immobilization stress induces anxiety and gastrointestinal inflammation in mice [81]. Gut microbes exhibit a significant influence on the early-life programming of brain circuits and the normal physiology of the host by modulating anxiety-like behaviors, cognitive functions, responses to depression and stress factors, and interactions with *E. coli* [37,81]. Several experiments involving the administration of a *Lactobacillus rhamnosus* (JB-1) supplements to healthy men have shown positive effects on stress-related behaviors [93]. Moreover, the increased abundance of *Lactobacillus* by ginseng extract contributes to probiotic amplification [25], suggesting that ginseng has the potential to improve depression, anxiety, and memory loss [7,74]. Ginseng effectively regulates stress-induced hormonal changes and immune responses to maintain homeostasis [7]. Several studies in germ-free mice have provided evidence to support the idea that the microbiome plays an important role in brain function related to neural function, neuroprotection, and stress hormone signaling [94]. Chronic stress leads to a significant disruption of the gut microbiota [18,27,81]. For example, germ-free mice show exaggerated anxiety and stress-related behaviors compared to conventional mice without certain pathogens. However, after treatment with *Bifidobacterium* (*B.*) *infantis*, the behavior of germ-free animals was completely normalized [95]. Mice subjected to immobilization stress also develop an overgrowth of Proteobacteria, including *E. coli* [81]. Ingestion of *E. coli* also causes gastrointestinal inflammation and anxiety in mice [81]. FRG ameliorated anxiety/depression in immobilization stress-exposed mice [42]. These studies suggest that psychological stress is strongly associated with intestinal infections and inflammation, thereby contributing to GBA dysfunction. GBA disturbances are the most frequent cause of gastrointestinal symptoms [96].

KRG ameliorates inflammation and helps combat depression by effectively suppressing stress [97]. These findings suggest that the gut microbiome modulates the microbiome-gut-brain and HPA axes, creating a bidirectional communication with the brain.

5. Conclusion

The dynamic structure and composition of the human microbiome plays an important role in maintaining overall health by interconnecting and cooperating to enhance functional stability. However, gut dysbiosis results in gastrointestinal symptoms and CNS disorders that affect the GBA (Fig. 1, Table 1). Ginseng has gained significant attention owing to its potential impact on human health. Ginseng acts as a prebiotic that modulates beneficial gut microbiome composition and growth, leading to potential health benefits, including maintaining barrier integrity, improving cognitive functions to reduce the risk of gut and gut pathologies, and neurodegenerative disorders (Fig. 2, Table 2). Collectively, ginseng treatment can regulate gut microbiome diversity and improve colitis by increasing probiotics such as *Bifidobacterium, Bacteroides*, and *Akkermansia* genera, and the Verrucomicrobia phylum. Furthermore, ginseng reduces pathogenic bacterial genera such as *Clostridium* and the Proteobacteria phylum to protect against gut and neurological disorders (Figs. 1 and 2, Tables 1 and 2). We summarize the implications of gut microbiome modulation to review the potential therapeutic applications of ginseng, particularly in the context of common gut and neurodegenerative diseases, conditions that highlight the bidirectional communication between the gut and brain via the microbiome-gut-brain axis (Fig. 2). A comprehensive understanding of these interactions is needed to develop new therapeutic strategies that harness the synergistic potential of ginseng and its microbiome for the management of various health conditions. However, further research is required to establish its efficacy and safety as a complementary treatment for complicated conditions. Individuals interested in using ginseng for health-related purposes should consult a healthcare professional to determine its suitability and ensure its safe and appropriate use.

Author contributions

HI, YK, MJ, and DKR collected, analyzed, and reviewed the literature, and wrote the main manuscript. HI, MJ, and DKR prepared the figures and tables. HI, YK, MJ, and DKR added and checked references.

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