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Plant-derived natural products improve disease: focus on gut-brain axis

Chen Song[a,b,c], Wenjing Lang[a], Li Meng[a,*], Wenxiang Ping[a], Jingping Ge[a,b,*]

[a] *Engineering Research Center of Agricultural Microbiology Technology, Ministry of Education & Heilongjiang Provincial Key Laboratory of Plant Genetic Engineering and Biological Fermentation Engineering for Cold Region & Key Laboratory of Microbiology, College of Heilongjiang Province & School of Life Sciences, Heilongjiang University, Harbin 150080, China*

[b] *Heilongjiang Provincial Key Laboratory of Ecological Restoration and Resource Utilization for Cold Region, Heilongjiang University, Harbin 150080, China*

[c] *Key Laboratory of Science and Engineering for the Multi-modal Prevention and Control of Major Chronic Diseases, Ministry of Industry and Information Technology, Zhengzhou 450000, China*

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ABSTRACT

Dysbiosis of the gut microbiota may lead to a wide range of metabolic, neurological, intestinal and cardiovascular disorders and even to tumorigenesis. Evidence suggests that the gut-brain axis (GBA) plays a crucial role in the treatment of these diseases. Many plant-derived natural actives modulate the gut microbiota and its metabolites, gut hormones and neurotransmitters through a variety of mechanisms, and these actions contribute to the alleviation of irritable bowel syndrome, type 2 diabetes mellitus, cancer, and brain disorders. This review focuses on how natural products act through the GBA to protect the central nervous system, regulate metabolism and promote apoptosis in cancer cells. The role of gut microbiota metabolites and neurotransmitter release in modulating inflammation-related factors, promoting or reducing oxidative stress, and activating or inhibiting related signaling pathways is also discussed. This comprehensive overview of the complex GBA mechanisms deepens the understanding of how natural products can target the GBA to treat disease, providing valuable insights into the development and utilization of these natural interventions.

1. Introduction

Natural products (NPs) derived from plants are bioactive compounds extracted from various plant species. Some NPs that are both food and medicine possess numerous functions related to health maintenance, wellness, prevention, and disease treatment[1]. These compounds have been utilized as diet for therapeutic purposes since ancient times. They are currently widely employed in the management of various diseases such as type 2 diabetes mellitus (T2DM), Parkinson's disease (PD), irritable bowel syndrome (IBS), Alzheimer's disease (AD), anxiety disorders, and anti-tumor effects. Increasing evidence suggests a direct correlation between gut microbiota imbalance and human health. As a result, there has been a growing trend towards improving dietary intake and utilizing NPs for treatment. The internal administration of traditional Chinese medicine deeply rooted in Chinese history, is highly favored for its minimal side effects and significant therapeutic benefits[2]. Currently, numerous research findings suggest that NPs have the potential to modulate the gut-brain axis (GBA) and exert a beneficial influence on both gut microbiota and health.

The pathogenesis of diseases is intricate and complex, and an expanding body of research indicates that NPs can effectively induce disease remission by regulating mechanisms such as oxidative stress, inflammation, mitochondrial dysfunction, neurotransmitter levels, and immunity. For instance, naringenin, a flavonoid compound, effectively suppresses the activity of microglial cells and the release of pro-inflammatory factors, thereby alleviating their involvement in neuroinflammation associated with neurodegenerative diseases[3]; *Artemisia argyi* polysaccharide regulate the composition of the gut microbiota in lipopolysaccharides-treated mice, inhibit the production of inflammatory factors in intestinal tissue and restores intestinal function[4]. Saponins maintain gut microbiota diversity and suppress

* Corresponding author at: College of Heilongjiang Province, Heilongjiang University, Harbin 150080, China.
E-mail address: gejingping@126.com (J.P Ge); mengli198026@126.com (L. Meng)
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intestinal inflammation in patients with colon cancer and IBS[5]. These findings suggest that NPs play a crucial role in regulating the gut microbiome and brain function, thereby improving symptoms.

The mechanism of GBA remains incompletely understood, and exploring more active components of substances to regulate the GBA to improve gut microbiota and brain disorders holds a broad prospect. The primary aim of this article is to understand the ameliorative effects of NPs modulating the GBA among patients with various diseases. Consequently, this review encompasses the research progress on the role of NPs in modulating the GBA through various pathways to treat conditions such as T2DM, PD, IBS, AD, anxiety disorders, and tumors.

2. GBA

The gut-brain (or brain-gut) axis is a sophisticated communication network established through the interplay between the gut microbiota and the central nervous system (CNS). This bidirectional signaling pathway encompasses the CNS and the enteric nervous system (ENS) (e.g., the vagus nerve), as well as immune, endocrine, and metabolic connections[6]. Interventions in one system can indirectly influence the other. Central to this axis is the interaction between the gut microbiota and the brain, with the functional status of the gut often mirroring the state of the brain's nervous system[7]. Emerging research has demonstrated that gut microbes can communicate with the brain (Fig. 1), though the precise mechanisms underlying this communication remain incompletely understood. A two-way signaling pathway between the brain and gut microbiota consists of the nervous, immune, and endocrine systems. Intestinal hormones, short-chain fatty acids (SCFAs), microorganisms, and their metabolites in the intestinal system can communicate with the brain directly or indirectly through the gut-brain neural network.

Gut microbiota produce a range of metabolites, such as SCFAs and neurotransmitters, which directly influence host neural functions. These metabolites interact with the afferent branches of the vagus nerve, conveying signals to the CNS and thereby modulating physiological and behavioral responses. Once received, these signals are processed within the CNS, generating appropriate responses. Subsequently, efferent signals from the brain modulate gastrointestinal functions, influencing gut motility and the secretion of digestive enzymes[8]. The microbiota also impacts the immune system, promoting anti-inflammatory cytokines and supporting neural health while maintaining gut barrier integrity to protect the CNS[9]. Additionally, the microbiota influences the endocrine system; enteroendocrine cells in the gut secrete hormones such as serotonin and gastrin, affecting brain function and behavior. The vagus nerve plays a crucial role in this signaling, with its activity linked to gut microbiota health, influencing mood and behavior[10].

While the precise mechanisms of the GBA are yet to be fully elucidated, there is growing evidence supporting the potential of modulating gut microbiota to treat neurological and psychiatric disorders. For instance, human milk oligosaccharides have shown potential in influencing the GBA by modulating gut microbiota, presenting a promising therapeutic avenue[11]. Dietary interventions and probiotics also emerge as viable strategies for mental health disorders[12]. The GBA represents a complex network through which the gut and brain exert reciprocal influences. Although many aspects of this communication pathway remain to be explored, current research underscores the significant role of the gut microbiota in modulating brain function. Continued investigation into the

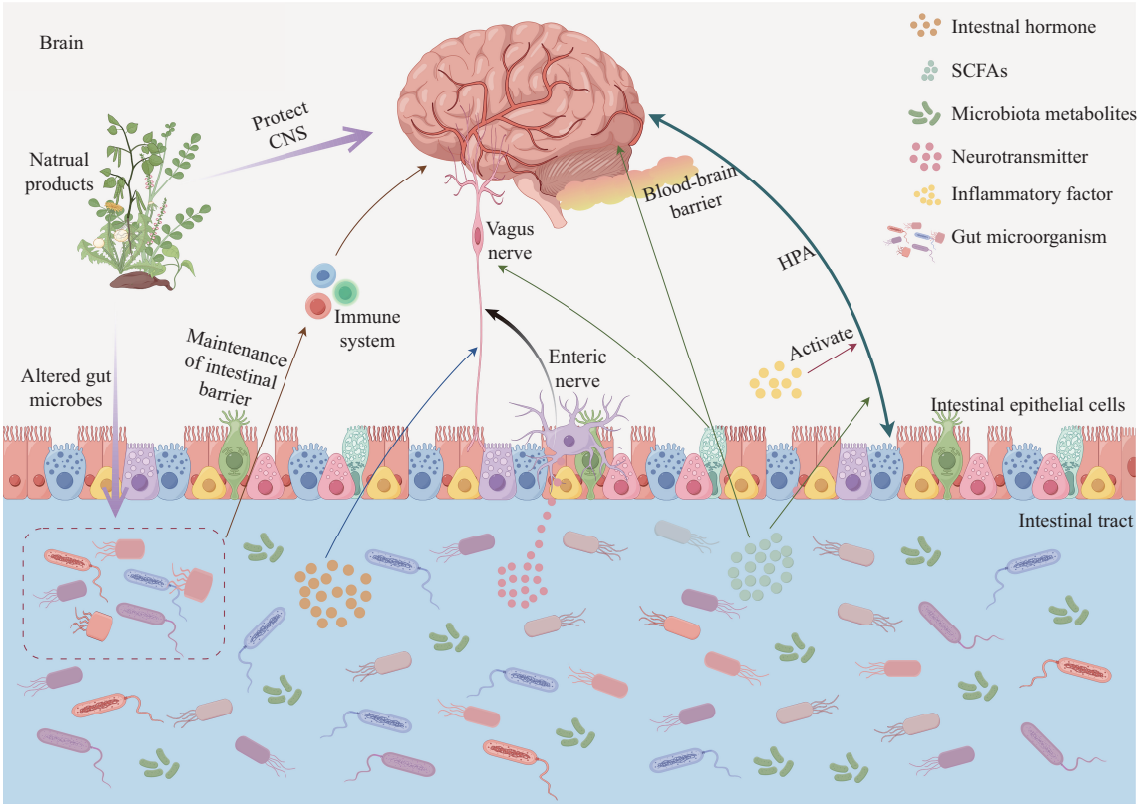

Fig. 1 Schematic diagram of communication pathways between gut microbes and the brain.

mechanisms of the GBA holds the promise of novel therapeutic approaches for a range of neuropsychiatric conditions.

2.1 NPs and the GBA

The chemical structures of NPs exhibit complexity and diversity, with the diversity of plant-derived NPs being determined by their intricate structures, which, in turn, dictate their functional applications. Based on their chemical structure and active ingredients, these products can be categorized into alkaloids, flavonoids, terpenoids, polysaccharides, quinones, phenols, and phenylpropanoids. They exhibit valuable biological activities such as antioxidant, anti-inflammatory, and neurotransmitter modulatory properties[13]. NPs play a crucial role in treating neurological, metabolic diseases, tumors and immune system diseases while simultaneously inducing beneficial alterations in the gut microbiota. Many NPs exhibit antimicrobial properties, inhibiting the proliferation of pathogenic bacteria and fostering the growth of beneficial microbiota without disrupting the overall gut balance[14]. The human intestinal microbiota interacts dynamically with natural substances (such as flavonoids), the microbiota can modify the chemical structure of these compounds, generating new metabolites and chemical changes. Conversely, these natural substances and their metabolites can regulate the composition and structure of the intestinal microbiota, leading to beneficial outcomes[15]. These interactions are often associated with health benefits, including reduced inflammation, enhanced immune responses, and improved nutrient absorption[16]. For instance, the consumption of kale can alter the abundance of intestinal microflora, increase lactic acid content, and promote intestinal motility[17]. Moreover, natural substances influence hormones that act on the hypothalamus, sending satiety signals *via* the vagus nerve, thereby regulating food intake and supporting weight loss[18]. Plant-derived NPs are extensively applied in fields like food, pharmaceuticals, and cosmetics, due to their diverse biological activities such as antioxidant, anti-inflammatory, and neurotransmitter-modulatory properties[19]. *Hypericum* is currently used in the treatment of mild depression, wounds and burns, diarrhea, pains, and fevers[20]. *Garcinia Cambogia* not only has a high dietary value, but the active substances isolated from *G. cambogia* also have a high medicinal potential. They are used in the treatment of cardiovascular diseases, cancer, inflammation, obesity, diabetes, etc.[21]. Many NPs including curcumin, centella, ginseng, a special extract of ginkgo biloba, and cannabis are used to relieve neuroimmune diseases such as AD, PD, depression, and anxiety[22-25]. NPs also play a therapeutic role in treating conditions like HIV, where betulinic acid, a natural product, has shown significant inhibitory effects[26]. Ultimately, NPs offer preventive and therapeutic potential through their ability to modulate the GBA, impacting energy metabolism, oxidative stress, inflammation, and apoptosis, which are key pathways in managing chronic diseases.

2.2 Disease and the GBA

The relationship between diseases and the GBA is increasingly recognized as pivotal in understanding disease pathogenesis. The occurrence and exacerbation of many diseases are intricately linked to the GBA, such as the gut-brain-skin axis, the gut-brain-immune-sleep axis, and the auditory-GBA[27]. Interventions targeting the GBA with modulation of the gut microbiome emerging as a pivotal component in treating sleep-related disorders and optimizing the sleep cycle. Moreover, it serves as a significant modulatory mechanism in addressing skin disorders like psoriasis[28]. The gut microbiota is particularly susceptible to physical and psychological stressors that activate the hypothalamic-pituitary-adrenal axis (HPA), which is involved in the metabolism of sebaceous glands in the skin, endocrine glands in the brain, and dietary metabolism in the gut. Therefore, dietary modification of the microorganisms responsible for acne formation and consequently of the central and peripheral nervous system and bodily hormones can alleviate acne formation[29]. Furthermore, modulation of the GBA holds promise in alleviating physiological aging, addressing neurodevelopmental disorders, autism spectrum disorders, substance abuse disorders, and even alcohol addiction[30]. Most neonatal autism is maternally related, with significant impacts arising from changes in maternal gut flora on the development of autism in children. Alterations in the mother's microbiome can directly affect the structure and composition of the offspring's gut microflora, potentially influencing brain development. Maternal microbial dysbiosis during pregnancy can produce pro-inflammatory bacterial metabolites, leading to cytokine imbalances that exacerbate autism-related characteristics in children[31]. Additionally, dysbiosis of the maternal flora in aging, where the senescence-associated microbiome is altered and transmitted to offspring, increases the risk of disease. As we age, the aging process also directs changes in the composition of the microbiota and microbial-derived metabolites, a decrease in the integrity of the intestinal epithelial barrier in the gastrointestinal tract, increased levels of pro-inflammatory cytokines, and disruption of tissues and barriers, leading to systemic inflammation and the ensuing development of age-related diseases (e.g., AD, PD)[32]. The continuous accumulation of senescent cells, abnormal production of mitochondrial reactive oxygen species (ROS), metabolic transformation, and the production of aging-related secreted phenotypic factors lead to senescent cell accumulation and also increase the susceptibility of older adults to chronic diseases. The occurrence of many diseases is closely related to the GBA, and the intestinal microbiota impacts diseases in various ways (neurological, endocrine, immune). The intricate relationship between the GBA and disease pathogenesis highlights the potential of targeting the gut microbiota for therapeutic interventions, paving the way for NPs to play a crucial role in disease treatment through modulation of the GBA. Recent studies have demonstrated the effectiveness of using NPs to treat disease through the GBA, continued exploration is imperative.

3. GBA mechanism of disease amelioration by NPs

3.1 Obesity and T2DM

As the population becomes increasingly obese, the probability of developing T2DM rises correspondingly. Over 80% of T2DM cases are associated with obesity. Obesity leads to abnormal insulin secretion and decreased insulin sensitivity, which in turn affect blood sugar and lipid levels. T2DM is a systemic inflammatory disease characterized by defective pancreatic β-cells, leading to insufficient insulin secretion and a range of severe complications, including

cardiovascular and renal diseases, as well as CNS disorders such as learning and memory impairments, inattention, and cognitive deficits. The prevalence and mortality rates of T2DM are rising. A notable feature of T2DM is the reduced abundance and diversity of gut microbiota. The gut microbiome plays a crucial role in regulating satiety and appetite through the production of metabolites, primarily SCFAs, bile acids, and serotonin (5-hydroxytryptophan, 5-HTP). These signals influence other endocrine regulators to promote metabolism and inhibit food intake. Furthermore, the gut microbiome regulates the release and production of 5-HT, directly affecting CNS appetite signals through neural pathways[33]. Gut endocrine cells secrete glucagon-like peptide-1 (GLP-1), which transmits satiety signals to the CNS *via* receptors on the vagus nerve. Additionally, treatment with *Lactobacillus rhamnosus* JB-1 can alter the expression of gamma-aminobutyric acid (GABA) receptors in the brain, leading to obesity. GABA, an inhibitory neurotransmitter in the CNS, is involved in regulating food intake[34]. The gut microbiome-metabolite-stimulated secretion of GLP-1, apelin, growth hormone-releasing peptide which affects the mesolimbic dopamine activity, peptide YY, and oxytocin-related peptide can act on the CNS to suppress appetite, regulate adipose tissue metabolism, and lower blood glucose[35]. There is evidence that the numbers of *Bifidobacterium* and *Lactobacillus* are negatively correlated with the concentration of growth hormone-releasing peptide and positively correlated with the concentration of leptin in plasma. Plant-derived NPs can stimulate the gut microbiota and their metabolites, influencing SCFAs and promoting insulin secretion, directly affecting the CNS, which in turn reacts in the intestine, thereby influencing appetite, modulating host gut microbiota and inflammation, and lowering blood glucose[36]. Fig. 2 summarizes the various GBA mechanisms of select NPs and their bioactive compounds on T2DM.

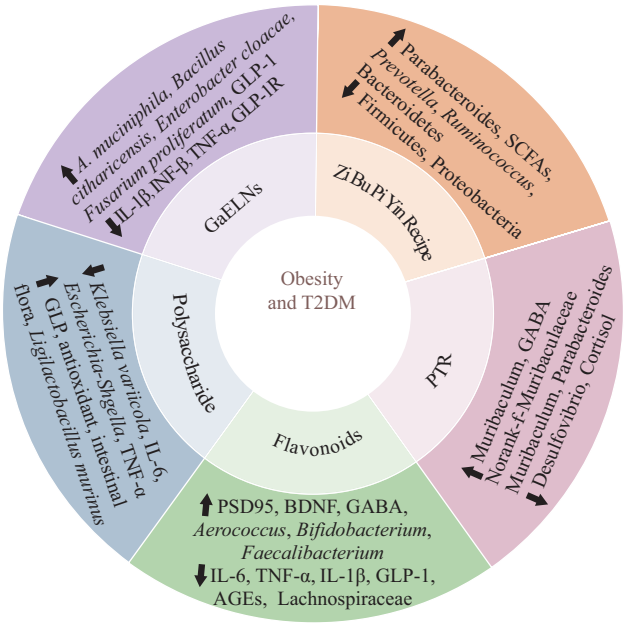

Fig. 2 The effects and mechanisms of NPs on T2DM. ↑ represents increase, and ↓ represents decrease. In short, NPs, as active substances that can regulate gut microbiota, affect flora abundance, change insulin signaling pathway, regulate lipid metabolism, inhibit appetite, regulate obesity and improve T2DM.

Studies have suggested that pathogenic bacteria isolated from the intestines of diabetic patients can induce obesity in germ-free mice upon injection[37]. This discovery suggests that altering the gut microbiome could further improve the health of diabetic patients. Metabolomic changes in the gut may affect the metabolic structure of the brain through the GBA. Outer membrane vesicles (OMV) released by human intestinal *A. muciniphila* trained with garlic exosome-like nanoparticles (GaELNs) reversed high-fat diet (HFD) induced T2DM in mice. OMVs released from GaELNs-trained *A. muciniphila* can be transported to the brain, where they are taken up by microglia, thereby suppressing brain inflammation induced by a HFD, and increases GLP-1 plasma levels. Inhibiting inflammation and crosstalk of GLP-1R with the insulin pathway requires increased levels of neurotransmitters and thus increased levels of insulin receptor substrate expression[38]. ZiBuPiYin recipe (ZBPYR) treatment significantly increased the content of related flora and SCFAs in the intestinal tract of Zucker diabetic fatty rats (ZDF rats). It can affect amino acid levels by regulating the metabolic pathway of BCAA, and change the composition of T2DM microbiome and the content of related metabolites SCFAs. It can remotely affect hippocampal metabolic changes and reverse intracranial insulin resistance, thus affecting cognitive and behavioral disorders induced by T2DM[39]. Flavonoids from *Astragalus membranaceus* can improve cognitive impairment induced by diabetes and HFD and STZ by preserving the hippocampal structure, and increase the amount of GABA in the gut, reshaping the composition of the intestinal microbiome, promoting the integrity of the blood-brain barrier (BBB), lowering levels of inflammatory cytokines and advanced glycation end-products (AGEs), and maintaining the stability of the internal environment of the brain[40]. The mechanism of the hypoglycemic effect of *β*-glucan mushrooms is that beneficial microorganisms release SCFAs to promote the secretion of intestinal hormones related to insulin, such as GLP, and indirectly help the β-cells of the pancreas release insulin and utilize glucose, which can reduce the pro-inflammatory response caused by immune system dysregulation in T2DM, thereby helping to enhance insulin sensitivity. Reduce fat accumulation and help restore the insulin signaling pathway that has disappeared due to obesity and visceral fat accumulation. Increasing the translocation of GLUT4 to the cell membrane enhances glucose uptake, secretes anorectic neuropeptides (such as leptin), promotes glycogen synthesis, inhibits gluconeogenesis, maintains the tight junctions of the small intestine, thereby promoting intestinal integrity[41]. Natural active ingredients (such as polysaccharides) cannot pass through the BBB directly. They need to be mediated by the gut microbiota to metabolize large molecular substances into small molecular metabolites, then pass through the BBB to improve T2DM complications related to cognitive function.

The diet of most people consists of high-sugar and high-fat energy-dense foods, while physical activity has decreased, leading to an increase in energy intake, which increases the metabolic burden of the intestine, resulting to the disruption of the balance of specific microbial communities and the onset of disease states due to the accumulation of microbial by-products. Plant-based NPs can regulate the intestinal microbiota, affect the brain, enhance satiety, regulate appetite signals, and change the pathological intestinal microbial structure. However, the low bioavailability of plant-based NPs, individual differences in the experimental population, the uncertainty of specific mechanisms of action, and the fact that most clinical studies have remained at the cell and animal experiment stage make them limited. Therefore, it is necessary to

further explore the specific molecular mechanisms by which plant-based NPs affect the metabolic axis through the GBA, including how they affect intestinal microbial communities, intestinal hormone secretion, and CNS signal transmission. More clinical trials should be conducted, considering individual differences in intestinal microbiota, for long-term effect studies and safety evaluations, optimizing dosage to improve therapeutic effects and reduce side effects, and validating the safety and effectiveness of plant-based NPs in treating T2DM in the human body through the GBA.

3.2 NPs modulate the GBA mechanism in neurological diseases

3.2.1 Parkinsonism

PD is a prevalent neurodegenerative disorder. Key factors associated with the incidence of PD include age, gender, quality of life, ethnicity, and genetic factors related. Despite extensive research, the precise pathogenesis and etiology of PD remain elusive. Most PD patients have gastrointestinal dysfunction (such as constipation) and gut microbiome dysbiosis, which usually appear several years before any symptoms appear. The gut microbiome and the metabolic byproducts it produces, such as SCFAs, can regulate the peripheral immune system through the GBA. SCFAs may play a role in PD in relation to $CD3^+$ T cells and $TLR4^+$ cells, and indirectly affect neuroinflammatory neurotransmitter synthesis, mitochondrial function, and intestinal barrier integrity, which in turn affects brain function and influences the onset and progression of the disease[42]. Nonetheless, numerous studies have demonstrated the potential benefits of NPs in alleviating PD symptoms. In particular, various herbal formulas and plant extracts have been shown to exert neuroprotective effects (Table 1) .

The aggregation of *α*-synuclein (*α*-syn) in the nucleus is a potential factor contributing to the pathogenesis of PD. One hypothesis suggests that PD begins in the gastrointestinal tract through the aggregation of misfolded *α*-syn, which leads to *α*-syn being retrogradely transported from the gut to the brain *via* the vagus nerve. Gut microbiota metabolites can affect *α*-syn aggregation, regulate inflammation and immune responses, and influence the progression of the disease and the neurotoxic effects of related proteins[43]. Polyphenols extracted from tea can inhibit the growth of pathogenic microorganisms such as *Helicobacter pylori* and *Staphylococcus aureus* in PD patients and promote the growth of beneficial microorganisms such as *Lactobacillus* and *Bifidobacterium*, *Akkermansia muciniphila*, *Bacteroides*, and *Prevotella* to enhance the gut microbiome[44]. Chicory and swertia-derived chicoric acid (CA) improves colon epithelial integrity and fundamentally restores intestinal microbiome composition and SCFAs by inhibiting TLR4/MyD88/NF-κB signaling cascades and regulating intestinal dysbiome. It showed neuroprotective effects in MPTP-induced PD mice[45].

Due to high intestinal permeability or dysregulation of microbial community, pro-inflammatory intestinal environment may initiate or exacerbate the progress of PD[46]. In the condition of PD, the activity of the enzyme complex on the inner membrane of mitochondria is reduced, and the oxidative phosphorylation of mitochondria is inhibited, so that the electrons in the respiratory chain are unstable, and a large number of ROS are produced. At the same time, *α*-syn further aggravated mitochondrial dysfunction. Mitochondrial modification is usually mediated by bioactive metabolites produced by microbes in the gut. Some examples of these metabolites include succinate, fumarate, citrate, succinate, cytochrome c and lactate[47]. Plant-derived NPs can slow or prevent the onset of PD by reducing inflammation and oxidative stress, as well as mechanisms of mitochondrial

Table 1
Mechanisms of natural products in the treatment of PD.

Natural products	Component	Subjects	Effect	Mechanisms	Reference
Tea leaf	Polyphenol	Not available	Improve the five-year composition of intestinal bacteria in PD patients and play a protective role in PD.	↓*H. pylori*, *Staphylococcus* ↑Examples include *Lactobacillus*, *Bifidobacterium*, *A. muciniphilas*, *Bacteroides*, *Faecalis prevotelli*	[44]
Chicory	Chicoric acid	C57BL/6J mice	Improve gut microbiota imbalance, inhibit inflammation, play a protective role in PD.	↓TNF-α, IL-1β, phylum: Bacteroidetes, genera: *Parabacteroide* ↑ Phylum: Firmicutes, genera: *Lactobacillus*, *Ruminiclostridium*	[45]
Gastrodia elata	Polysaccharide	C57BL/6J mice	Improve the ecological imbalance of intestinal microbiota and prevent mitochondrial apoptosis.	↓TNF-α, IL-1β, IL-6, Firmicutes, Lactobacillaceae ↑*Bacteroidetes*, *Bacteroides*, *Clostridium*, *Prevotella*, *Faecalibacterium*	[50]
Not available	Resveratrol	C57BL/6J mice	Improving dyskinesia and striatal pathological through oxidative stress.	↓ TLR4, MyD88, NF-κB in the colon tissue	[49]
Not available	Curcumin	C57BL/6J mice	Improved motor deficits, intestinal barrier dysfunction, and short-chain fatty acid ratio in PD mouse models.	↓ Firmicutes/Bacteroidetes, *α*-syn, acetic acid/butyrate ↑ *Turicimonas*, *Culturomica*	[51]
Ping-wei-san plus herbal	Not available	C57BL/6 mice	Regulate the gut microbiota of PD mice, change the biological pathway of metabolites, affect the expression of functional pathway proteins, and produce therapeutic effects.	↓Bacteroidota, Proteobacteria, Campilobacterota, Patescibacteria ↑Firmicutes, Verrucomicrobiota	[52]

dysfunction. The resveratrol hydroxypropyl-*β*-cyclodextrin inclusion complex can increase the production of these active metabolites in probiotics, enhance the homeostasis of mitochondrial dynamics, play an antioxidant role, and alleviate the consequences of PD[48]. Moreover, resveratrol can also reduce *α*-syn aggregation in PD mice, improve intestinal barrier function and reduce neuroinflammation[49]. Gastrodia polysaccharide (GEP) has been shown to alleviate the motor dysfunction of MPTP-induced mouse PD mice, the ecological dysregulation of PD-associated intestinal microbiota (*Akkermansia*, *Lactobacillus*, *Bacteroides*, *Prevotella* and *Faecalis*), and increase the content of SCFAs in the colon. It also repaired the intestinal barrier of PD mice to inhibit *α*-syn accumulation and reduce the loss of dopaminergic neurons in the brain. In addition, GEP improves PD by preventing mitochondrial apoptosis in PD rats. It also inhibits neuroinflammation (TNF-α, IL-1β, and IL-6) through TLR4/NF-κB pathway inactivation[50]. Curcumin modifies the intestinal microbiota and the concentration and proportion of its metabolite SCFAs (acetic acid/butyric acid) in PD model rats, indicating the inhibition of PD[51]. Ping wei san plus herbal significantly increased the abundance of *Firmicutes* and *Verrucomicrobiota* in PD model rats. Reduce *Bacteroidota*, *Proteobacteria*, *Campilobacterota* and *Patescibacteri*a, restore mitochondrial function and have neuroprotective effect, thus producing therapeutic effect[52]. The intestinal regulation of NPs provides a downregulation of the pathogenesis of PD.

Although PD cannot be completely cured, targeting the intestinal microbiota may offer a promising therapeutic approach. Natural compounds can modulate the intestinal microbiota to inhibit *α*-syn aggregation, reduce oxidative stress, suppress pro-inflammatory cytokines to alleviate inflammation, and enhance mitochondrial function.

3.2.2 AD

AD is the most widespread neurodegenerative disease in the world. The onset of AD is accompanied by cognitive decline, executive dysfunction, olfactory disorders, and depression is also a complication of AD[53]. Therefore, the development of more effective drug and food homologous products for the treatment of AD is indispensable. Hence, this paper summarizes some NPs targeting AD and the mechanism of their active substances (Table 2).

Many studies have shown that NPs and their bioactive compounds have beneficial effects on different mechanisms of action of AD. Although AD primarily affects the CNS, evidence suggests that gut and intestinal dysfunction, as well as alterations in the gut microbiome, are also significant factors. Pathogenic bacteria (*H. pylori*) activate and induce the expression of AD-related signature markers amyloid *β*-protein (Aβ) and trigger neuroinflammation through the STAT3 pathway to affect neurological compartments[54]. Bacterial amyloids, present in the human gut microbiome, have been shown to seed the aggregation of Aβ *in vitro*, indicating that cross-seeding aggregation might contribute to AD onset[55]. In germ-free AD mouse models, probiotics such as *Lactobacilli*, *Bifidobacteria*, and *Clostridium* sporogenes have been shown to reduce Aβ deposition, improve neuroinflammation, and alleviate cognitive dysfunction[56]. Microbial metabolites, such as tryptophan derivatives, enter microglia and astrocytes, modulating AD progression by influencing their function[57]. The reduction of butyrate-producing microbiota is associated with increased gray matter loss in the brain, linked to AD cognitive impairment. There is a correlation between neuroinflammation and low levels of SCFAs such as butyrate[58]. Supplementation with SCFAs can alleviate cognitive dysfunction and Aβ accumulation in AD mice, while reducing malondialdehyde (MDA) levels and oxidative damage. Gut microbiota have also been

Table 2
Mechanisms of natural products in the treatment of AD.

Natural products	Component	Subjects	Effect	Mechanisms	Reference
Not available	Ferulic acid	Not available	Protects nerves, relieves oxidative stress, improves motor behavior, and reverses cell vitality.	↓ *Bacteroides*, ROS, $A\beta_{40-42}$	[60]
Not available	Berberine	5xFAD transgenic mice	Improve cognitive impairment, change gut microbiota composition, inhibit inflammation, relieve AD.	↓ TNF-α, IL-6, Aβ, *Enterococcus*, *Ligilactobacillus*, *Akkermansia*, *Roseburia*, *Lachnoclostridium* ↑ *Enterococcus*, *Roseburia*, *Ligilactobacillus*, *Akkermansia*, *Lachnoclostridium*	[61]
Curcuma longa	Curcumin	Not available	Improves spatial learning and memory, relieves intestinal inflammation, and reduces Aβ.	↓ *Prevotella*, Coriobacterales, ↑ Lactobacilli, Bacteroidaceae	[62]
Not available	Quercetin	AD-like mice and SH-SY5Y Cells	Regulate gut microbiota dysregulation and reduce toxicity and improve cognitive impairment.	↓ Pathogenic: *Enterococcus Fusobacterium*, Aβ ↑ *Bacteroides*, *Bifidobacterium*, *Lactobacillus*, *Clostridia*	[63]
Kai-xin-san	Saponins	SD rats	Significantly improve the cognitive impairment in AD model rats, reduce neuron damage, reduce neuroinflammation and colonic inflammation, regulate the composition of gut microbiota, and play an anti-AD role.	↓ $A\beta_{1-42}$, TNF-α, IL-1β, IL-6, *Allobaculum*, *Clostridium sensu stricto* 1 ↑ *L. murinus*, *Alloprevotella*, *Limosilactobacillus*, *Ligilactobacillus*, Prevotellaceae_NK3B31_group, *Blautia*, *Alistipes*	[64]

Table 2 (*Continued*)

Natural products	Component	Subjects	Effect	Mechanisms	Reference
Not available	Resveratrol	Triple transgenic mice	Relief of symptoms and neuroprotection from AD.	↓ TNF-α, IL-6, Aβ, BACE1, Aβ, ROS ↑ BDNF	[65]
Triphala	Polyphenol	APP/PS1 mice, C57BL6 mouse	Alleviates cognitive deficits, inflammation, and oxidative stress.	↓ BACE, TNF-α, IL-10 ↑ AChE, BACE	[66]
Chaihu Shugan San	Not available	SAMP8 mouse and SAMR1 mouse	Improves learning function and memory deficits.	↓ Aβ ↑ *L. reuteri*	[67]

linked to the brain. Studies have shown an increased abundance of pro-inflammatory bacteria and a decreased abundance of anti-inflammatory bacteria in cognitively impaired patients. One year of vitamin D intake altered microbiota abundance in AD patients and reduced some Aβ-related biomarkers to slow cognitive decline[59].

Ferulic acid, a naturally occurring compound in grains, fruits and vegetables, can change gut microbiota diversity, reduce *Bacteroides* abundance, reduce cross the BBB, change *β*-secretase expression to reduce amyloid preconditioning protein degeneration (amyloid precursor protein, APP) metabolism and improve brain oxidative damage. It also reduces the formation of $A\beta_{40-42}$ fibril[60]. Berberine treated AD model mice and found that intestinal permeability increased, and the abundance of *Enterococcus*, *Ligilactobacillus*, *Akkermansia*, *Roseburia*, and *Lachnoclostridium* increased. In addition, the abundance of *Paraprevotella*, *Alloprevotella*, and *Bacteroide* decreased to inhibit the decreased activation of microglia induced by Aβ to alleviate the inflammation of AD mice and thus improve AD[61]. Curcumin extracted from *C. longa* can reduce the abundance of anaerobic bacteria and *H. pylori* and increase the ratio of Bacteroidetes/Firmicutes in AD animal models to improve cognitive function[62]. At the same time, it can enhance intestinal barrier function and relieve intestinal inflammation, improve spatial learning and memory ability, and reduce the load of Aβ in the hippocampus. Quercetin, extracted from plant tissue, has been shown to reduce pathogenic *Enterococcus* and *Fusobacterium* while increasing the number of gut microbes, including *Bacteroides*, *Bifidobacterium*, *Lactobacillus*, and *Clostridia*, which reduce AD caused by $A\beta_{1-42}$[63]. Kai-xin-san prepared from ginseng radix et rhizoma, poria and polygalae radix can change the composition of gut microbiota and significantly increase species diversity. Reduce the dynamic balance of gut microbiota in AD rats and improve the symptoms of AD rats[64]. Resveratrol has been shown to up-regulate brain-derived neurotrophic factor (BDNF) expression, reduce Aβ load and improve brain function by regulating the microbiota and neurotransmitter in AD mouse models through the GBA as a signaling molecule[65]. It does so by alleviating gut microbiome dysbiosis, particularly for oxidative stress and inflammation-related bacteria such as *Alistipes*, *Helicobacter*, *Rikenella*, *Desulfovibrio*, and *Faecalibaculum*, reducing Aβ aggregation and deposits in the hippocampus, and reducing induced ROS. Polyphenols extracted from triphala can significantly improve cognitive function and participate in maintaining intestinal homeostasis by regulating the APP pathway, reducing inflammation, and restoring the GBA by increasing intestinal microbiota such as *Bacteroidetes*, *Proteobacteria*, and *Actinomycetes*[66]. Chaihu shugan san water extract was able to target the gut microbiota, increase the abundance of beneficial bacteria, reduce harmful bacteria and neuron damage and Aβ deposition to improve memory deficits and learning ability in mice[67].

In summary, the therapeutic potential of NPs for AD *via* the GBA encompasses several mechanisms. 1) Modulation of gut microbiota: Probiotics, dietary fibers, and polyphenols can alter the composition of the gut microbiota. A healthy gut microbiome produces metabolites such as SCFAs, which can cross the BBB to exert anti-inflammatory and neuroprotective effects. 2) Reduction of gut and systemic inflammation: NPs possess anti-inflammatory properties, thereby mitigating inflammation both in the gut and systemically. 3) Enhancement of gut barrier function: NPs can strengthen tight junctions in intestinal epithelial cells, reducing gut permeability. These mechanisms underscore the potential of NPs in AD treatment. Nevertheless, further clinical research is required to validate these effects and determine optimal dosages and administration methods.

3.2.3 Stress and anxiety disorder

Effective management of stress and anxiety is crucial. Extensive research indicates that heightened stress and anxiety behaviors are intricately linked to oxidative stress, neuroinflammation triggered by microglia, mitochondrial damage and neurotransmitters (Table 3). Manipulating the microbiota-gut-brain axis (MGBA) and the HPA axis represents promising avenues for anxiety treatment. Evidence suggests that stress may primarily drive changes in the gut microbiome, with patients frequently reporting gastrointestinal symptoms[68]. According to a study, those who experience social exclusion have higher *Prevotella* abundances but significantly lower Firmicutes/Bacteroidetes ratios and *Faecalibacterium* spp. abundances[69]. *Lactocaseibacillus rhamnosus* can change the gut microbiome and metabolites effectively to slow down peripartum women's peripartum mood and anxiety disorders[70]. SCFAs exert beneficial effects by regulating the tryptophan metabolism, inflammation, and neurotransmitters, while reducing the abundance of *Faecalibacterium*, *Anaerostipes*, *Allobaculum*, *Blautia*, *Peptococcus*, *Rombustia* in anxiety-like rats[71]. Modulating the gut microbiome in patients with illness is likely to improve stress and anxiety symptoms.

Table 3
The mechanisms of natural products in alleviating stress and anxiety.

Natural products	Component	Subjects	Effect	Mechanisms	Reference
Not available	polyphenols	Rodent	Alleviates oxidative stress and inflammation and regulates the HPA axis.	↓ MDA, NF-κB, IL-1α, IL-1β ↑CAT, BDNF	[72]
Not available	Tryptophan-rich	C57BL/6 mice	Improve depressive and anxious behaviors and neuroinflammation as well as neurological disorders, and restore the intestinal barrier and mitochondrial function damage.	↓*Escherichia*, TNF-α, Il-6, Il-1β, *A. muciniphila*, *Streptococcus*, *Butyricimonas*, *Coprobacillus* ↑Lachnospiraceae, *Lactobacillus*, BDNF, 5-HT, *Bifidobacterium*	[74]
Gastrodia	GEB	ICR mice	Changes the abundance of intestinal microbiome composition in anxiety-like mice.	↑*Lactobacillus*, *Corynebacterium*, *Staphylococcus*, *Bacteroides*, *Psychrobacter*, *Alistipes*	[77]
Blackcurrant juice	Anthocyanins	Wistar rats	Relieves anxiety, memory and cognitive function, Altered gut microbes.	↓Kynurenine/tryptophan ↑BDNF, *Bifidobacterium longum, Bifidobacterium bifidum*	[78]
Not available	Quercetin	C57BL/6 mice	Reduces anxious behavior and improves mitochondrial damage.	↓OCR, IL-1β, TNFα, ROS, MMP ↑OCR, ATP	[79]
Baihe Dihuang decoction	*Lilium lancifolium* Thunb, *Rehmannia glutinosa* Libosch	Sprague-Dawley rats	It improves anxiety-like behavior and metabolites related to amino acid-related metabolic pathways, changes intestinal microbiome structure.	↓IL-1β, IL-6, TNF-α, IL-18, *Bacteroidota*, *Proteobacteria*, *Actinobacteria* ↑*Patescibacteria*	[80]
Ginkgo biloba extract	Flavonoids	C57BL/6J mice	Changes in bile acid metabolism and gut microbiota play anti-stress and anxiety roles.	↓*Eubacterium*, *Lactobacillus* ↑Deoxycholic acid, cholic acid, BDNF, *Paraprevotella*, *Alloprevotella*, *Helicobacter*, *Parasutterella*, *Bacteroides*	[81]

NPs have emerged as promising candidates for alleviating stress and anxiety. For example, plant-derived polyphenolic compounds mitigate stress and anxiety through diverse mechanisms[72]. The gut microbiome directly regulates the secretion of 5-HT by intestinal epithelial cells, which acts as a mediator between the ENS and the gut, although it cannot enter the BBB directly, gut-derived 5-HTP can pass through the BBB to promote brain 5-HT production and exert an anti-anxiety effect[73]. Tryptophan-rich diets have been shown to alleviate intestinal barrier damage, regulate the structure of the gut microbiome, reduce neuroinflammation, increase BDNF expression, and elevate 5-HT levels[74]. Stress model mice fed with cinnamaldehyde exhibit reduced anxiety-like behavior[75]. Additionally, administration of demaghi alleviated anxiety and depression in aluminum chloride-induced model mice, and improved memory and cognitive function[76].

G. elata Blume (GEB) is extracted from the dried root mass of the orchid plant gastrodia, and it can regulate the composition and abundance of gut microbiota in patients with mental disorders. GEB increases the abundance of *Lactobacillus*, *Corynebacterium*, *Staphylococcus*, *Bacteroides*, *Psychrobacter*, and *Alistipes*. Moreover, GEB can directly penetrate the BBB and regulate neurological diseases[77]. Anthocyanins found in blackcurrant juice can increase BDNF concentration, reduce inflammation, and increase the abundance of *Bifidobacterium*, thereby alleviating psychological health disorders and improving stress-induced cognitive impairment and mood[78]. Chen et al.[79] treated methamphetamine (MA)-induced anxiety model mice with quercetin, showing it could reduce ROS, modulate mitochondrial membrane potential (MMP) levels, and increase OCR and ATP production. This treatment alleviated MA-induced mitochondrial dysfunction and morphologic abnormalities, inhibited microglia activation, and reduced the levels of IL-6, IL-1β, and TNF-α, suggesting quercetin's ability to alleviate anxiety-relieving behaviors. Baihe Dihuang decoction (BDD) effectively alleviate hippocampal neuron damage and the abnormal activation of microglia in the hippocampus. BDD led to significant changes in the abundance of 10 microorganisms at the species level, as well as significant alterations in fecal metabolites and hippocampal neurotransmitters related to amino acid metabolic pathways, such as *D*-glutamine and *D*-glutamate, alanine, arginine, proline, and tryptophan metabolism. These changes significantly improved the anxiety-like behavior of rats induced by chronic restraint stress (CRS)[80]. *Ginkgo biloba* extract (GBE) has been found to regulate the metabolism of intestinal microbiota in mice, playing an anti-stress and anti-anxiety role. GBE acts on the bile acid metabolism of the intestinal microbiota and can prevent despair, anxiety-like, and social avoidance behaviors in mice subjected to unpredictable mild stress (UMS) with insufficient distribution of brain dopamine[81].

In conclusion, modulating the GBA through natural interventions holds promise for mitigating neurological disorders, including PD, AD, and stress-related conditions.

3.3 NPs modulate the GBA mechanism in IBS

Gastrointestinal disorders are prevalent across age groups, with a significant proportion of individuals experiencing chronic intestinal

issues. IBS is one of the most common functional gastrointestinal disorders, usually characterized by abdominal pain after food intake and erratic bowel habits[82]. While IBS is not life-threatening, it significantly reduces the quality of life due to its recurrent symptoms. Effective treatments for IBS remain limited, although studies indicate an association with the GBA due to microbiota imbalance influencing gut-brain signaling and intestinal function[83]. Research suggests natural product extracts effectively alleviate IBS symptoms by addressing intestinal mucosal damage, immune response, visceral hypersensitivity (VH), and inflammation (Table 4).

Experimental findings demonstrate that anti-inflammatory strategies effectively alleviate IBS symptoms by reducing systemic immune-inflammatory markers[84], and that excessive activation of intestinal immunity can exacerbate IBS symptoms. For instance, the *Da-Jian-Zhong* decoction causes a significant increase in the relative abundance of *Bacteroides* in the intestinal microbiome of IBS patients at the genus level, and an increase in the relative abundance of *Lactobacillus* and *Parabacteroides* at the genus level, while the relative abundance of Firmicutes bacterium and *Rumenococcus* are reduced. It significantly reduces the Th17/Treg ratio, and NPs regulate changes in the intestinal microbiome by interacting directly with immune cells or by regulating the metabolites of bacteria to further influence colonic immune cells, thereby reducing the induced VH and diarrhea[85]. Liupao tea extract, containing catechins, polyphenols, polysaccharides, and caffeine, modulated gut microbiota imbalance, enhanced microbial diversity, and reduced pro-inflammatory cytokines IL-6, IL-1β, and TNF-α. Alleviating gastrointestinal injury and IBS symptoms[86]. VH and gut dysbiosis significantly contribute to the development and occurrence of IBS, which is exacerbated by stress. Yuan et al. showed that apigenin was able to inhibit mast cell activation through the toll-like receptor 4 (TLR4)/NF-κB/myeloid differentiation primary response gene 88 (*Myd88*) signaling pathway, inhibit stress-induced activation of colonic mast cells and microglia, and regulate intestinal mucosal barrier function and alter intestinal bacterial abundance, suggesting that it could alleviate VH to achieve therapeutic IBS[87].

The serotonin 5-HT/tryptophan hydroxylase (TPH) signaling pathway is also targeted for IBS treatment, with herbs and plant extracts showing promise in preclinical models[88]. Shi et al.[89] treated a trinitrobenzene sulfonic-induced post-inflammatory-irritable bowel syndrome (PI-IBS) rat model of visceral hyperalgesia with cynaropicrin. The experimental results showed that cynaropicrin could decrease the colon 5-HT content and inhibit the colonic TPH expression in model rats, and also inhibit the number of enterochromaffin cells and the levels of TNF-α and IL-6 cytokines in enterochromaffin cells had an obvious analgesic effect on PI-IBS model rats. Wu et al.[90] showed that the ethanolic extract of Maojian green tea flavonoids reduced intestinal peristalsis by modulating the expression of proteins in pathways related to 5-HT. That is, it decreased the expression of TPH and the expression

Table 4
Mechanisms of natural products in the treatment of IBS.

Natural products	Component	Subjects	Effect	Mechanisms	Reference
Da-Jian-Zhong decoction	Not available	SD rats	Altered the gut microbiota in IBS toward a community and intestinal immune response, especially with respect to the Th17/Treg balance.	↓*Bacteroides*, *Lactobacillus*, *Paracoides*, Th17/Treg ↑Firmicutes bacterium, *Ruminococcus*	[85]
Liupao tea	Not available	Specific-pathogen-free rats	Improve gastrointestinal dysfunction, inflammation and water metabolism disorders, reverse gut microbiota imbalance.	↓IL-6, IL-1β, TNF-α, *Firmicutes*, *Patescibacteria* ↑AQP3, *Lactobacillus*	[86]
Not available	Apigenin	SD rats	Apigenin regulates gut microbiota and improves visceral hypersensitivity and barrier function.	↓*Limosilactobacillus*, *Escherichia-Shigella*, *Enterococcus*, *Bifidobacterium*, *Streptococcus* ↑unclassified_f_Muribaculaceae, Prevotellaceae_NK3B31_group, Lachnospiraceae_NK4A136_group, unclassified_f_Lachnospiraceae	[87]
Plant extract	Quercetin, resveratrol, oridonin	Rodent	Improved allergies and abnormal bowel movements and increased pain threshold pressure and decreased colon ECs numbers.	↓5-HT ↑IL-10, AQP3, AQP8 in colon and serum	[88]
Cynara scolymus	Cynapicrinon	SD rats	Relieves IBS analgesia and hypersensitive visceral reactions.	↓5-HT, TPH, colonic EC cells, TNF-α, IL-6	[89]
Mao Jian Green Tea	Flavonoids	SPF rats	Promote gastrointestinal peristalsis, relieve constipation effect.	↓5-HT, TPH, Lachnospiraceae ↑CaM-MLCK, Bacteroidetes/Firmicutes, Ruminococcaceae	[90]

of serotonin transporter and also decreased 5-HT secretion, thus activating the calmodulin (CaM)/myosin light chain kinase (MLCK) pathway and increasing 5-HT_4 receptor expression. In addition, the diversity of the gut microbiota increased the proportion of beneficial bacteria and modulated the amount of 5-HT-associated microbiota.

In summary, natural bioactive compounds can repair the intestinal mucosal barrier in IBS, modulate gut microbiota diversity, regulate inflammatory responses, and influence hormonal pathways involved in intestinal motility. These NPs facilitate interactions between intestinal microbes and immune cells, highlighting their therapeutic potential for managing IBS[91].

3.4 GBA mechanism of NPs against tumor

Tumors can be categorized into benign and malignant types, with a very low recovery rate for malignant tumors due to the increased difficulty posed by tumor metastasis. Recent researches have highlighted the potential link between intestinal microbes and tumors, with specific microorganisms playing a positive or reverse role in tumor therapy. *Pseudomonas aeruginosa* causes the death of necrotic tumor cells *in vivo*, significantly inhibiting tumor growth, and reshaping the tumor microenvironment[92]. The community of microorganisms associated with tumors, including fungi (candida, yeast), can activate the level of pro-inflammatory factors in the gut, which are related to the pathogenesis of gastrointestinal cancer and tumors[93]. Mice with glioblastoma exhibit altered Firmicutes/Bacteroidetes ratios in their gut microbiome, indicating dysbiosis. Levels of norepinephrine and 5-HIAA, as well as SCFAs, were lower in mice with glioblastoma and humans with the disease[94]. SCFAs can cross the BBB and affect glial cells and neurons through epigenetic modifications. The beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* promote immune regulation and have therapeutic effects on tumors. In addition, bile acids and SCFAs, metabolites of gut microbiota, regulate the pathogenesis, prevention and treatment of tumors[95]. The gut microbiome influences brain tumors by modulating the development and function of immune cells and generating metabolites that accumulate in the tumor microenvironment. For instance, in a mouse model of glioblastoma, the use of antibiotics (ABX) altered the intestinal microbiome and immune microenvironment, affecting tumor growth[96]. Consequently, NPs that regulate intestinal microbial communities have emerged as a novel approach for intervening in and treating tumors.

The regulation mechanisms of tumors includes immune regulation (immune system and immune cells), and microbial metabolism (SCFAs and endogenous chromite, neurotransmitters, and intestinal hormones)[97]. For example, Huo xiang zheng qi (HXZQ) can inhibit the expression of genes and proteins related to the Nrf2/NF-κB/NLRP3 signaling pathway, the release of inflammatory factors, and the expression of oxidative stress markers. At the phylum level, HXZQ increased the proportion of Bacteroidetes and decreased that of Firmicutes. At the genus level, HXZQ decreased the abundance of genera such as *Candidatus Arthromitus* and *Dorea*; it also increased the abundance of butyrate-producing bacteria, including *Anaerotruncus*, *Prevotella*, *Butyricimonas*, and other genera. Butyrate, a 4-carbon SCFA produced by specific microbial communities from dietary fiber, has anti-inflammatory properties that enhance intestinal mucosal immunity and barrier function. This may be a potential mechanism by which HXZQ prevents and treats cancer[98]. Furthermore, certain plant-derived compounds exhibit promising anticancer properties. Gallic acid and caffeic acid, for instance, prolonged the lifespan of mice with ehrlich ascites tumors by inhibiting vascular endothelial growth factor (VEGF), matrix metalloproteinase 2 (MMP-2), and cyclooxygenase-2, while maintaining M1 macrophage activity[99]. Additionally, *β*-cyclodextrin-resveratrol inclusion complexes can change the immune microenvironment of tumors and inhibit macrophage polarization while activating $CD8^+$ T cells to achieve the purpose of inhibiting tumor growth[100]. Taraxosterol increased the proportion of $CD4^+$ T cells and Caspase-3 in hepatocellular carcinoma mice, inhibited Bcl-2, inhibited tumor cell proliferation, and inhibited tumor growth[101]. Psychological stress, commonly experienced by cancer patients, can disrupt gut flora and accelerate tumor progression[102]. Plant-derived NPs have been shown to modulate the gut microbiome, reduce stress-related behaviors, and inhibit tumor growth[103]. For instance, a mendelian randomization study method to shown that Lactobacillales and family Clostridiaceae 1, were positively correlated with the occurrence of brain tumors, while genus Defluviitaleaceae UCG011 and genus *Flavonifractor* were negatively correlated with the occurrence of brain tumors[104]. In patients with meningioma, the number of Firmicutes and their ratio to Bacteroidetes, Verrucobacteria and Akkermansia decreased, while Enterobacteriaceae increased, and oral administration of plant-derived NPs (eg. saponin) was able to alter the composition of the gut microbiome, reversing the composition of the microbiome in this disease state[105]. Moreover, fibres-rich foods such as broccoli, oats, quinoa, and apples can increase the abundance and diversity of gut microbes and SCFAs, reducing chemotherapy-induced neuroinflammation[106]. Altogether, these findings underscore the therapeutic potential of NPs in regulating the GBA to treat cancer by modulating the gut microbiome and its metabolites.

In conclusion, NPs have the potential to modulate the body's immune response and gut microbiota, impede tumor cell proliferation, induce apoptosis, and destroy the metastatic ability of tumor cells (Fig. 3).

4. Prospect

There is growing evidence supporting the efficacy of NPs in alleviating a wide range of diseases including but not limited to T2DM, PD, IBS, AD, anxiety, and tumors through modulation of the GBA, as reviewed in this article. However, the role of NPs extends beyond these examples, and their mechanisms in modulating the GBA are complex, involving multiple targets, systems, and connections. While NPs have shown promising results in managing these diseases, our understanding of the intricate gut microbiome-brain relationship remains limited. This area is underdeveloped, with numerous therapeutic targets and mechanisms yet to be fully explored. Therefore, further exploration of novel active substances and their mechanisms within the GBA is crucial. Modulating the GBA with NPs offers new strategies and opportunities for developing pharmacological interventions and advancing therapies against intestinal, neurological diseases, and tumors, thereby holding significant therapeutic potential across these diverse conditions.

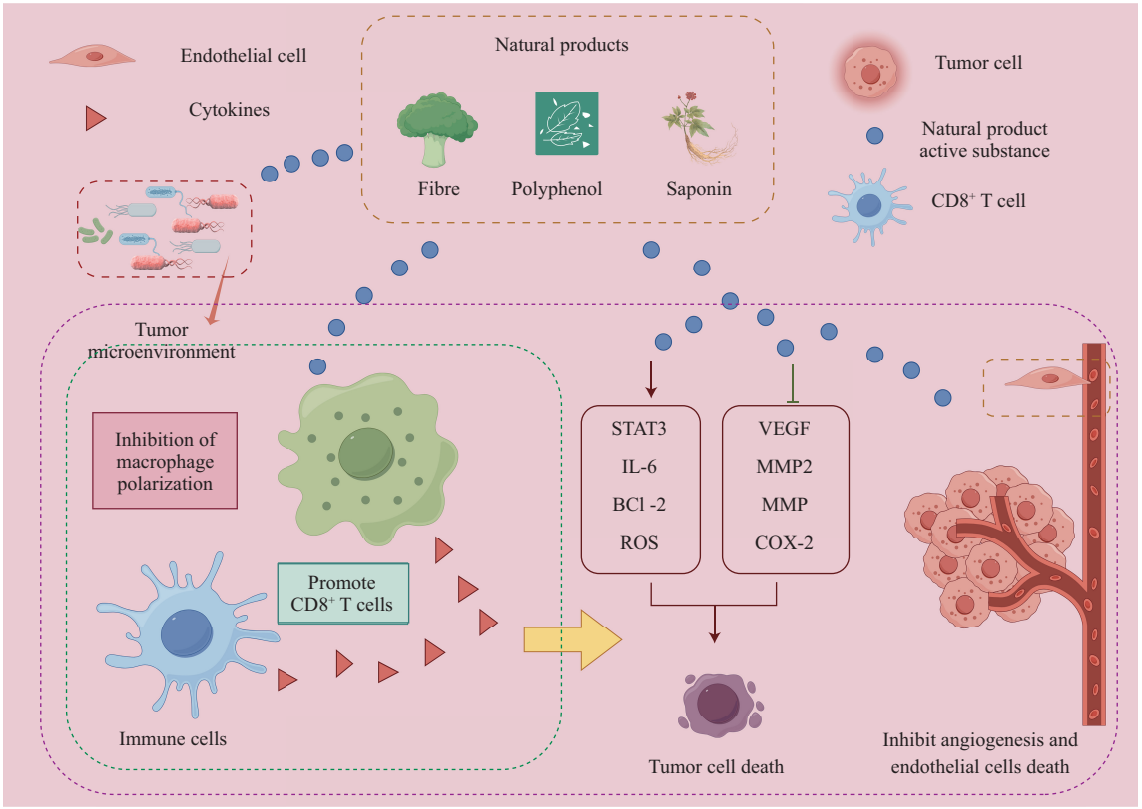

Fig. 3 The effects and mechanisms of NPs on antitumor. Active substances in NPs such as fibre, polyphenols, and saponins can regulate the gut microbiome, inhibit the polarization of macrophages, promote the proliferation and differentiation of immune cells, promote STAT3, IL-6, BCL-2, ROS, and inhibit VEGF, MMP2, MMP, and COX-2. And inhibited tumor-related angiogenesis and apoptosis of vascular endothelial cells. Blocking the expression of oncogenes in tumor cells leads to the death of tumor cells.

Declaration of competing interest

The authors have declared no conflict of interest.

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