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Gut microbiota regulation by natural polysaccharides: A strategy for disease intervention and probiotic stabilization

Song Wei ^a, Yang Sun ^b, Lili Zhao ^c, Xiujuan Li ^{d,*}, Jingwei Xue ^{e,*}^a School of Pharmacy, Qingdao University, Qingdao 266021, China.^b Yunnan Key Laboratory of Modern Separation Analysis and Substance Transformation, College of Chemistry and Chemical Engineering, Yunnan Normal University, Kunming, Yunnan, China^c The Affiliated Taian City Central Hospital of Qingdao University, Taian, 271000, China.^d Pharmaceutical Department, The Affiliated Taian City Central Hospital of Qingdao University, Taian, 271000, China.^e Tumor Precise Intervention and Translational Medicine Laboratory, The Affiliated Taian City Central Hospital of Qingdao University, Taian, 271000, China.

ABSTRACT: Natural polysaccharides serve a dual role in the context of probiotics: as selective prebiotic substrates that stimulate the growth and metabolic activity of beneficial microorganisms, and as versatile biopolymer backbones that can be enzymatically or chemically modified to enhance functional properties. Recent studies have demonstrated that probiotic fermentation can markedly alter the molecular weight, branching degree, and conformational structure of polysaccharides, leading to improved antioxidant, antimicrobial, and gut microbiota–modulating activities. Moreover, polysaccharide-based biomaterials such as microcapsules, edible films, and hydrogels have emerged as promising carriers for probiotic encapsulation and targeted delivery, effectively enhancing probiotic survival during processing, storage, and gastrointestinal transit. This review systematically summarizes the latest advances on the interplay between natural polysaccharides and probiotics, highlights the novel concept of polysaccharides as both prebiotics and biopolymer modifiers, and discusses their translational potential in functional food development and health promotion.

Keywords: polysaccharides; probiotics; diseases; probiotic fermentation; biomaterial

1. Introduction

In recent years, probiotics and their interactions with the gut microbiota have attracted increasing scientific and industrial attention. In 2001, the World Health Organization and the Food and Agriculture Organization defined probiotics as “live microorganisms which, when administered in adequate amounts, confer a health benefit on the host” ^[1]. A growing body of evidence indicates that a stable and diverse gut microbiota is essential for maintaining digestive, metabolic, and immune homeostasis, whereas dysbiosis is associated with gastrointestinal disorders, metabolic syndrome, and other systemic diseases ^[2–5]. The global probiotic market reached USD 4.62 billion in 2019 and is expected to expand to USD 7.59 billion by 2026 ^[6], underscoring the increasing demand for probiotic-based functional foods.

*Corresponding author

lixujuan2@qdu.edu.cn (Xiujuan Li)

xuejingwei11111@163.com (Jingwei Xue).

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However, much of the existing literature focuses broadly on the health benefits of probiotics without critically examining the specific mechanisms through which they interact with dietary components, namely polysaccharides, to exert these effects. While numerous reviews have summarized the general functions of prebiotics, there remains a notable gap in understanding how probiotic-metabolized polysaccharides directly influence microbial survival, functionality, and host health. This review aims to address this gap by providing a critical synthesis of recent advances, emphasizing the bidirectional interactions between probiotics and polysaccharides, and highlighting underexplored areas such as enzymatic modification and targeted delivery applications with particular attention to mechanistic links among polysaccharide structure, probiotic metabolism, and host outcomes.

Natural polysaccharides represent one of the most important dietary sources of carbohydrates. Due to their complex chemical structures and resistance to gastric acid digestion, polysaccharides can reach the intestine intact, where they serve as substrates for gut microbiota. This process promotes the proliferation of beneficial bacteria and stimulates the production of metabolites such as short-chain fatty acids, thereby playing a significant role in preventing and ameliorating various diseases including obesity ^[7], diabetes ^[8], inflammatory bowel disease ^[9], and colorectal cancer ^[10]. Consequently, polysaccharides are not only crucial nutritional factors for maintaining gut microecological homeostasis but also important prebiotics.

Owing to the structural features of polymeric carbohydrates and fibers, polysaccharides are inherently resistant to direct degradation and absorption in the gastric acidic environment, allowing them to be efficiently delivered to the intestinal tract. This property provides a unique natural targeting advantage for the treatment of intestinal diseases. Interestingly, recent studies have revealed that probiotics themselves secrete various glycoside hydrolases and polysaccharide lyases during fermentation, which can effectively modify the molecular weight, branching degree, and conformation of natural polysaccharides, thereby enhancing their antioxidant, antimicrobial, and immunomodulatory activities ^[11]. For instance, *Lactobacillus fermentum* NB02 with feruloyl esterase activity increased phenolic release from oat bran and enhanced antioxidant properties during fermentation ^[12]. These enzymatic modifications represent a key mechanism by which probiotics enhance polysaccharide functionality. This aspect of probiotic action has not been comprehensively covered in previous reviews.

At the application level, probiotics as live microorganisms often face challenges such as exposure to oxygen, acids, bile salts, and processing conditions during delivery, leading to reduced viability or even inactivation. To address this issue, researchers have developed polysaccharide-based probiotic delivery systems, including microcapsules, edible films, and hydrogels. These polysaccharide-derived materials exhibit excellent biocompatibility, biodegradability, and mucoadhesiveness, providing a protective barrier for probiotics. They significantly enhance the survival rates of probiotics during production, storage, and gastrointestinal transit, while enabling targeted release ^[13, 14]. This aligns with recent summaries of biopolymer-based oral delivery strategies regulating gut homeostasis, which highlight how material design influences gastrointestinal fate and bioactivity ^[15]. Yet, current literature lacks systematic comparison and

critical evaluation of these systems regarding their efficacy, scalability, and clinical applicability, a gap that this review aims to fill.

In this review, we systematically summarize recent progress on the interactions between natural polysaccharides and probiotics. We first synthesize evidence on disease regulation mediated by polysaccharide–microbiota–host crosstalk; next, we assess fermentation-driven modification of polysaccharides and the consequent enhancement of bioactivity; and lastly, we examine biomaterial applications that leverage polysaccharide matrices to protect and deploy probiotics in complex gastrointestinal environments. This structure is intended to connect mechanistic insights with application-oriented design, thereby providing a coherent basis for future functional-food and therapeutic development.

2. Polysaccharides regulate human diseases through gut microbiota

The intestine is the largest digestive organ in the human body, often referred to as the 'second brain' due to its intricate structure. It harbors tens of thousands of gut microbiota that play a crucial role in health. Research indicates that disturbances in intestinal flora are closely linked to the development of numerous diseases, including intestinal disorders, neurodegenerative diseases, diabetes, obesity, malignant tumors, cardiovascular diseases, and immune dysfunction (**Fig. 1**). Furthermore, researchers have identified that natural polysaccharides possess significant benefits in regulating gut microbiota and intervening in various human diseases. As illustrated in **Fig. 2**, different polysaccharides may modulate distinct gut microbial communities and signaling mechanisms across various diseases, thereby exerting targeted therapeutic effects.

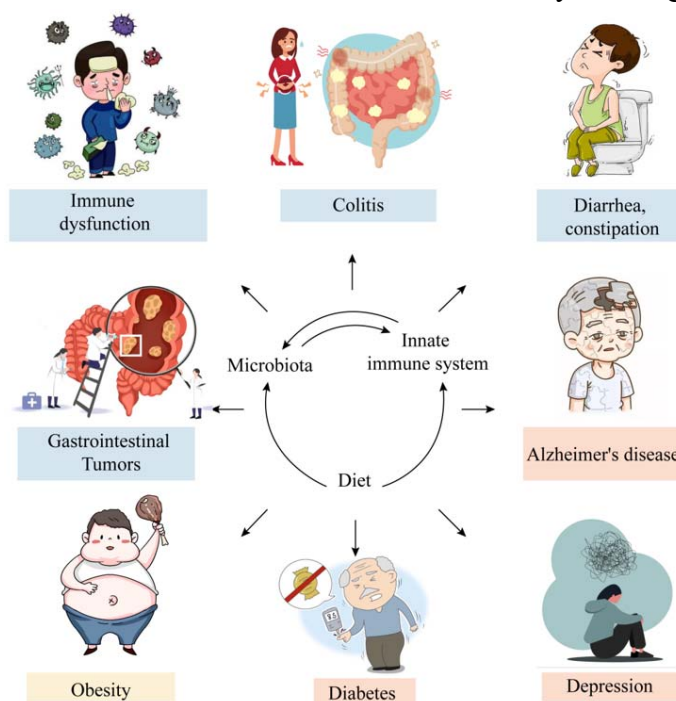


Fig. 1. Association between intestinal flora disturbances and the development of systemic diseases. Dysbiosis of the gut microbiota is implicated in the pathogenesis of a wide range of diseases, such as intestinal disorders, neurodegenerative diseases, diabetes, obesity, malignant tumors, cardiovascular diseases, and immune dysfunction. This schematic illustrates the potential mechanistic links and pathways through which microbial imbalance contributes to these conditions.

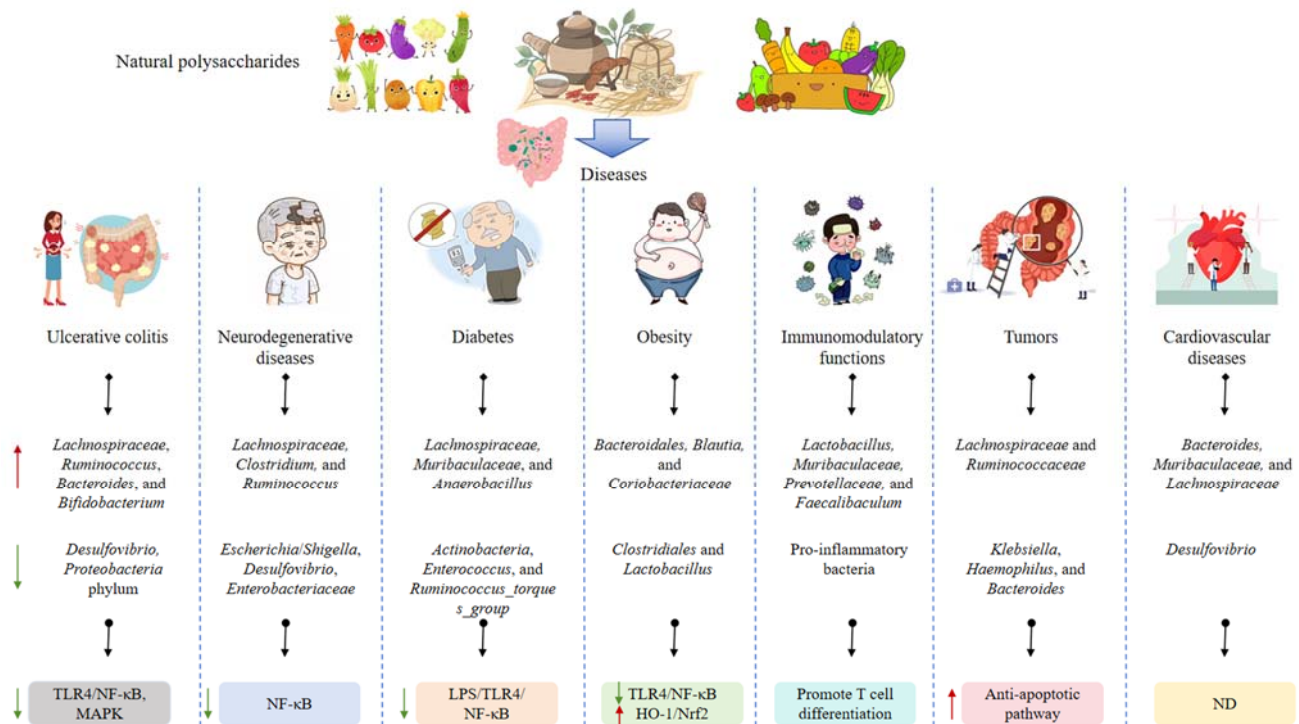


Fig. 2. Targeted modulation of gut microbiota and signaling mechanisms by natural polysaccharides in multiple diseases. Different natural polysaccharides selectively regulate specific gut microbial communities (e.g., SCFA-producing bacteria, mucin-degrading bacteria) and signaling pathways (e.g., TLR4/NF-κB, intestinal barrier proteins) across diverse disease contexts. This schematic summarizes their disease-specific mechanisms and therapeutic potential.

2.1 Ulcerative colitis

Ulcerative colitis is a chronic gastrointestinal inflammatory disease characterized by recurrent inflammation of the colonic mucosal layer, with episodes of recurrence and remission. Currently, the treatment methods for ulcerative colitis remain elusive, and available interventions primarily focus on maintenance and remission. However, commonly used antibiotics in clinical practice often develop resistance and can trigger serious adverse reactions. Given the diverse microbiota present in the colon, addressing abnormalities in the colonic microbiota may offer benefits for patients with ulcerative colitis. During the progression of colitis, an imbalance in the gut microbiota occurs, marked by a decrease in microbial diversity and beneficial symbiotic bacteria, alongside an increase in pathogenic bacteria^[16]. The normal gut microbiota predominantly consists of *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*. However, as colitis progresses, the relative abundance of *Firmicutes* diminishes, while certain bacteria within the *Proteobacteria* phylum emerge as potential pathogens associated with inflammatory bowel disease. The colonization of these harmful bacteria can exacerbate the symptoms of ulcerative colitis^[17]. Therefore, it is essential to identify new drugs that are both safe and effective for patients with ulcerative colitis. Natural polysaccharides exhibit a broad range of pharmacological effects, particularly in the regulation of gut microbiota (**Table 1**).

Table 1 Natural polysaccharides regulate ulcerative colitis through probiotics.

Source	Compound name	Mw/ kDa	Monosaccharide composition (mol% or mole ratio)	Intestinal flora	Disease	Mechanisms	References
<i>Mesona chinensis</i> Benth <i>Pleurotus tuber-regium</i> mycelium	MBP	157	Glc:Xyl:Gal:GalA=1.49:2.54:0.68:6.33	Decrease (<i>Helicobacter</i> and <i>Prevotella</i>); (<i>Lactobacillus</i> and <i>Coprococcus</i>)	Ulcerative colitis	MBP could alleviate colitis symptoms by inhibiting the activation of TLR4/MAPK/NF-κB pathway.	[21]
	PTRP	4.50 ×10 ³	Fuc:Gal:Glu:Man:Rib:GlcA=0.93:7.56:76.25:14.25:0.55:0.46	Increase (<i>Turicibacter</i> , <i>Ruminococcus</i> , <i>Prevotella</i> , <i>Odoribacter</i> , <i>Bacteroides</i> , and <i>Bifidobacterium</i>)	Ulcerative colitis	PTRP repaired gut microbiota disorder in colitis mice through regulating the distribution and abundance of gut microbiota.	[18]
				Increase (<i>Alistipes finegoldii</i> and <i>Bacteroides stercorisoris</i>)			
<i>Eurotium cristatum</i>	ECP	71.06	Man, Glc, Gal, Rib, Ara, Fuc, GlcA	Decrease (<i>Escherichia coli</i> , <i>Enterococcus faecium</i> , <i>Clostridium perfringens</i> , <i>Bacteroides caccae</i> , <i>Rothia aeria</i> , and <i>Prevotella melaninogenica</i>)	Ulcerative colitis	ECP could inhibit the activation of NF-κB pathway and MAPK pathway in Ulcerative colitis.	[25]
Selenium-containing tea	SeTP-1	47.0	Man:Glc:Gal:Xyl:Ara=1.01:3.59:0.21:1.14:0.19	Increase (e.g., <i>norank_f_Muribaculaceae</i> , <i>Lactobacillus</i> , and <i>Bifidobacterium</i>);	Ulcerative colitis	ASeTP remodeled the gut microbiota by accelerating the proliferation of beneficial bacteria and inhibiting pathogenic microorganisms.	[19]
	SeTP-2	43.6	Man:Glc:Gal:Xyl:Ara=2.85:0.68:9.70:0.93:2.00:0.87	Decrease (e.g., <i>Akkermansia</i> , <i>Desulfovibrio</i> , <i>Parasutterella</i> , and <i>Romboutsia</i>)			
	SeTP-3	34.9	Man:Glc:Gal:Xyl:Ara=1.38:0.34:15:30:0.18:1.28				
<i>Scutellaria baicalensis</i> Georgi	SP2-1	3.72 ×10 ³	Man:Rib:Rha:GlcA:Glc:Xyl:Ara:Fuc=5.06:21.24:1.00:20.25:3.49:50.90:228.77:2.40	Increase (<i>Firmicutes</i> , <i>Bifidobacterium</i> , <i>Lactobacillus</i> , and <i>Roseburia</i>); Decrease (<i>Bacteroides</i> , <i>Proteobacteria</i> and <i>Staphylococcus</i>)	Ulcerative colitis	SP2-1 suppressed the production of proinflammatory cytokines, enhanced the function of the intestinal barrier, promoted the proliferation of beneficial bacteria, and inhibited harmful bacteria, thereby ameliorating colitis.	[26]
<i>Armillariella tabescens</i> mycelia	AT	18.6 ~ 1.35 ×10 ³	Ara:Fuc:Man=1.0:2.7:1.6	Increase (<i>Firmicutes</i>); Decrease (<i>Bacteroidetes</i> and <i>Proteobacteria</i>)	Ulcerative colitis	AT could increase the levels of SCFAs and colonic barrier function. AT improved the microbial community structure through selectively enriching beneficial bacterial species.	[27]
Ginseng	GPs	13.402	Ara, Rha, Gal, Glc, Xyl	Increase (<i>Lactobacillus</i>)	Ulcerative colitis	GPs remarkably influenced the levels of microbial tryptophan metabolites, diminished the intestinal permeability and strengthened intestinal barrier integrity via inhibiting the 5-HT/HTR3A signaling pathway.	[23]
<i>Dendrobium fimbriatum</i> Hook	cDFPW1	40	Man, Glc	Increase (<i>Romboutsia</i> , <i>Lactobacillus</i> , and <i>Odoribacter</i>); Decrease (<i>Parasutterella</i> , <i>burkholderia</i> , <i>aballeronia-paraburkholderia</i> , and <i>Acinetobacter</i>)	Ulcerative colitis	cDFPW1 improved intestinal barrier function, regulated intestinal microbiota, reduced oxidative stress and inflammatory response.	[28]
<i>Polygonatum cyrtonema</i>	PSP-W-1	14.4	Gal	Increase (<i>norank_f_Muribaculaceae</i> , <i>Lactobacillus</i> and <i>norank_f_norank_o_Clostridia</i> UCG- 014); Decrease (<i>Bacteroides</i> and <i>Escherichia-Shigella</i>)	Ulcerative colitis	PSP-W-1 could significantly reduce colonic pathological damage, repaired intestinal barriers (occludin and ZO-1), and alleviated colitis symptoms by regulating intestinal microbiota.	[29]

Note: *Mesona chinensis* Benth polysaccharides, MBP; *Pleurotus tuber-regium* mycelium polysaccharides, PTRP; *Eurotium cristatum* polysaccharides, ECP; Selenium-containing tea polysaccharides, SeTP; *Scutellaria baicalensis* Georgi polysaccharides, SP2-1; *Armillariella tabescens* mycelia polysaccharides, AT; *Ginseng* polysaccharides, GPs; *Dendrobium fimbriatum* Hook polysaccharides, cDFPW1; *Polygonatum cyrtonema* polysaccharides, PSP-W-1; Glucose, Glc; Xylose, Xyl; Galactose, Gal; Galacturonic acid, GalA; Fucose, Fuc; Mannose, Man; Ribose, Rib; Glucuronic acid, GlcA; Arabinose, Ara.

Across diverse models, natural polysaccharides consistently restructure the gut microbiota by promoting SCFA-producing taxa and suppressing pathobionts. These changes are concurrently associated with a strengthened intestinal epithelial barrier and the dampening of pro-inflammatory signaling pathways, such as TLR4/NF- κ B and MAPK. First, several interventions consistently promote SCFA-linked beneficial genera while constraining dysbiosis-associated taxa: for example, polysaccharides from *Pleurotus tuber regium* mycelium, selenium-containing tea polysaccharides, and *Pinus massoniana* pollen polysaccharides collectively increase representatives such as *Turicibacter*, *Ruminococcus*, *Prevotella*, *Bacteroides*, *Bifidobacterium* (and related families including *Muribaculaceae*, *Rikenellaceae*, *Lachnospiraceae*), while reducing organisms associated with colitis activity such as *Desulfovibrio* and other Proteobacteria-affiliated pathobionts [18–20]. Second, beyond compositional shifts, defined signaling pathways are modulated: *Mesona chinensis* Benth polysaccharide (MBP) not only reverses DSS-induced dysbiosis (e.g., decreasing *Helicobacter* and *Prevotella* while increasing *Lactobacillus* and *Coprococcus*) but also attenuates inflammation via inhibition of the TLR4/MAPK/NF- κ B axis [21]. Third, barrier-protective actions recur across studies: intracellular polysaccharides have been shown to ameliorate histological injury, promote goblet cell differentiation, enhance MUC2 formation, and upregulate tight-junction proteins (ZO-1, occludin, claudin-1), thereby reinforcing epithelial integrity [22]. Complementing these effects, ginseng polysaccharides restore microbial balance (notably *lactobacilli*), modulate microbial tryptophan metabolites, reduce intestinal permeability, and improve barrier function through inhibition of the 5-HT/HTR3A pathway [23]. Additionally, sulfated polysaccharides from *Pacific abalone* (AGSP) mitigate DSS-elevated *Bacteroidetes* linked to colitis severity and may limit microbiota-driven mucin degradation, providing a plausible explanation for preserved mucus layers [24].

In summary, evidence converges on a convergent mechanism whereby diverse natural polysaccharides ameliorate UC. They orchestrate a beneficial shift in the gut microbiota, enriching SCFA-producing commensals (e.g., *Lachnospiraceae*, *Ruminococcus*, *Bacteroides*, *Bifidobacterium*) while suppressing pathobionts (e.g., *Desulfovibrio* and *Proteobacteria*). Concurrently, they inhibit pro-inflammatory TLR4/NF- κ B and MAPK signaling and reinforce the mucosal barrier by upregulating MUC2 and tight junctions. These integrated actions collectively reduce inflammation and mucosal damage, underscoring the promise of natural polysaccharides as multi-target therapeutic candidates for UC management with favorable safety profiles.

2.2 Neurodegenerative diseases

Dysbiosis of the gut microbiota can lead to the production of harmful substances, damage to the intestinal mucosa and immune system, and increased permeability of both the intestinal barrier and the blood-brain barrier, thereby inducing neuroinflammation in the brain and elevating the risk of neurodegenerative diseases [30]. Specifically, when the gut microbiota is imbalanced, various microorganisms and toxins in the intestine can disrupt the stability and integrity of the intestinal mucosa. This disruption allows gut microbiota, particularly Gram-negative bacteria, and their metabolites to enter circulation through the intestinal barrier, resulting in elevated serum levels of lipopolysaccharides (LPS) and pro-inflammatory cytokines.

Subsequently, these peripheral cytokines are transported to the brain via the gut-brain axis pathway, inducing neuroinflammation (**Fig. 3**). The gut-brain axis is a bidirectional communication network that encompasses the central nervous system, autonomic nervous system, enteric nervous system, immune system, and endocrine system, connecting to both the cognitive center and peripheral gut function of the brain. It monitors and integrates gut function and cognitive processes through this axis^[31]. According to the concept of the gut-brain axis, dysfunction of the gut can lead to dysfunction of the central nervous system. As serum concentrations of lipopolysaccharides and inflammatory cytokines increase, 'leaky gut' exacerbates neuroinflammation. The brain and gut regulate each other through multiple bidirectional mechanisms, influencing each other's functions, including gut barrier permeability, gut microbiota composition, neurotransmitter release, and central nervous system inflammation, which, in turn, affects stress, anxiety, depression, and cognition. In recent years, natural polysaccharides have played a significant role in the treatment of neurodegenerative diseases through the gut-brain axis (**Table 2**).

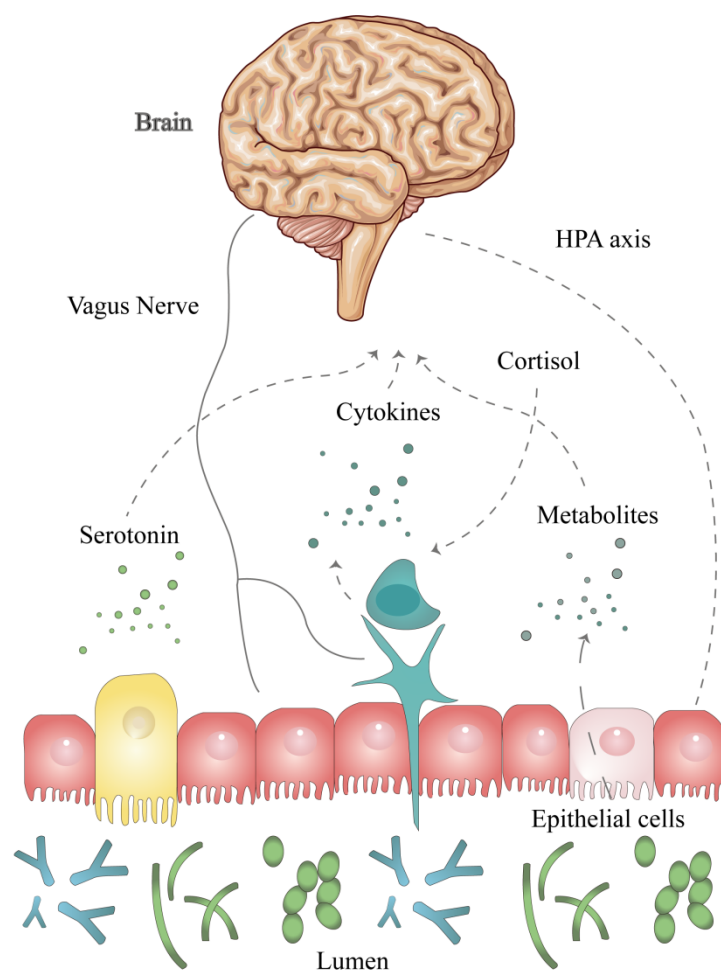


Fig. 3. Mechanism of neuroinflammation induced by gut microbiota dysbiosis through the gut-brain axis. An imbalanced gut microbiota disrupts intestinal mucosal integrity, enabling Gram-negative bacteria and their metabolites (e.g., LPS) to translocate into systemic circulation. This leads to increased serum levels of lipopolysaccharides and pro-inflammatory cytokines, which are transported to the brain via the gut-brain axis, ultimately triggering neuroinflammation and potential neurological dysfunction.

Table 2. Natural polysaccharides regulate neurodegenerative diseases through probiotics.

Source	Compound name	Mw/kDa	Monosaccharide composition (mol% or mole ratio)	Intestinal flora	Disease	Mechanisms	References
<i>Lactiplantibacillus plantarum</i>	Yellow okra polysaccharide	1~2767	Glc:Man:Gal:Ara:Xyl:Fru:Rha=20.1:16.7:19.2:13.5:5.7:16.7:4.2	Increase (<i>Lactobacillaceae</i> and <i>Lactobacillus</i>)	Alzheimer's disease	Yellow okra polysaccharide microcapsules had regulatory effects on <i>Lactobacillaceae</i> and <i>Lactobacillus</i> in AD mice.	[32]
Ginkgo biloba leaves	GPS	296.96	Man:Rha:GlcA:Gal:Ara=29.73:31.54:24.81:5.72:8.30	Increase (<i>Lactobacillus</i>)	Depression	GPS reversed depression-associated gut dysbiosis and increased the richness of <i>Lactobacillus</i> species which has been proven to be a path to relieve depression.	[33]
<i>Dendrobium officinale</i>	DOP	746.52	Man:Glc=2.55:1.00	Increase (<i>Akkermansia</i> and <i>Alistipes</i>); Decrease (<i>Clostridia</i>)	Cognitive impairment	DOP reshaped the perturbation of gut microbiota, and reduced inflammatory cells infiltration and strengthened mucosal integrity.	[34]

Note: Ginkgo biloba leaves polysaccharides, GPS; *Dendrobium officinale* polysaccharides, DOP; Alzheimer's disease, AD; Glucose, Glc; Mannose, Man; Galactose, Gal; Arabinose, Ara; Xylose, Xyl; Fructose, Fru; Rhamnose, Rha; Glucuronic acid, GlcA.

2.2.1 Alzheimer's disease

Alzheimer's disease (AD) is an irreversible neurodegenerative condition that can lead to neurotoxicity and an imbalance in gut microbiota. Recent evidence indicates that gut microbiota plays a significant role in the pathogenesis of Alzheimer's disease. Researchers have observed differences in the abundance of various bacteria, such as *Bacteroidetes*, *Firmicutes*, and *Bifidobacterium*, between healthy individuals and AD patients [35]. Notably, increased intestinal permeability and systemic inflammation resulting from an ecological imbalance in the gut may induce Alzheimer's disease pathology and cognitive impairment via the gut-brain axis [36]. Taken together, clinical and preclinical data point to a convergent model in which AD is associated with gut dysbiosis, barrier disruption, and inflammation along the gut-brain axis, providing a rationale for microbiota-directed strategies (e.g., prebiotic/polysaccharide interventions) to modify disease-relevant pathways. Recent studies suggest that alterations in gut microbiota during the onset of Alzheimer's disease may be mitigated through prebiotic therapy [37, 38]. A clinical study reported a decrease in the level of rectal true bacteria and an increase in the abundance of *Escherichia coli*/*Shigella* in amyloid-positive patients, which may correlate with the systemic inflammatory state observed in patients with cognitive impairment [39].

Mechanistically convergent polysaccharide interventions illustrate these trends. *Sparsis crispa* polysaccharides have been shown to reshape the composition of the gut microbiota, particularly by promoting the proliferation of butyrate-producing bacteria, including *Intestinimonas*, the [*Eubacterium*] *ventriosum* group, *Lachnospiraceae_UCG010*, and *Lachnospiraceae_UCG001*, while inhibiting the growth of inflammation-related bacteria such as *Escherichia coli*/*Shigella*. Additionally, *Sparsis crispa* polysaccharides improved learning and spatial recognition deficits in Alzheimer's disease mice, reduced amyloid formation, and regulated neurotransmitter levels, including γ -aminobutyric acid, glutamate, and acetylcholine, in the brain [40] (Fig. 4). Similarly, *S. chinensis* polysaccharides have been found to enhance learning and memory abilities, reduce neuroinflammation, and restore the integrity of the intestinal barrier. Mechanistically, SCP2 significantly regulated 19 endogenous metabolites in Alzheimer's disease rats and reversed gut microbiota disorders. In summary, SCP2 may exert neuroprotective effects by reshaping the gut microbiota, improving the intestinal barrier, promoting the production of SCFAs, reducing neuroinflammation, and alleviating cognitive impairment in Alzheimer's disease rats [41].

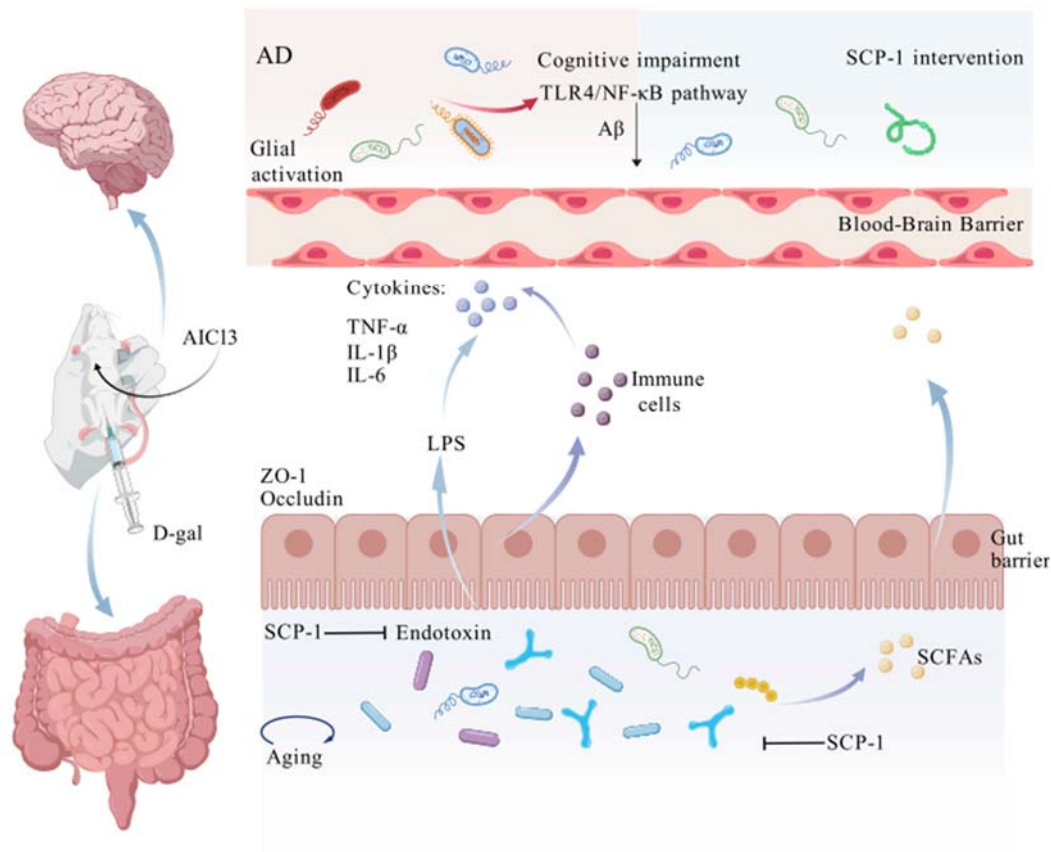


Fig. 4. Effects of *Sparsis crispa* polysaccharides on gut microbiota modulation and amelioration of Alzheimer's disease in mice.

Sparsis crispa polysaccharides reshape the gut microbial composition by promoting beneficial butyrate-producing bacteria (e.g., *Intestinaimonas*, [*Eubacterium*] *ventriosum* group, *Lachnospiraceae_UCG010*, and *Lachnospiraceae_UCG001*) and suppressing inflammation-related bacteria (e.g., *Escherichia coli/Shigella*). These changes correlate with improved cognitive performance, reduced amyloid formation, and regulated neurotransmitter levels (e.g., γ -aminobutyric acid, glutamate, and acetylcholine) in the brain, demonstrating a gut-brain axis mechanism in alleviating Alzheimer's disease.

2.2.2 Elderly Cognitive Impairment

Preliminary evidence suggests that gut dysbiosis may trigger innate immune responses and contribute to mild chronic inflammation, which can lead to age-related diseases [42], cognitive impairment, and the aging process itself [43, 44]. Furthermore, studies indicate that as individuals age, the diversity of gut microbiota in older adults diminishes [45], with a notable decrease in *Bifidobacterium* alongside an increase in *Firmicutes* and *Proteobacteria* [46, 47]. In summary, the rapid alterations in gut microbiota associated with aging are closely linked to host immune responses, cognitive decline, and behavioral deficits observed in older adults [48, 49]. Collectively, these findings delineate an “aging-associated dysbiosis” characterized by reduced diversity, loss of key commensals (e.g., *Bifidobacterium*), expansion of *Firmicutes/Proteobacteria*, epithelial leakiness, and low-grade inflammation, thereby providing a rationale for polysaccharide-based, microbiota-directed strategies to support late-life cognitive health.

Current evidence indicates that polysaccharides initiate their protective effects by restructuring the gut microbiota composition and promoting the production of SCFAs. Polysaccharides derived from *Oudemansiella raphanipes* have been shown to improve age-related cognitive decline via the microbiota-gut-brain axis. ORP-1 and its gut microbiota-derived metabolites, SCFAs, primarily restore a healthy gut microbiota by increasing the abundance of beneficial bacteria such as *Dubosiella*, *Clostridiales*, and *Prevotellaceae*, while reducing the prevalence of harmful bacteria like *Desulfovibrio*. This intervention addresses age-related gut microbiota dysbiosis. Furthermore, these compounds enhance the integrity of the gut barrier by mitigating age-related alterations in tight junction (TJ) and mucin 2 (MUC2) protein expression, decreasing age-related increases in circulating inflammatory factors, and improving cognitive decline by reversing deficits in memory and synaptic plasticity-related protein levels. Additionally, they inhibit microglia-mediated synaptic phagocytosis and the overactivation of neuroinflammation [50].

Furthermore, polysaccharides exert their neuroprotective effects by reinforcing gut and blood-brain barrier integrity, while concurrently suppressing neuroinflammation and oxidative stress. *Polygonatum sibiricum* polysaccharides have demonstrated the ability to enhance cognitive function in aging mice and regulate oxidative stress via the 'microbiota-gut-brain' axis. Mechanistically, PSP effectively mitigated pathological changes and oxidative stress in the hippocampus while improving cognitive performance. Concurrently, there was an observed increase in the abundance of *Bacteroidota*, accompanied by a decrease in the abundance of *Firmicutes*, *Patescibacteria*, *Actinobacteriota*, and *Campilobacterota* [51]. Similarly, fucoidan has been shown to ameliorate LPS-induced neuronal cell damage and cognitive dysfunction in mice. LPS treatment significantly elevated the abundance of *Akkermansiaceae*, pro-inflammatory *Enterobacteriaceae*, and *Erysipelotrichaceae*, microbial groups associated with intestinal permeability, while concurrently decreasing the abundance of the anti-inflammatory bacterium *Oscillospiraceae*. Fucosan demonstrated neuroprotective effects against LPS-induced cognitive impairment in mice by reducing neuroinflammation, promoting neurogenesis, and decreasing both blood-brain barrier and intestinal barrier permeability [52]. Taken together, these studies converge on a mechanism whereby polysaccharides reinforce epithelial/BBB barriers and suppress neuroinflammatory and oxidative stress pathways, with microbiota shifts tracking these host benefits.

Furthermore, research indicates that mice with disrupted circadian rhythms exhibit deficits in recognition and spatial memory. *Dendrobium officinale* polysaccharides alleviated cognitive impairment in a mouse model of circadian rhythm disorder by modulating the gut microbiota. DOP reshaped the gut microbiota disturbances associated with circadian rhythm disorders, leading to an upregulation of *Akkermansia* and *Alistipes* abundance and a downregulation of *Clostridia* abundance. Additionally, DOP was effective in restoring tissue pathological changes, reducing inflammatory cell infiltration, and enhancing mucosal integrity [34]. This illustrates that microbiota-directed polysaccharides can exert neurocognitive benefits even when cognitive decline is secondarily driven by circadian misalignment, expanding the translational relevance of these interventions.

2.2.3 Depression

In the early 2000s, researchers identified a potential association between depression and inflammation, noting that patients with depression exhibited a heightened immune response to chemicals produced by *Morganella* and other Gram-negative bacteria present in their intestines. Subsequent research appears to reinforce the notion that inflammation induced by gut microbes can influence mood. The gut microbiota, often referred to as the 'organs' of the human body, maintains a dynamic balance over extended periods. However, as depression progresses, it may disrupt this microbial ecosystem [53]. At the phylum level, the abundance of *Bacteroidetes*, *Aspergillus*, *Clostridium*, and *Raccoonaceae* significantly increases in patients with depression, whereas the abundance of *Ruminococcus*, *Prevotella*, *Lactobacillus*, and *Paecillaceae* notably decreases. The pathogenic mechanisms associated with these specific intestinal bacteria likely involve the activation of peripheral immunity and inflammatory responses, which result in the release of inflammatory factors that can penetrate the central nervous system, thereby contributing to the onset of depression. Consequently, investigating the impact of gut inflammation on depression through the microbiota-gut-brain axis is crucial for developing strategies to alleviate depressive symptoms (Fig. 5).

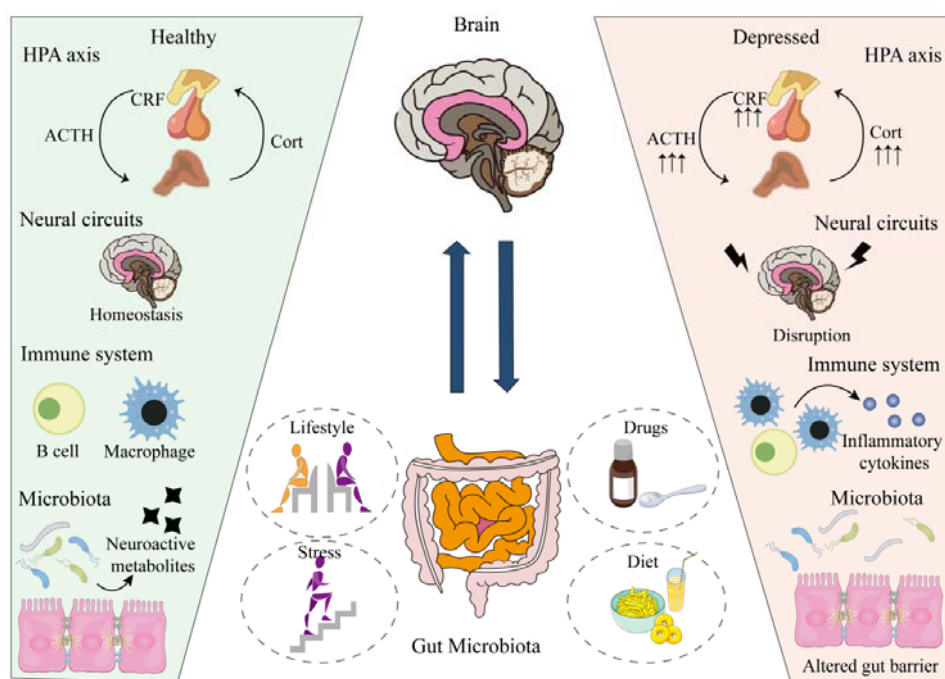


Fig. 5. This diagram illustrates the relationship between the gut microbiota and brain function in both healthy and depressed states, highlighting the role of the HPA axis, immune system, and lifestyle factors.

The polysaccharide exerts its antidepressant effects by modulating the microbiota/SCFA axis and suppressing mucosal immunity. *Paeonia lactiflora* Pall. polysaccharides have been shown to modulate depression-associated intestinal ecological dysregulation, enhancing species richness, reducing inflammatory factor levels and NLRP3 inflammasome activation, and mitigating colonic mucosal and neuronal damage. These effects culminate in the improvement of depressive-like behavior and neurotransmitter release in CUMS mice [54].

Depression-like behavior in colitis mice was alleviated as levels of SCFAs increased. Furthermore, abnormal intestinal bile acids may be linked to depression in patients. Recent studies have demonstrated that *Garcinia cambogia* polysaccharides can effectively ameliorate the imbalance of intestinal flora and disturbances in the metabolism of SCFAs and bile acids in mice with a colitis model. This intervention contributed to the restoration of intestinal Th17/Treg homeostasis and, consequently, attenuated dextran sulfate sodium (DSS)-induced intestinal inflammation and depressive-like behaviors through the microbiota-gut-brain axis ^[55]. Together, these data establish the routing of metabolism through SCFAs and bile acids as a nodal mechanism through which polysaccharides recalibrate peripheral immunity and mood-relevant behaviors.

Similarly, The polysaccharide exerts its antidepressant effects by fortifying the gut and brain barriers, curbing neuroinflammation, and fostering neurogenesis. *Polygonum sibiricum* polysaccharides exhibited antidepressant-like effects in mice with chronic unpredictable mild stress-induced depression by modulating the microbiota-gut-brain axis. Specifically, fecal microbiota transplantation (FMT) significantly increased serum levels of 5-hydroxytryptamine and norepinephrine, reduced pro-inflammatory cytokine levels in the hippocampus, and decreased serum corticosterone levels of pro-adrenocorticotrophic hormone in chronic mild stress (CMS)-induced mice. Additionally, FMT significantly enhanced colonic expression of ZO-1 and occludin while decreasing serum levels of lipopolysaccharide and interferon- γ ^[56].

Previous studies have demonstrated that *Lactobacilli* positively influence the alleviation of depression. Polysaccharides derived from *Ginkgo biloba* leaves have been shown to reverse gut dysbiosis associated with depression and increase the abundance of *Lactobacilli*, which is recognized as a pathway for alleviating depressive symptoms. *Lactobacillus reuteri*, a member of the *Lactobacillus* genus, exhibits an antidepressant effect that aligns with the beneficial impacts of *Lactobacilli* on various previously reported mental disorders. Given that *Lactobacillus* probiotics share similar biological characteristics, we hypothesize that this genus of probiotics plays a significant regulatory role in antidepressant treatment ^[33]. In summary, while the etiology of depression remains unclear, it is evident that microbes play a crucial role. Research into the effects of natural polysaccharides on alleviating depression through modulation of the gut microbiota holds promise for providing new hope to patients suffering from depression.

In summary, despite the diverse botanical origins of the discussed polysaccharides and their application across different neurological disorders, including Alzheimer's disease and depression, several unifying mechanisms of action emerge through the gut-brain axis. A key conserved microbial target is the promotion of beneficial SCFA-producing bacteria (e.g., *Lachnospiraceae*, *Clostridium*, *Ruminococcus*) and the reduction of inflammation-associated pathobionts (e.g., *Escherichia/Shigella*, *Desulfovibrio*, *Enterobacteriaceae*). Commonly, these polysaccharides enhance intestinal barrier integrity by upregulating tight junction proteins (e.g., ZO-1, occludin) and mucin (MUC2), and reduce systemic and neuroinflammation by inhibiting NF- κ B-dependent pathways and pro-inflammatory cytokine release. Furthermore, they ameliorate neurological impairments by modulating neurotransmitters, inhibiting neuroinflammation, and protecting synaptic

function. This collective evidence underscores that although the source polysaccharides vary, their beneficial effects converge on core mechanisms: microbial SCFA production, gut barrier restoration, and inflammatory downregulation, ultimately preserving cognitive function and emotional homeostasis.

2.3 Diabetes

Patients with diabetes exhibit reduced bacterial diversity in their intestinal flora, accompanied by significant alterations in microbial populations, particularly in butyric acid-producing bacteria, which play a crucial role in modulating immune tolerance and enhancing the integrity of the intestinal barrier [2]. Abnormal changes in intestinal flora can damage the intestinal epithelium and disrupt the integrity of the intestinal barrier, potentially resulting in the leakage of bacterial endotoxins that trigger systemic inflammation and subsequently disrupt Glucose metabolism [57]. Several clinical studies have indicated that the intestinal flora of patients with Type 2 Diabetes (T2D) contains elevated concentrations of harmful intestinal metabolites, such as indole and hydrogen sulfide, which may compromise intestinal integrity and contribute to increased levels of inflammatory factors in the body [58].

Conventional therapeutics and natural polysaccharides differ markedly in how they modulate the gut ecosystem. Metformin, a widely utilized first-line hypoglycemic agent, is constrained by adverse reactions and has been shown to significantly reduce the diversity of gut microbiota. In contrast, natural polysaccharides not only modulate microbial diversity but also beneficially reshape its composition, thereby playing a crucial role in the pathophysiology of diabetes and associated immune responses by influencing host physiology and metabolism (**Table 3**).

The therapeutic potential of polysaccharides in T2D largely converges on the restoration of SCFA production and the reinforcement of the intestinal barrier. For instance, the increase in SCFAs following treatment with astragalus polysaccharides can alleviate diabetic symptoms in db/db mice by enhancing the expression of G protein-coupled receptors 41 and 43, as well as tight junction proteins (occludin and ZO-1), stimulating the secretion of GLP-1, and improving intestinal integrity [59]. SCFAs, among the most abundant microbial metabolites in the gut, exert a wide range of effects on host health. Treatment with *Phellinus linteus* polysaccharides has been shown to increase the abundance of SCFA-producing bacteria in a model of type 2 diabetes in rats. This increase in both the abundance and content of SCFA-producing bacteria in the cecum enhances intestinal ecological balance, aids in maintaining intestinal barrier function, and reduces chronic inflammation and insulin resistance induced by a high-fat diet [60].

Table 3. Natural polysaccharides regulate diabetes through probiotics.

Source	Compound name	Mw/kDa	Monosaccharide composition (mol% or mole ratio)	Intestinal flora	Disease	Mechanisms	References
<i>Lycium barbarum</i> L.	LBP	38.54	Rha:GlcA:Glc:Gal:Xyl:Ara=8.37:2.21:7.95:26.38:7.91:47.18	Increase (<i>Allobaculum</i>)	Diabetes	LBP improved glucose metabolism by enhancing intestinal barrier function and alleviating systemic inflammation.	[66]
<i>Moutan Cortex</i>	MC-Pa	164.0	D-Glc:L-Ara=3.31:2.25	Enhance (<i>Muribaculaceae_unclassified</i> , <i>Akkermansia</i> , and <i>Ruminococcus</i>)	Diabetes	MC-Pa ameliorated diabetic kidney disease via modulating gut microbiota dynamically in rats.	[67]
<i>Fructus mori</i>	FMP	102.33 (53.47%), 8.71 (12.40%), and 5.62 (34.13%)	Ara:Rha:Man:Gal:Glc:GalA:GlcA=17.88:7.71:5.52:6.69:52.09:6.01:4.10	Increase (<i>Allobaculum</i> and <i>Bifidobacterium</i>); Decrease (<i>Shigella</i>)	Diabetes	FMP alleviated diabetic symptoms by regulating intestinal microbiota and intestinal barrier against TLR4/NF- κ B pathway.	[68]
<i>Dendrobium officinale</i>	DOP	107.15	Man:Glc=85.75:12.82	Increase (<i>Allobaculum</i> , <i>Bifidobacterium</i> , and <i>Lactobacillus</i>); Decrease (<i>Helicobacter</i>)	Diabetes	DOP significantly upregulated the mRNA expression of tight junction proteins Claudin-1, Occludin, and ZO-1 through the LPS/TLR4/TRIF/NF- κ B axis, reducing intestinal inflammation and oxidative stress damage, and repairing the intestinal barrier.	[61]

Note: *Lycium barbarum* L. polysaccharides, LBP; *Moutan Cortex* polysaccharides, MC-Pa; *Fructus mori* polysaccharides, FMP; *Dendrobium officinale* polysaccharides, DOP; Rhamnose, Rha; Glucuronic acid, GlcA; Glucose, Glc; Galactose, Gal; Xylose, Xyl; Arabinose, Ara; Mannose, Man; Galacturonic acid, GalA.

Beyond SCFA production, a consistent mechanistic pattern observed across multiple polysaccharide interventions is the coordinated enhancement of gut barrier integrity and suppression of pro-inflammatory signaling. *Dendrobium officinale* polysaccharides significantly up-regulated the mRNA expression of tight junction proteins Claudin-1, Occludin, and ZO-1 through the LPS/TLR4/TRIF/NF- κ B axis, thereby attenuating intestinal inflammation and oxidative stress damage, and facilitating the repair of the intestinal barrier [61]. The disruption of gut microbiota in patients with T2DM is indicated by an increased *Firmicutes/Bacteroidetes* ratio, which is negatively correlated with glucose homeostasis [62, 63]. AEPSa significantly reduced the *Firmicutes/Bacteroidetes* ratio by enhancing the relative abundance of the *anaplastic bacillus* group, suggesting its potential to ameliorate gut microbiota disorders in T2DM mice. The underlying mechanism may involve the increase of *Allobaculum*, *Alistipes*, *Lachnospiraceae_NK4A136_group*, and *norank_f_Muribaculaceae*, while decreasing the influence of *Enterococcus* and *Ruminococcus_torques_group* on the TLR4/NF- κ B pathway to alleviate hyperglycemia [64]. Similarly, *Morchella esculenta* mushroom polysaccharides modulated the composition of the intestinal microbiota by reducing harmful bacterial populations (*Actinobacteria*, *Bacillus*, *Facklamia*, and *Synechococcus*) and increasing beneficial bacteria (Thick-walled phylum and *Lactobacillus*). Furthermore, MEP has the potential to decrease endotoxemia and improve intestinal permeability by altering functional metabolic pathways [65].

In summary, despite the structural diversity of the polysaccharides examined, they converge on several key microbial and host pathways to ameliorate T2D. A common microbial target is the restoration of beneficial SCFA-producing bacteria (e.g., *Lachnospiraceae*, *Muribaculaceae*, and *Anaerobacillus*), which helps to reverse the decreased F/B ratio often observed in T2D, while reducing the abundance of harmful bacteria (e.g., *Actinobacteria*, *Enterococcus*, and *Ruminococcus_torques_group*). At the host level, these polysaccharides consistently enhance intestinal barrier integrity by upregulating tight junction proteins (ZO-1, occludin, and claudin-1), suppress systemic inflammation through inhibition of the LPS/TLR4/NF- κ B signaling pathway, and improve glucose homeostasis by modulating GLP-1 secretion and reducing insulin resistance. This coordinated regulation of the gut microbiota and host inflammatory and metabolic pathways underscores the potential of natural polysaccharides as multi-target therapeutic agents for T2D management.

2.4 Obesity

Obesity, a significant public health concern worldwide, has been classified as a disease state and is linked to numerous health complications. While various treatment methods for obesity have been developed, including surgical interventions and lifestyle modifications aimed at weight control, these approaches may yield only short-term results. If patients do not adhere to the guidance provided by dietitians and healthcare professionals, they are likely to experience weight regain, potentially exacerbating their condition. Evidence suggests a consistent association between gut dysbiosis and the onset of obesity. Researchers have compared the gut microbiota composition of obese and lean individuals, revealing an increasing trend in *Firmicutes* and a corresponding decrease in *Bacteroidetes* [69]. This shift in the relative proportions of *Firmicutes* to *Bacteroidetes* alters fermentation processes, which may elucidate the mechanisms underlying weight gain [70]. Dietary therapy for obesity has become a central focus of research. Recent evidence increasingly suggests that

obesity negatively impacts the diversity and richness of the gut microbiota. Dietary fiber and indigestible polysaccharides have been shown to prevent chronic high-fat diet-induced obesity, intestinal dysbiosis, increased intestinal permeability, and endotoxemia, all of which are associated with enhanced diversity and functionality of the gut microbiota (**Table 4**).

Converging evidence shows that polysaccharide treatment reverses the obesity-linked rise in the *Firmicutes/Bacteroidetes* ratio and improves metabolic parameters at the same time. Treatment with *Lycium barbarum* polysaccharides significantly improved the symptoms of hyperglycemia, hyperlipidemia, and lipid metabolism disorders in obese mice ^[71]. Isinglass polysaccharides regulate intestinal barrier function and alleviate obesity in mice on a high-fat diet through the HO-1/Nrf2 pathway and the gut microbiota environment. The results concerning gut microbiota indicate that CIP reduced the abundance of *Firmicutes* while increasing the abundance of *Bacteroidetes*. Notably, CIP intervention led to an increase in the abundance of *Blautia* and *Coriobacteriaceae* ^[72].

Beyond the *Firmicutes/Bacteroidetes* ratio, different polysaccharides demonstrate targeted modulation of specific bacterial taxa associated with physiological improvement. *Undaria pinnatifida* polysaccharides have been shown to regulate diet-induced gut microbiota dysbiosis, characterized by an increase in *Bacteroidales* and a decrease in *Clostridiales* and *Lactobacillus*, which are positively correlated with physiological improvement ^[73]. Similarly, *Tremella fuciformis* polysaccharides inhibited obesity by regulating inflammation and the gut-brain microbiota axis. Furthermore, TP improved gut microbiota dysbiosis by reducing the *Firmicutes/Bacteroidetes* ratio and modulating the relative abundance of specific gut microbiota ^[74].

At the host level, polysaccharides exert anti-obesity effects through a coordinated multi-target mechanism that integrates barrier protection, anti-inflammatory, and antioxidant actions. Mechanistically, the positive anti-obesity effects of polysaccharides from unripe raspberry fruits may be associated with their modulation of intestinal flora, enhancement of intestinal barrier function, and inhibition of the TLR4/NF- κ B signaling pathway ^[75]. This underscores a broader pattern: the anti-obesity efficacy of polysaccharides is not solely dependent on microbial restructuring but also on the subsequent suppression of systemic inflammation and the reinforcement of the gut barrier.

In summary, a synthesis of the presented evidence reveals that polysaccharides from diverse natural sources converge on several core mechanisms to counteract obesity. A key conserved microbial target is the reversal of obesity-associated dysbiosis, specifically by decreasing the *Firmicutes/Bacteroidetes* ratio and enriching for beneficial taxa such as *Bacteroidales*, *Blautia*, and *Coriobacteriaceae*, while often reducing the abundance of *Clostridiales* and *Lactobacillus*. At the host level, these polysaccharides consistently enhance intestinal barrier integrity, mitigate chronic inflammation through the inhibition of the TLR4/NF- κ B pathway, and activate antioxidant defenses via the HO-1/Nrf2 signaling axis. By collectively modulating the gut microbiota composition, strengthening the gut barrier to reduce endotoxemia, and dampening systemic inflammation and oxidative stress, natural polysaccharides emerge as potent multi-target agents that restore metabolic homeostasis and offer a promising dietary strategy for the management of obesity.

Table 4. Natural polysaccharides regulate obesity through probiotics.

Source	Compound name	Mw/kDa	Monosaccharide composition (mol% or mole ratio)	Intestinal flora	Disease	Mechanisms	References
Raspberry	RP2	18	Man:Rha:Glc:Gal:Ara=0.06:0.33:1.00:0.08:0.31:0.15	<i>Lactobacillus taiwanensis</i> , <i>Bifidobacterium pseudolongum</i> , <i>Turicibacter</i> and	Obesity	The positive effects of RP2 anti-obesity may be associated with its regulation of gut microbiota, intestinal barrier, and inhibition of TLR4/NF-κB signaling pathway.	[75]
<i>Platycodon grandiflorum</i>	PGNP	13.6	Glc:Fru=10.9:84.1	Decrease (<i>Firmicutes/Bacteroidetes</i>)	Obesity	PGNP effectively increased species diversity of gut microbiota and reversed the HFD-induced imbalance in the gut microbiota.	[76]
WuGuChong	PEW	32.9	Rha, Glc, Man, Gal, Ara, Xyl, GlcA, GalA	Increase (<i>Firmicutes/Bacteroidetes</i> , <i>Proteobacteria</i>)	Obesity	PEW reduced obesity caused by high-fat diet in mice by regulating the composition of gut microbiota.	[77]
<i>Tremella fuciformis</i>	TP	10.07-66.29	Man:Rha:GlcA:Glc:Gal:Xyl=15.95:0.31:2.47:1.20:3.18:1.72	Decrease (<i>Firmicutes/Bacteroidetes</i>)	Obesity	TP inhibited obesity by modulating inflammation and the microbe-gut-brain axis.	[74]

Note: Raspberry polysaccharides, RP2; *Platycodon grandiflorum* polysaccharides, PGNP; WuGuChong polysaccharides, PEW; *Tremella fuciformis* polysaccharides, TP; Mannose, Man; Rhamnose, Rha; Glucose, Glc; Galactose, Gal; Arabinose, Ara; Fructose, Fru; Xylose, Xyl; Glucuronic acid, GlcA; Galacturonic acid, GalA.

2.5 Immunomodulatory functions

The intestine, recognized as the largest digestive and absorptive organ in the human body, also plays a crucial role as an immune organ, helping to resist the invasion of pathogenic microorganisms. In a healthy intestinal system, a robust intestinal mucosal immune barrier, along with a diverse gut microbiota, contributes significantly to intestinal homeostasis. The integrity of the intestinal mucosal barrier serves as the foundation of intestinal immunity, establishing a strong defense system that prevents harmful substances and pathogens from entering the body. Importantly, alterations in intestinal flora can disrupt the intestinal mucosal barrier and diminish mucosal immunity. It is well established that a vast population of microorganisms resides in our distal gut. The functions of these bacteria are pivotal in shaping and regulating the immune system^[78] (**Fig. 6**). Gut microbes are protected within the gut, influenced by the intestinal immune system, and play a critical role in modulating both innate and acquired immunity by regulating immune system development and maintaining the integrity of the gut barrier^[79]. The human intestinal flora, in symbiosis with the host, plays a crucial role in the development of the immune system by activating gut-associated lymphoid tissues and regulating the secretion of sIgA as well as nutrient absorption^[80, 81]. Notably, polysaccharides serve as the primary nutrients that shape the gut flora^[82]. These polysaccharides can counteract immune suppression and possess the potential to act as less toxic immunomodulators. The metabolites derived from polysaccharides, including SCFAs, can directly promote the proliferation of beneficial symbiotic bacteria, enhance both intestinal and systemic immunity, and confer benefits to the host, while also being associated with a reduced risk of various diseases (**Table 5**).

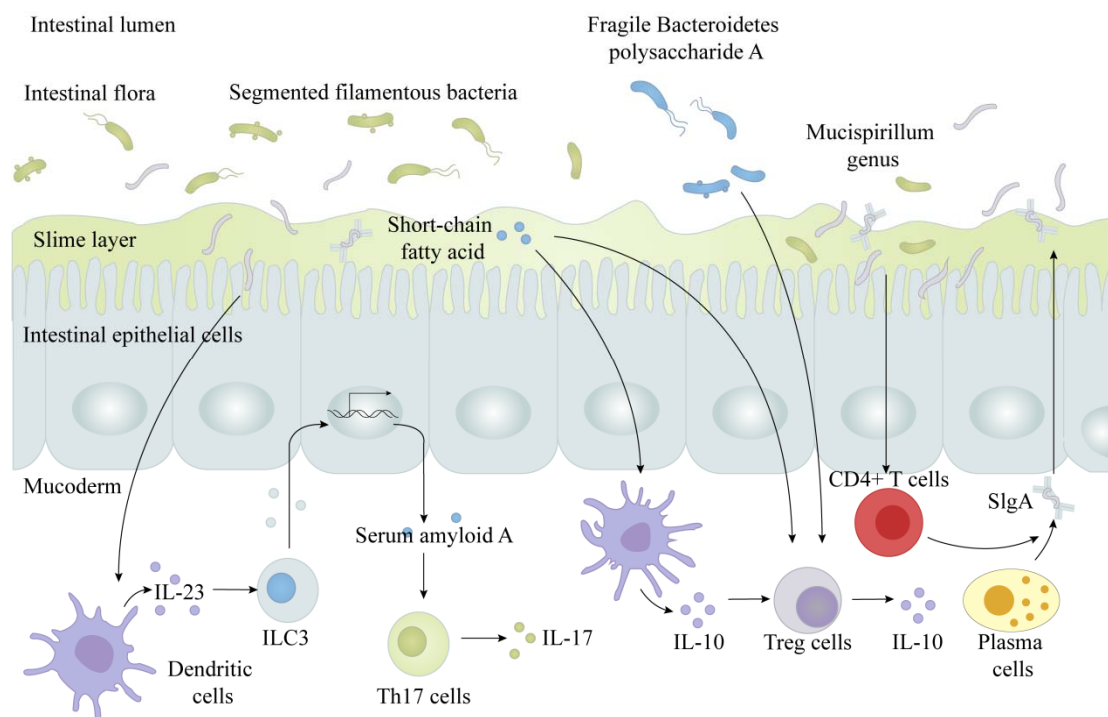


Fig. 6. This schematic diagram illustrates the mechanisms through which specific commensal gut microbiota members regulate intestinal immune responses by modulating the differentiation of T helper cells.

Table 5. Natural polysaccharides regulate immunomodulatory functions through probiotics.

Source	Compound name	Mw/kDa	Monosaccharide composition (mol% or mole ratio)	Intestinal flora	Disease	Mechanisms	References
<i>Atractylodes lancea</i> Rhizome	SALP	7.2	Man:Rib:Rha:GlcA:GalA:Glc:Gal:Ara=3.58±0.11:3.23±0.17:1.69±0.08:1.55±0.11:9.74±0.51:37.89±1.19:16.71±0.58:25.61±0.85	Increase (<i>Lactobacillus</i> and <i>Faecalibaculum</i>)	Immunity	ALP promoted the expression of T cells and secretion of sIgA and reversed the decrease in SCFAs levels and promoted the expression of G protein coupled receptor 43 (GPR43).	[83]
	FALP		Man:Rib:Rha:GlcA:GalA:Glc:Gal:Ara=3.34±0.02:4.17±0.09:1.47±0.02:1.27±0.01:6.13±0.23:40.02±0.61:15.43±0.28:28±0.44				
Alhagi honey	AH	46.8	Rha:Man:Glc:Gal=2.11:3.80:4.19:7.43	Increase (<i>Bacteroides</i> , <i>Coprococcus</i> , <i>Ruminococcus</i> , <i>Parabacteroides</i> , and <i>Lactobacillus</i>); Decrease (<i>Prevotella</i>)	Immunity	The results indicated that the improvement of intestinal barrier function was achieved by increasing the secretion of immunoglobulin A (sIgA) and beta blockers.	[89]
<i>Dendrobium officinale</i>	DOW-5B	39.4	GlcA:Glc=1.2:19.4	Increase (<i>Ruminococcus</i> , <i>Eubacterium</i> , <i>Clostridium</i> , <i>Bifidobacterium</i> , <i>Parabacteroides</i> , and <i>Akkermansia muciniphila</i>)	Immunity	Intestinal microbes derived butyrate was related to the immunomodulatory activities of DOW-5B.	[86]
<i>Lycium barbarum</i>	LBP	1207	Man, Rib, Rha, GlcA, GalA, Glc, Gal, Xyl, Ara	Increase (<i>Rickenellaceae</i> , <i>Prevotellaceae</i> , and <i>Bifidobacteriaceae</i>)	Immunity	LBP increased the diversity of gut microbiota and the relative abundance of bacteria, such as <i>Rickenellaceae</i> , <i>Prevotellaceae</i> , <i>Bifidobacteriaceae</i> , etc., which was positively correlated with immune traits.	[90]
<i>Astragalus polysaccharides</i>	APS-a1	2.62×10 ³	Glc, Gal, Ara	Increase (<i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>Roseburia</i> , and <i>Desulfovibrio</i>); Decrease (<i>Oscillibacter</i> , <i>Tyzzrella</i> , and <i>Lachnoclostridium</i>)	Immunity	APS significantly improved immune suppression in mice, indicating an increase in immune organ index, promotion of immune cell proliferation, and upregulation of intestinal inflammation.	[91]
	APS-b1	4.95×10 ³					
Turmeric	TPs-0	116.89	Glc, Gal, Ara	Increase (<i>Lactobacillus</i> and <i>Bacteroides</i>) Decrease (<i>Staphylococcus</i>)	Immunity	TPs-0 and TPs-3 improved intestinal pathological injury, promoted CD4 ⁺ T cell secretion, regulated related cytokine expression, and reduced key protein levels in the NF-κB/iNOS pathway.	[92]
	TPs-3	134.20	Glc, Gal, Xyl, GalA, GlcA				
<i>Cyclocarya paliurus</i>	S-CPP	52.625/12.230	Gal:Ara:Glc:Rha:Fru:Xyl:Man=0.336:0.311:0.275:0.011:0.007:0.036:0.024	Increase (<i>norank_f_Muribaculaceae</i> , <i>Lachnospiraceae</i> -Nk4A136-group, and <i>Alloprevotella</i>)	Immunity	S-CPP increased the levels of interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) in small intestine tissue and serum, upregulated IL-1β gene levels, Occludin and cludin-1 gene and protein levels, thereby enhancing intestinal mucosal immunity.	[93]
<i>Gastrodia elata</i>	GEPs	292.596	Glc:Gal:GalA=88.21:4.48:4.40	Increase (<i>Muribaculaceae</i> , <i>Prevotellaceae</i> , and <i>Bacteroidaceae</i>)	Immunity	GEPs could increase the level of butyric acid in the colon, suggesting that the enhancement of immunity by GEPs may be related to the increase in scfa content.	[85]

Note: *Atractylodes lancea* Rhizome polysaccharides, ALP; Alhagi honey, AH; *Dendrobium officinale* polysaccharides, DOW-5B; *Lycium barbarum* polysaccharides, LBPs; *Astragalus* polysaccharides, APS; *Turmeric* polysaccharides, TPs; *Cyclocarya paliurus* polysaccharides, S-CPP; *Gastrodia elata* polysaccharides, GEPs; Mannose, Man; Ribose, Rib; Rhamnose, Rha; Glucuronic acid, GlcA; Glucose, Glc; Galactose, Gal; Arabinose, Ara; Galacturonic acid, GalA; Xylose, Xyl; G protein coupled receptor 43, GPR43; Secretion of immunoglobulin A, sIgA; Interleukin-1β, IL-1β; Tumor necrosis factor-α, TNF-α.

A key immunomodulatory mechanism of polysaccharides involves their capacity to restore gut barrier integrity and enhance secretory immunity, particularly in compromised states. *Atractylodes lancea* Rhizome polysaccharides have been shown to effectively enhance immune organ indices and blood cell counts, stimulate cytokine secretion, and promote the expression of occludin and ZO-1. Additionally, ALP has the capacity to enhance T cell expression and increase sIgA secretion. Furthermore, ALP mitigated the disruption of gut microbiota in mice treated with cyclophosphamide (cy), increased the relative abundance of *Lactobacilli* and fecal bacteria, and reversed the decline in SCFAs levels [83]. This triad of barrier restoration, microbial normalization, and immune potentiation is a recurring theme. *Glycyrrhiza* polysaccharides reversed CTX-induced damage to intestinal structures and increased the number of cuprocytes, as well as the counts of CD4+ and CD8+ T lymphocytes, and mucin content. This effect was particularly notable in maintaining the balance of helper T lymphocyte 1 and helper T lymphocyte 2 (Th1/Th2) [84].

Beyond general immune enhancement, a consistent pattern across studies is the pivotal role of SCFA-producing bacteria as mediators of the immunomodulatory effects of polysaccharides. *Gastrodia elata* polysaccharides restored the composition and abundance of gut microbiota and increased the concentration of SCFAs in colon contents. The abundance of SCFA-producing bacteria, such as *Muribaculaceae*, *Prevotellaceae*, and *Bacteroidaceae*, was also enhanced [85]. Butyrate, a short-chain fatty acid, plays a crucial role in maintaining the homeostasis of the intestinal microenvironment. *Dendrobium officinale* polysaccharides promoted the production of butyrate by intestinal microorganisms, primarily by *Parabacteroides_sp_HGS0025*. Furthermore, *Parabacteroides_sp_HGS0025* was positively correlated with butyrate levels, as well as with the production of IgM, IL-10, and TNF- α in the gut and mouse blood, respectively. These findings suggest that *Dendrobium* polysaccharides may exert immune functions, potentially mediated by butyrate [86].

The immunomodulatory potential of polysaccharides extends to the management of specific autoimmune conditions, largely through microbiota-dependent gene regulation. Rheumatoid arthritis (RA) is a highly prevalent autoimmune disease. Research has identified key bacteria associated with the occurrence and development of RA, including *norank_f_norank_o_clostridia_ucg-014*, *Lactobacillus*, *norank_f_ocillospiraceae*, and *norank_f_desulfovibrioseae*. *Angelica sinensis* polysaccharides have been shown to regulate the expression of intestinal Cldn5, Slit3, and Rgs18 through gut microbiota, thereby improving rheumatoid arthritis symptoms [87]. Similarly, *Lycium barbarum* polysaccharides significantly altered the structure of the intestinal flora, which was accompanied by a remission of RA. Specifically, LBP intervention reduced the relative abundance of *Lachnospiraceae_NK4A136_group* and *uncultured_bacterium_f_ruminococcaceae* while significantly increasing the abundance of *Romboutsia*, *Lactobacillus*, *Dubosiella*, and *Faecalibaculum*. Mechanistically, LBP reshaped the composition of the gut microbiota, which may produce SAM, leading to DNA hypermethylation of RA-related genes in the host intestinal epithelium and subsequently reducing their expression, thereby alleviating RA [88].

In summary, the diverse array of polysaccharides discussed herein orchestrates a harmonized restoration of immune homeostasis through convergent microbial and host pathways. A central microbial target shared across different immune contexts is the enrichment of beneficial, SCFA-producing bacteria (*Lactobacillus*, *Muribaculaceae*, *Prevotellaceae*, and *Faecalibaculum*) which in turn suppress pro-inflammatory taxa. These microbial shifts are coupled with a consistent enhancement of intestinal barrier integrity, evidenced by the upregulation of tight junction proteins (e.g., ZO-1, occludin) and increased mucin production. At the immune level, polysaccharides commonly enhance sIgA secretion, promote balanced T-cell differentiation (e.g., Th1/Th2 equilibrium and increased CD4⁺/CD8⁺ counts), and modulate cytokine production (e.g., IL-10, TNF- α). Importantly, these effects are frequently mediated through microbial metabolites, particularly SCFAs like butyrate, which serve as critical immunomodulatory messengers. Thus, despite their varied sources, natural polysaccharides emerge as potent modulators that bridge the gut-immune axis by simultaneously targeting microbial ecology, barrier function, and systemic immunity, offering a multifaceted strategy for immune-related disorders.

2.6 Tumors

The gut microbiota, recognized as a functional organ, plays a crucial role in preventing colorectal cancer and fostering intestinal immunity. Recent studies suggest that dietary polysaccharides may modulate colon cancer-associated metabolism and alleviate metabolic disturbances in colon cancer by altering the structure and abundance of intestinal flora (**Table 6**). During the fermentation process of the gut microbiota, polysaccharides can enhance the production of various metabolites, such as SCFAs, which significantly influence the host's physiological functions, immune system, and metabolism. The anti-tumor effects of polysaccharides can be partially attributed to their regulation of gut microbiota^[94] and the increased levels of SCFAs in feces^[95]. There is growing evidence that polysaccharides serve as potential immunogens, enhancing the gut immune system's defense against intestinal pathogens and reducing the incidence of colitis and colon cancer. SCFAs are important microbial metabolites that play a crucial role in host physiology by providing nutrition for colon cells, maintaining epithelial health and homeostasis, inhibiting the growth of harmful bacteria, and preventing the onset of colorectal cancer.

A central anti-tumor mechanism of polysaccharides involves their capacity to restore a healthy gut microbial ecosystem, characterized by the enrichment of SCFA-producing bacteria and the suppression of pro-inflammatory pathobionts. Polysaccharides from *Rhizopus nigricans* may interact with intestinal bacteria, thereby promoting the activity of SCFA-producing bacteria, which could have multiple physiological effects on enhancing intestinal immunity^[96]. This microbial remodeling is a consistent precursor to the direct anti-cancer effects observed at the cellular level. Furthermore, the fermentation products of polysaccharide hydrolysates (PHPs) have been shown to effectively promote apoptosis in HT-29 cells by increasing the production of reactive oxygen species (ROS), enhancing the expression of the apoptotic proteins Bax and Bak, and inhibiting the expression of Bcl-2 and phosphorylated AKT^[97].

The therapeutic potential of polysaccharides is particularly evident in their ability to counteract the cancer-associated dysbiosis that often undermines conventional treatments. Most cancer patients exhibit disturbances in their intestinal flora, characterized by a reduction in bacteria from acetate- and butyrate-producing families, alongside an increase in LPS-producing genera such as *Klebsiella* and *Haemophilus*. A healthy gut microbiome is known to enhance the efficacy of anti-cancer drugs. Polysaccharides can effectively restore this microbial balance, thereby functioning as promising chemoadjuvants. Polysaccharides derived from *Tetrastigma hemsleyanum* have been shown to increase ileal secretory immunoglobulin A (SIgA) levels and cecal SCFAs content, while also improving the diversity of the intestinal microbial community. These polysaccharides regulate the relative abundance of dominant flora from the portal level down to the genus level and restore the tumor-induced disruptions in intestinal flora [98].

This chemosensitizing effect is a key translational benefit, as polysaccharides can ameliorate the adverse effects of chemotherapy while enhancing its anti-tumor activity. Furthermore, polysaccharides from *Albucca bracteata* have been found to enhance the efficacy of 5-FU in inhibiting colorectal cancer, potentially by down-regulating β -catenin, improving the overall composition of the gut microbiome, and increasing SCFA levels [99]. Similarly, oyster polysaccharides may alleviate 5-FU-induced intestinal mucosal inflammation and malnutrition by modulating gut microbiota, thereby enhancing the prognosis for chemotherapy patients. This protective effect is associated with the regulation of gut microbiota structure by CHP, which promotes the growth of propionate- and butyrate-producing microorganisms while decreasing the abundance of *Bacteroides*, *Prevotellaceae* UCG-001, and *Rikenellaceae* RC9_gut_group, subsequently influencing the TLR signaling pathway [100].

In summary, the collective evidence underscores that polysaccharides from various sources exert anti-colorectal cancer effects through highly convergent mechanisms targeting the gut microbiota and host pathways. A universal microbial target is the enrichment of beneficial, SCFA-producing bacteria (e.g., families like *Lachnospiraceae* and *Ruminococcaceae*), which leads to increased fecal SCFA levels, while simultaneously suppressing pathogenic, LPS-producing genera (e.g., *Klebsiella*, *Haemophilus*, *Bacteroides*). These microbial changes are consistently accompanied by enhanced intestinal immunity, evidenced by elevated SIgA levels. At the host level, polysaccharides commonly induce tumor cell apoptosis via the upregulation of pro-apoptotic proteins (Bax, Bak) and ROS generation, and inhibition of anti-apoptotic pathways (Bcl-2, p-AKT). Furthermore, they strengthen the intestinal barrier and mitigate inflammation, often through modulation of the Wnt/ β -catenin and TLR signaling pathways. By simultaneously remodeling the gut microbiota, boosting anti-tumor immunity, and directly promoting cancer cell death, dietary polysaccharides emerge as potent adjuvants that can improve conventional chemotherapy outcomes and restore gut homeostasis in colorectal cancer.

Table 6. Natural polysaccharides regulate colorectal cancer through probiotics.

Source	Compound name	Mw/ kDa	Monosaccharide composition (mol% or mole ratio)	Intestinal flora	Disease	Mechanisms	References
<i>N. commune</i>	NVPS	240	Glc:Ara:Xyl:Man:Gal=1:4.96:182.02:0.97:3.15	Increase (<i>Butyricoccus</i> , <i>Butyrivibrio</i> , and <i>Butyrimonas</i>)(<i>Lachnospiraceae</i> UCG 001, <i>Lachnospiraceae</i> UCG 006, and <i>Blautia</i>)	Colorectal cancer	SCFA was the main final product of carbohydrate metabolism, which can inhibit the proliferation of tumor cells and protect the intestine from invasion by colitis and colorectal cancer.	[101]
<i>Lachnum sp.</i>	LEP	1.31×10 ³	Gal,Man	Increase (<i>Alistipes</i> , <i>Alloprevotella</i> and <i>Ruminiclostridium</i>) Decrease (<i>Parabacteroides</i> , <i>Escherichia_Shigella</i> , <i>Desulfovibrio</i> , and <i>Helicobacter</i>)	Colorectal cancer	LEP reduced tumor incidence, restored intestinal barrier integrity, and alleviated excessive inflammation by regulating Bacteroidetes.	[102]
<i>Ziziphus jujuba</i> Mill.	JP	89.90	Ara:Gal:Glc:Rha:Man=49.67:29.01:11.43:5.38:4.51	Decrease (<i>Firmicutes/Bacteroidetes</i>)	Colorectal cancer	JP could prevent colon cancer through improving the intestinal ecological imbalance caused by colitis.	[103]

Note: *N. commune* polysaccharides, NVPS; *Lachnum sp.* polysaccharides, LEP; *Ziziphus jujuba* Mill. polysaccharides, JP; Glucose, Glc; Arabinose, Ara; Xylose, Xyl; Mannose, Man; Galactose, Gal; Rhamnose, Rha.

2.7 Cardiovascular diseases

High-fat diets (HFDs) can lead to various health issues, including dysbiosis of the gut microbiota and cardiac dysfunction. Gut bacteria play a direct or indirect role in the development and progression of myocardial injury through microbial metabolite-host interactions. In particular, metabolites derived from intestinal microbes, such as trimethylamine n-oxide (TMAO)^[104] and phenylacetylglutamine^[105], are thought to elevate the risk of atherosclerosis and thrombosis. Consequently, enhancing dietary quality and incorporating nutrient-rich sources to regulate gut microbiota presents a potential strategy for mitigating cardiovascular disease^[106].

A shared therapeutic strategy among polysaccharides involves the amelioration of high-fat diet-induced cardiovascular injury by targeting gut microbiota dysbiosis and its downstream consequences. *Lycium barbarum* polysaccharides alleviated myocardial injury in mice on a high-fat diet by modulating the gut microbiome and fecal metabolome. Specifically, LBP reduced intestinal permeability and levels of inflammatory cytokines, thereby maintaining a healthy intestinal microenvironment and mitigating myocardial injury^[107].

While the specific microbial shifts may vary, a common outcome is the restoration of a more favorable gut ecosystem, often marked by a reduction in the F/B ratio. *Hordeum vulgare* L. polysaccharides did not significantly affect the diversity of gut microbiota in high-fat diet-treated mice; however, *Hordeum vulgare* L. polysaccharides actively reshaped the gut microbiota structure by increasing the relative abundance of *Bacteroides*, *Muribaculaceae*, and *Lachnospiraceae*, while decreasing the *Firmicutes/Bacteroides* ratio and the relative abundance of *Desulfovibrio*^[108]. This recalibration of the *Firmicutes/Bacteroides* ratio emerges as a key microbial signature associated with cardioprotection. Similarly, *Dendrobium officinale* polysaccharides reconstructed the composition of intestinal flora by lowering the *Firmicutes/Bacteroides* ratio, effectively inhibiting the histopathological progression of atherosclerosis in mice, and significantly reducing blood lipid levels, inflammatory factors, and the production of malondialdehyde^[109].

In summary, despite their diverse botanical origins, the polysaccharides discussed share convergent mechanisms in alleviating cardiovascular dysfunction induced by a high-fat diet through targeted modulation of the gut microbiota and associated host pathways. A common microbial target is the restoration of a healthier gut microbial structure, characterized by a reduced *Firmicutes/Bacteroidetes* ratio and an increased abundance of beneficial families such as *Bacteroides*, *Muribaculaceae*, and *Lachnospiraceae*, while suppressing pro-inflammatory and harmful genera like *Desulfovibrio*. These microbial changes contribute to a reduction in detrimental gut-derived metabolites (e.g., TMAO) and lower systemic inflammation. At the host level, these polysaccharides consistently improve lipid profiles, decrease oxidative stress (e.g., malondialdehyde), reduce pro-inflammatory cytokines, and enhance intestinal barrier integrity to diminish endotoxemia. Collectively, by simultaneously remodeling the gut microbiota composition and mitigating key cardiovascular risk factors (dyslipidemia, inflammation, and oxidative stress) dietary polysaccharides emerge as potent prebiotic agents

that protect against myocardial injury and atherosclerosis, highlighting their potential as integrative interventions for cardiovascular diseases.

3. Gut microbiota fermentation and digestion of polysaccharides

Humans consume a wide variety of plants daily, many of which cannot be degraded by the enzymes encoded in the human genome. In contrast, complex polysaccharides can be metabolized by a diverse array of microorganisms present in the gut ^[82] (**Fig. 7**). Generally, the complexity of a polysaccharide correlates with the number of enzymes required for its breakdown. However, humans possess only 17 enzymes specifically encoded for the digestion of food polysaccharides, particularly for certain types of these polysaccharides ^[110]. The gut microbiota, on the other hand, can produce hundreds of enzymes with distinct catalytic specificities, far surpassing the range of enzymes available in the human genome ^[111, 112]. Carbohydrate-active enzymes (CAZymes) produced by the gut microbiota are essential for breaking down glycoconjugates and polysaccharides, thereby releasing fermentable monosaccharides that serve as energy sources for intestinal cells and/or bacteria. Among the gut microbiota, *Bacteroides* thetaiotaomicron is a notable representative species of *Bacteroides*, encoding more enzymes than any other phylum and is recognized as the most effective bacterium for polysaccharide degradation. Additionally, Anabaena is one of the major bacterial phyla found in the human gut microbiota ^[113]. Bacteriophages can derive energy from indigestible polysaccharides through the expression of polysaccharide utilization sites ^[114], which include the genera *Bacteroidetes* and *Prevotella*. Researchers used *Bacteroidetes* as a model and proposed that three polysaccharide utilization loci (PULs) may be involved in the degradation of *Achyranthes bidentata* polysaccharide (A23-1). A23-1 was found to be degraded into monosaccharides and fragments. Acetate and propionate are the primary final products produced by the genus *Bacteroidetes* ^[115]. Previously, researchers isolated several gut bacteria from human fecal samples that can utilize pectin for cell growth, most of which belong to the *Bacteroides* genus. These bacteria secrete glucanase to hydrolyze pectin into oligosaccharides of isomaltose (IMOs), which are considered beneficial prebiotics for gut bacteria such as *Bifidobacterium* and *Lactobacilli*, either through direct absorption or further degradation. Kim et al. found that LM742 glucan was resistant to digestive enzymes under human gastrointestinal conditions. Individual cultures of 30 intestinal bacteria with LM742 glucan demonstrated growth of *Bacteroidetes* spp., and in vitro human fecal fermentation with LM742 resulted in the symbiotic growth of *Bacteroidetes* spp. In fecal fermentation, LM742 glucan led to increased concentrations of SCFAs, valeric acid, and pantothenic acid ^[116]. *Bacteroides* thetaiotaomicron (BT) and *Bacteroides ovatus* (BO) are capable of utilizing a wide range of polysaccharides. Shi et al. isolated four types of biodegradable polysaccharides from *Fusarium oxysporum* (FBTPS-3) found in human feces, identifying them as ovate pseudomonas, uniform pseudomonas, fragile pseudomonas, and polymorphic pseudomonas. Among the four genera of *Bacteroidetes* that can grow on FBTPS-3 as a carbon source, the oval *Bacteroidetes* exhibited the highest capacity for utilizing FBTPS-3 during a 24-hour fermentation period. These four genera of *Bacteroidetes* metabolize FBTPS-3, leading to the production of acetic acid, propionic acid, and isovaleric acid. Furthermore, transcriptome analysis of *Pseudomonas aeruginosa* indicated that FBTPS-3 upregulated

602 genes, which included two clusters of carbohydrate-active enzymes and four polysaccharide utilization loci (PUL). Notably, PUL 1 encompasses the GH28 family, which is capable of hydrolyzing rhamnogalacturonic acid and other pectin substrates ^[117]. Although the pectin-activated polysaccharide utilization site (PUL) has been identified, the degradation mechanism remains unclear due to the complex structure of the side chains. Researchers characterized the gene loci encoding proteins expressed by *Bacteroidetes polymorpha* (BT) that are involved in pectin capture, input, debranching, and degradation into monosaccharides ^[118]. Hyaluronic acid (HA) is widely used as a dietary supplement and can be degraded by intestinal flora. The fermentation of HA promotes the production of significant amounts of acetate, propionate, and butyrate by the genera *Bacteroides*, *Bifidobacterium*, *Dialister*, and *Fecal*. Polysaccharide lyases (PLs) and glycoside hydrolases (GHs) were identified from *Bacillus subtilis* E3, including GH88, PL8, PL29, PL35, and PL33, which elucidate the structure of fermentation products ^[119].

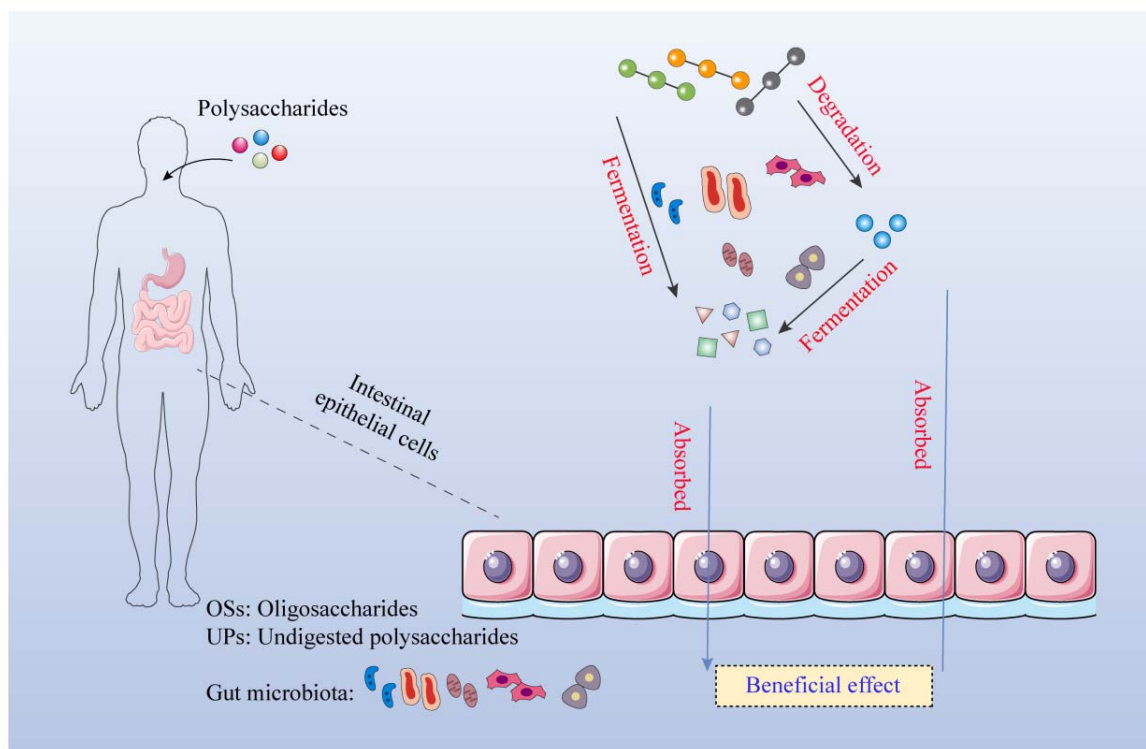


Fig. 7. The diagram demonstrates how dietary polysaccharides undergo partial digestion and absorption by host enzymes, while the remaining undigested components (UPs and OSs) serve as substrates for gut microbial fermentation. This process generates various beneficial metabolites that contribute to host health, including energy sources, immune modulation, and maintenance of gut barrier function.

The intricate metabolic capacity of the gut microbiota, as described above, provides a fundamental blueprint for the utilization of polysaccharides. This natural process of microbial degradation and fermentation is not only crucial for host health but also inspires targeted biotechnological applications. By harnessing and specializing these inherent microbial capabilities, scientists have developed controlled fermentation strategies using specific probiotic strains. This approach intentionally modifies the structure of polysaccharides to enhance their beneficial properties, thereby bridging the gap between natural gut fermentation and directed functional enhancement.

4. Probiotic fermentation modified polysaccharides

The study on the structure-activity relationship of natural polysaccharides indicates that their original structure may not yield the optimal state for activity. Furthermore, their bioavailability and activity are influenced by structural characteristics such as molecular weight, monosaccharide composition, type of glycosidic bonding, and microscopic morphology ^[120-122]. It has been reported that the structural features of polysaccharides significantly determine their biological activities ^[120]. Consequently, various physical, chemical, and biological methods have been employed to modify the structure of natural polysaccharides to enhance their biological activities. However, chemical modification presents drawbacks, including toxicity and a lack of selectivity associated with the use of organic solvents, which limits its application in the functional food industry for public health reasons ^[123]. Enzymatic methods can specifically modify distinct regions of macromolecular chains without compromising their biological functions. Enzymology fundamentally represents a biotransformation process in which a diverse array of enzymes produced by microorganisms, such as glycosidases, cellulases, lipases, proteases, and invertases, catalyze multiple reactions, including hydrolysis, oxidation, reduction, esterification, and isomerization. These reactions facilitate the structural modification of the target substrate. Compared to conventional chemical modification methods, enzymatic approaches offer several advantages, including mild reaction conditions, high specificity, and environmental friendliness ^[123, 124]. Related studies indicate that probiotic fermentation can influence the molecular weight, monosaccharide composition, glycosidic bonds, and apparent morphology of natural polysaccharides, thereby impacting their biological activity (**Table 7**). Furthermore, it is noteworthy that critical fermentation parameters, including the type of fermentation, media composition, and duration, can significantly influence the extent and nature of these structural modifications.

Table 7. The application of probiotic fermentation in the biological modification of natural polysaccharides.

Probiotics	Polysaccharide	Structure characteristics				Physicochemical properties				Bioactivities/ Disease	References	
		Molecular weight	Monosaccharide composition	Main chain	Apparent appearance	Solubility	Viscosity	Particle size	Thermal stability			
<i>Grifola frondosa</i>	Rice bran	↓	Glc:Ara:Gal:Man:Xyl=32:4:6:2:5→9:5:8:2:5	α -neutral pyranose without uronic acid						Antioxidant	[125]	
GCMCC5.39	<i>Tremella</i>										Moisturizing	[126]
<i>Lactobacillus fermentum</i>	<i>Litchi chinensis</i> Sonn.		Glc↓, Ara↑, GalA↑								Probiotic	[127]
<i>Lactobacillus plantarum</i> NCU116	<i>Momordica charantia</i> L.		Gal↑, Glc↓, Man↓					↓			Type 2 diabetes	[128]
<i>Lactobacillus paracasei</i>	<i>Polygonatum kingianum</i>	↓			Rough and porous→Smooth	↑		↓			Anti-aging	[129]
<i>Tetrastigma hemsleyanum</i> Diels et Gilg	<i>Sanghuangporus sanghuang</i> fungi	↓	Glc↓, Gal↑	1,4 -linked α-D-Glcp, 1,4 -linked β-D-Galp→1,2 -linked α-D-Galp, 1,2 -linked α-D-Manp								[130]
<i>Lactobacillus acidophilus</i>	<i>Gracilaria lemaneiformis</i>							↓			Food allergy	[131]
<i>Lactobacillus fermentum</i>	<i>Dimocarpus longan</i> Lour.	↓	Glc↓, Ara, Gal, Rha, Man↑		↑		↓	↓		Immunomodulatory	[132]	
<i>Lactic acid bacteria</i> and <i>Neurospora crassa</i>	Soybean				→Disperse and rough				↑			[133]
<i>Bacillus subtilis</i> Natto	Sea cucumber		Glc↓		→Smooth						Probiotic	[134]
<i>Lactobacillus rhamnosus</i> 6224, <i>Saccharomyces cerevisiae</i> W5	Blue honeysuckle	↓	GalA↑								Probiotic	[135]

<i>Lactiplantibacillus plantarum</i> ATCC14917	<i>Ganoderma lucidum</i>	↓	Man, Gal, GlcA↑, Xyl, Glc↓	Smooth and hard→Porous and loose				Antioxidant	[136]
<i>Lactobacillus</i>	<i>Eucheuma spinosum</i>	↓	GlcA↑		↑	↓		Mast cell membrane stabilizing	[137]
<i>Lactobacillus plantarum</i> NCU116	<i>Asparagus officinalis</i>	↓	Rha, GalA, GlcA↑				↓	Antioxidative, and immunoregulatory	[138]
<i>Lactiplantibacillus plantarum</i>	Lyjian okra	↓	Man, Glc, GlcA, Ara ↓, Rha, GalA, Gal↑		↑	↓		Antioxidative↓, and immunoregulatory↑	[139]
<i>Lactobacillus plantarum</i> CICC 23121	<i>Schisandra sphenanthera</i> fruit	↑		→loose	↑		↑	Probiotic	[140]
<i>Lactobacillus delbrueckii bulgaricus</i>	<i>Dendrobium officinale</i>	↓		→Porous, irregular	↑			Anti-photoaging	[141]
<i>Lactobacillus plantarum</i>	Bulbs of Lanzhou Lily	↓	Man, GlcA↓		↑		↓	Antioxidant	[142]
	Liupao tea	↓	Rha, Gal, GalA↑				↑	Anticoagulant	[143]
<i>Lactobacillus-fermented Nostoc commune</i> Vauch.	NCVP-F	↓	Man, GlcUA↑					Kidney injury	[144]
<i>Lactobacillus</i>	<i>Dimocarpus longan</i> Lour.		Glc↓, Rha, Gal ↑					Probiotic	[145]
<i>Bacillus subtilis</i> , <i>Lactobacillus plantarum</i> , and <i>Saccharomyces cerevisiae</i>	<i>Chenopodium album</i> L.							Antioxidant, Development-promoting activity	[146]
<i>Bifidobacterium</i>	<i>Cordyceps sinensis</i>	↓						Anti-inflammatory	[147]

4.1 Molecular weight

Due to their superior solubility and smaller molecular size, low molecular weight polysaccharides are more readily utilized by gut microbiota, leading to a faster and more efficient production of SCFAs compared to high molecular weight polysaccharides, thereby enhancing the regulation of gut microbiota [148, 149]. However, from the perspective of intestinal mucosal protection, polysaccharides with higher molecular weight exhibit more favorable effects. Molecular weight not only influences the solubility and viscosity of natural polysaccharides but also their biological activity and efficiency in cellular uptake.

During fermentation, probiotics such as lactic acid bacteria secrete specific carbohydrate-active enzymes (CAZys), including glycoside hydrolases, polysaccharide lyases, and carbohydrate esterases, which selectively cleave glycosidic bonds and modify the structural properties of polysaccharides. This enzymatic modification represents a key mechanism through which fermentation alters polysaccharide functionality. Hydrolytic enzymes secreted by probiotics can degrade polysaccharides into oligosaccharides or monosaccharides for utilization, consequently reducing their molecular weight [150]. For instance, *Lactobacilli* utilize CAZys to cleave specific glycosidic linkages in polysaccharides, leading to targeted reduction in molecular weight and exposure of functional groups. The molecular weight of unfermented rice bran polysaccharides primarily ranges from 10^3 to 10^4 Da, while after fermentation, this range shifts to 10^2 - 10^3 Da. This reduction in molecular weight, accompanied by an increase in uronic acid content, was correlated with enhanced antioxidant activity and improved regulatory effects on nitric oxide (NO) production [125].

A general pattern observed across multiple studies indicates that lactic acid bacteria fermentation typically reduces polysaccharide molecular weight while increasing the proportion of uronic acids, which correlates strongly with enhanced bioactivities such as antioxidant capacity. Following fermentation by *Lactobacillus paracasei*, the molecular weight distribution of *Polygonatum kingianum* polysaccharides altered from 50-650 kDa to 2-100 kDa. Notably, low molecular weight polysaccharides (PS2-4) isolated from the fermented product, ranging from 10-50 kDa, were associated with significant anti-aging activity in experimental animals [132]. Blue honeysuckle polysaccharides fermented by *Lactobacillus rhamnosus* 6224 and *Saccharomyces cerevisiae* W5 showed molecular weight reductions of 23.30% and 22.25% respectively, indicating that microbial fermentation consistently reduces polysaccharide molecular weight through enzymatic degradation [135].

Strategic selection of probiotic strains based on their enzymatic profiles enables targeted modification of polysaccharide structures. For example, strains rich in specific glycoside hydrolases can be employed to achieve controlled depolymerization, while those expressing esterases may enhance uronic acid content. The fermentation of *Lactobacillus* significantly reduced the molecular weight of polysaccharides derived from *Eucheuma spinosum*. This process not only decreases molecular weight but also modifies structural features such as glycosidic linkage patterns and degree of branching, ultimately improving bioavailability and bioactivity. Furthermore, Li et al. reported that fermentation of *Nostoc commune* Vauch. polysaccharide by lactic acid bacteria decreased its molecular weight from 501.267 kDa to 365.369 kDa [144]. It has been

established that lactobacilli employ specific CAZys to cleave glycosidic bonds in polysaccharide chains, systematically reducing molecular weight during fermentation ^[58].

Interestingly, some fermentation processes may increase molecular weight through enzymatic reassembly or selective degradation of low-molecular-weight fractions. The fermentation of *Bacillus sp. DU-106* resulted in an increase in the molecular weight of *Dendrobium officinale* polysaccharide from 4.92×10^5 Da (UDP-1) to 5.21×10^5 Da, which was concomitant with enhanced immunostimulatory activity of FDP-1 ^[151]. This demonstrates a clear association between structural change and functional outcome, though definitive proof of causality in such complex systems often requires further reductionist experimentation. This example nonetheless demonstrates that through careful selection of microbial strains and fermentation conditions, it is possible to strategically direct structural modifications toward specific functional outcomes.

Fermentation conditions, including strain selection, growth phase, and nutrient availability, significantly influence the molecular weight variation of natural polysaccharides. The accumulation of specific enzymes during the lag and log phases of microbial growth, combined with preferential utilization of certain polysaccharide fractions, determines the final structural properties and bioactivity of fermented polysaccharides. However, it is important to note that while the observed structural modifications (e.g., molecular weight reduction) are strongly correlated with enhanced bioactivity across numerous studies, establishing a direct causal link in fermented products can be complex. The concurrent changes in multiple structural parameters (e.g., molecular weight, monosaccharide composition, and glycosidic bonds) during fermentation make it challenging to attribute the improved bioactivity solely to one specific factor without further controlled experiments.

4.2 Monosaccharide Composition

The composition and proportion of monosaccharides not only influence the solubility and viscosity of natural polysaccharides but also their functions, biological activities, and applications. Probiotic fermentation, particularly by lactic acid bacteria, systematically modifies monosaccharide composition through the action of specific microbial enzymes such as glycosidases, polysaccharide lyases, and esterases. These enzymatic activities selectively cleave certain glycosidic bonds, leading to the degradation of specific monosaccharides (often Glc) and the relative accumulation of others (such as Gal, Ara, and UAs).

Probiotic fermentation typically alters the monosaccharide ratios of natural polysaccharides without changing their monosaccharide types. Gas chromatography (GC) analysis revealed that fermented rice bran polysaccharides consisted of Glc, Ara, Gal, Man, and Xyl, with a molar ratio of 9:5:8:2:5, compared to 32:4:6:2:5 before fermentation. This shift, characterized by a substantial decrease in Glc and increase in Ara and Gal, is consistent with the preferential utilization of Glc by probiotics and the selective degradation of certain glycosidic linkages, which was associated with enhanced antioxidant activity ^[125].

A general pattern observed across multiple studies indicates that lactic acid bacteria fermentation tends to reduce Glc content while increasing the proportion of Gal, Ara, and UAs. This modification is mechanistically linked to the enzymatic repertoire of *lactobacilli*, which often exhibit high activity of glycoside hydrolases targeting Glc-rich regions, while leaving other monosaccharide units relatively intact or

exposed. *Litchi pulp* polysaccharides underwent fermentation by *lactobacilli*, and monosaccharide composition analysis indicated that, relative to unfermented LP-0, the proportion of Glc decreased, while the proportions of Ara and GalA increased ^[127]. The polysaccharides from *Momordica charantia* L. were primarily composed of Glc, Gal, and GalA, with GalpA constituting approximately 54% (w/w) in this study. The percentage of Gal in MCP increased from 29.71% to 34.99% following fermentation, whereas Glc and Man decreased from 14.24% and 1.85% to 10.48% and trace amounts, respectively. These systematic changes suggest that fermentation can be strategically directed to enrich specific monosaccharide types through the selection of appropriate microbial strains with known enzymatic activities ^[128].

The monosaccharide types of *longan pulp* polysaccharide (LP) and its fermented counterpart (LP-F) are identical; however, there are significant differences in their monosaccharide compositions. Ara, Glc, and Gal serve as the primary monosaccharide components of both LP and LP-F. Notably, the molar ratio of Glc in LP-F decreased by 38.71% compared to LP, while the molar ratios of Gal and Ara increased by 11.28% and 11.80%, respectively. This consistent pattern of Glc depletion and Gal/Ara enrichment across studies suggests a general mechanism whereby probiotics metabolize readily available Glc while exposing structurally important Ara and Gal residues, thereby enhancing immune regulation and prebiotic activity ^[132].

Strategic fermentation using carefully selected probiotic strains enables targeted modification of polysaccharide composition. For instance, strains with high galactosidase activity can be employed to enhance Gal content, while those expressing uronic acid-metabolizing enzymes may increase the relative abundance of GalA. In the case of blue honeysuckle polysaccharide (BHP-U), the composition is predominantly made up of Gal, Xyl, and GalA, with respective ratios of 49.96:26.79:12.00. Gal is the dominant monosaccharide in unfermented blue honeysuckle; however, in fermented blue honeysuckle polysaccharides (BHP-L and BHP-S), GalA becomes the predominant monosaccharide, while both variants maintain nearly identical neutral polysaccharide compositions ^[135]. This shift toward uronic acid dominance is particularly significant as it is frequently correlated with enhanced antioxidant and immunomodulatory properties.

Additionally, probiotic fermentation can enhance the diversity of natural polysaccharides. The ratio of Glc, Gal, and Man in *Tetragium hemsleyanum* Diels et Gilg polysaccharide (THDP2) was found to be 9.5:4.1:1.1, indicating that Glc was the predominant monosaccharide, constituting 64.63% of the total components. The fermented polysaccharide, F-THDP2, was identified as a neutral heteropolysaccharide composed of Gal, Man, and caramel, with a molar ratio of 12.6:2.3:1.0. Notably, F-THDP2 was devoid of Glc, while the Gal content increased significantly, accounting for 79.25% of the total components. Researchers established that Glc in THDP2 was metabolized during fermentation through the action of glucosidases and subsequently converted into galactose via microbial metabolic pathways, demonstrating how fermentation can fundamentally alter monosaccharide profiles ^[130].

Furthermore, *Ganoderma lucidum* polysaccharide (GLP) was fermented using *Lactiplantibacillus plantarum* ATCC14917 to produce FGLP. In comparison to GLP, FGLP exhibited an increase in the content of Man, Gal, and GlcpA, a decrease in the levels of Glc and Xyl, and the emergence of a new monosaccharide, Ara. This transformation highlights the capacity of specific probiotic strains not only to modify existing

monosaccharide ratios but also to unveil previously masked monosaccharides through the degradation of surrounding structural elements, resulting in enhanced antioxidant activity ^[136].

In summary, the critical analysis of these studies reveals a consistent pattern: probiotic fermentation, particularly by lactic acid bacteria, systematically reduces Glc content while increasing the relative abundance of Gal, Ara, and UAs. These modifications are mediated by specific bacterial enzymes and can be strategically optimized through careful selection of microbial strains and fermentation conditions to achieve targeted structural and functional outcomes. It is important to note that while these structural changes are strongly associated with improved bioactivity, the evidence is largely correlative. Establishing definitive causality, the concept that a specific monosaccharide change directly causes a particular biological effect, often requires further reductionist approaches, such as testing isolated fractions with defined compositions in controlled systems.

4.3 Glycoside Bonds

The fermentation of probiotics significantly altered the structure and conformation of polysaccharides through the action of specific microbial enzymes that selectively target glycosidic bonds. Notably, lactic acid bacteria and *Bacillus* species produce a diverse array of carbohydrate-active enzymes (CAZys), including glycoside hydrolases, polysaccharide lyases, and glycosyltransferases, which systematically modify polysaccharide backbone structures and branching patterns.

A key general principle emerging from these studies is that probiotic fermentation often leads to the cleavage of specific glycosidic linkages, particularly 1,4- α/β and 1,3- β bonds, resulting in structural reorganization and the exposure of previously internal monosaccharide units. Notably, the chemical structure of the fermented polysaccharide (F-THDP2) exhibited substantial changes compared to the unfermented *Tetragastrum hemsleyanum* Diels et Gilg polysaccharide (THDP2). Significant differences in the glycosidic bonding of F-THDP2 were observed, particularly the establishment of a 1,2-linked α -D-Galp and a 1,2-linked α -D-Manp backbone, in contrast to the 1,4-linked α -D-Glcp and 1,4-linked β -D-Galp backbone present in THDP2. This transformation from 1,4-linkages to 1,2-linkages demonstrates how microbial enzymes can fundamentally reorganize polysaccharide architecture, potentially enhancing bioaccessibility and biological activity ^[130].

Strategic selection of probiotic strains based on their enzymatic profiles enables targeted modification of specific glycosidic bonds. For instance, strains rich in β -glucanases can be employed to specifically cleave 1,3- and 1,4- β linkages, while those expressing specific α -galactosidases may promote the formation of 1,2- α linkages. During the fermentation process, the polysaccharide backbone transitioned from a $\rightarrow 4$)- α -D-Glcp-(1 $\rightarrow$ and $\rightarrow 4$)- β -D-Galp-(1 $\rightarrow$ backbone to a $\rightarrow 2$)- α -D-Galp-(1 $\rightarrow$ and $\rightarrow 2$)- α -D-Manp-(1 $\rightarrow$ backbone ^[133]. Additionally, *Bacillus subtilis* typically produces β -glucanase, which specifically targets the 1,3 and 1,4 glycosidic bonds of β -glucan, resulting in the formation of oligosaccharides comprising 3 to 5 glucose units, along with free glucose ^[152].

The enzymatic mechanisms underlying these structural changes involve the specific recognition and cleavage of glycosidic bonds by microbial enzymes. β -glucanases from *Bacillus* species preferentially

hydrolyze 1,3- and 1,4- β linkages, while lactobacilli-derived enzymes often target 1,4- α linkages, leading to distinct structural outcomes. The significant reduction in glucose and glucosamine content within the monosaccharide composition of fermented sea cucumber polysaccharide (FSP) can be attributed to the partial degradation of polysaccharide (SP) by β -glucanase, which generates glucose that is subsequently utilized by *Bacillus subtilis* natto [134].

However, not all polysaccharide structures are equally susceptible to microbial degradation. The stability of certain glycosidic linkages during fermentation depends on both the specific enzyme repertoire of the probiotic strain and the inherent structural features of the polysaccharide substrate. In contrast, during the fermentation of tamarind seed polysaccharide (TSP), the molecular structure of TSP remained stable, with only a minor breakdown of glycosidic bonds occurring during gastrointestinal digestion [153].

Fermentation-induced structural modifications often follow predictable patterns: lactic acid bacteria commonly reduce molecular weight while altering linkage patterns, particularly enhancing the relative abundance of 1,2- and 1,6-linkages that are more accessible to microbial enzymes and potentially more bioactive. Both raw barley β -glucan (RBG) and fermented barley β -glucan (FBG) are polysaccharides characterized by β -(1 $\rightarrow$ 3) and β -(1 $\rightarrow$ 4)-linked glucans. Observations indicated a range of different molecular weights (from 1.13×10^5 Da to 6.35×10^4 Da) and varying ratios of β -(1 $\rightarrow$ 3) residues to β -(1 $\rightarrow$ 4) residues (from 1:1.98 to 1:2.50, and from 1:1.18 to 1:2.24). The fermentation of barley by *Lactobacillus plantarum* led to significant alterations in the primary structure of β -glucan, including changes in linkage ratios and molecular weight. These structural changes were correlated with enhanced in vitro physiological activities, including α -amylase inhibitory activity and cholesterol adsorption capacity, among other physiological effects [154].

In summary, the critical analysis of these structural modifications reveals that probiotic fermentation follows generalizable patterns of glycosidic bond cleavage and reorganization, primarily mediated through strain-specific enzymatic activities. These modifications can be strategically directed through careful selection of microbial strains with known enzymatic capabilities to achieve targeted structural outcomes with enhanced biofunctional properties.

4.4 Apparent morphology

The apparent morphology not only influences the dissolution rate and solubility of polysaccharides but also impacts their structural characteristics in solution, thereby affecting their biological activities and applications. Probiotic fermentation modifies polysaccharide morphology through enzymatic degradation and microbial metabolic activities that alter intermolecular interactions and structural organization. Specifically, lactic acid bacteria and *Bacillus* species produce extracellular enzymes and metabolites that disrupt hydrogen bonding networks and cleave specific glycosidic linkages, leading to reorganization of polysaccharide aggregates and surface features.

A general principle observed across studies is that probiotic fermentation typically transforms polysaccharide morphology from compact, smooth structures to more porous, irregular, or loose architectures. This structural loosening is frequently mediated by microbial enzymes that reduce hydrogen bonding density

and disrupt crystalline regions, thereby enhancing solubility and bioaccessibility. *Polygonatum kingianum* polysaccharide (PS) was fermented by *Lactobacillus paracasei* to yield PKPS. Following fermentation, PKPS transitioned from an initial rough and porous microtopography to a smoother state. Specifically, fermentation altered the original interconnections and aggregations of PKPS. This smoothing effect may result from the selective degradation of surface projections by microbial glycosidases, leading to a more homogeneous surface structure ^[129]. It has been reported that the porous surface morphology enhances the exposure of the active structural domains of polysaccharides, which can influence their biological activity ^[155].

The strategic selection of probiotic strains based on their enzymatic capabilities allows for targeted morphological modifications. Strains producing specific polysaccharidases can be employed to create controlled porosity, while those generating organic acids may promote structural loosening through pH-mediated disruption of hydrogen bonds. Following fermentation treatment, the surface microstructure of soybean soluble polysaccharides (SSPS) became more dispersed and rougher, thereby increasing the surface area of SSPS and significantly correlating with changes in their functional properties. This increased roughness and dispersion typically results from the partial enzymatic degradation of polysaccharide chains and the disruption of aggregate structures by microbial metabolites. Additionally, thermal stability assessments indicated that all SSPS exhibited improved thermal stability ^[133].

The enzymatic mechanisms underlying these morphological changes involve the synergistic action of multiple enzyme systems. Glycoside hydrolases from *Bacillus* and *Lactobacillus* species preferentially target amorphous regions of polysaccharides, creating micropores and increasing surface area, while leaving crystalline regions relatively intact. Sea cucumber polysaccharide (SP) possesses a smooth, irregular, and angular fragmented structure. After fermentation with *Bacillus subtilis* Natto, the shape and surface characteristics of FSP changed markedly. Since the relative molecular weight of FSP remained unchanged, this alteration was not attributed to the breakdown of glycosidic bonds. The transformation to a loose reticular structure demonstrates how microbial fermentation can modify supramolecular organization without significant depolymerization, likely through the action of enzymes that disrupt non-covalent interactions between polysaccharide chains ^[134].

The increase in surface roughness of natural polymers may be attributed to the general hydrogen bonding among sugar chains. When the glycosidic bond is broken, the hydrogen bond cross-linking density between the sugar chains decreases, resulting in larger structural domains ^[156]. This mechanism is particularly relevant for fermentation processes involving lactic acid bacteria, which produce organic acids that protonate carbohydrate hydroxyl groups, thereby reducing hydrogen bonding capacity and promoting structural expansion.

Following fermentation by *Lactobacillus plantarum* CICC 23121, the surface of *Schisandra sphenanthera* fruit polysaccharide NF-SSP appeared smooth with some cracks, whereas the fermented polysaccharide F-SSP exhibited a loose structure characterized by numerous irregular pores due to lactic acid production during fermentation ^[140]. The creation of irregular pores represents a common outcome of lactic acid bacteria fermentation, resulting from the combined action of acidic metabolites and extracellular enzymes

that preferentially degrade specific structural domains. In comparison to NF-SSP, F-SSP presents a looser surface and an increased pore count. The microstructure of F-SSP is associated with enhanced solubility of polysaccharides in aqueous solutions, which may facilitate their rapid utilization by probiotics ^[145].

These morphological modifications follow predictable patterns: lactic acid bacteria fermentation typically increases porosity and surface roughness through enzymatic degradation and acid-mediated structural reorganization, while *Bacillus* fermentation often creates more dramatic structural transformations through the action of potent hydrolytic enzymes. The surface ultramorphological structure of fermented dendrobium polysaccharide (FDOP) resembles a porous irregular foam block, indicating that FDOP possesses a softer and finer texture, as well as greater water solubility compared to DOP ^[141]. This foam-like structure is characteristic of extensively fermented polysaccharides and reflects significant reorganization of molecular architecture through both enzymatic degradation and microbial metabolite-induced structural changes.

In summary, probiotic fermentation systematically modifies polysaccharide morphology through enzyme-mediated degradation and metabolite-induced structural reorganization. These changes typically enhance solubility, increase surface area, and improve bioaccessibility, with the specific morphological outcomes depending on the enzymatic repertoire of the fermenting microorganisms and the structural characteristics of the substrate polysaccharide. While these morphological changes are consistently associated with improved functional properties across multiple studies, it is important to acknowledge that these relationships are primarily correlative. Establishing definitive causal links between specific morphological features and particular bioactivities would require more reductionist approaches using carefully controlled model systems.

5. Polysaccharide-based biomaterials to deliver probiotics

Probiotics are active microorganisms that confer health benefits to the host, yet their efficacy is often limited by high sensitivity to environmental stressors during production, storage, and gastrointestinal transit. To address these challenges, polysaccharide-based biomaterials have emerged as a highly promising solution owing to their non-toxicity, biocompatibility, biodegradability, and unique physicochemical properties. These materials can form protective barriers around probiotics, significantly enhancing their survival and functionality. This section critically examines recent advances in polysaccharide-mediated probiotic delivery, focusing on three key aspects: the use of polysaccharide nanomaterials for improving gastric acid resistance; the application of polysaccharide-based systems for stability maintenance and controlled transport of probiotics; and the design of polysaccharide matrices for reducing oxygen-induced damage and preserving probiotic activity. By exploring these strategies, we aim to highlight the potential of polysaccharide biomaterials to overcome major delivery challenges and facilitate the effective use of probiotics in food and pharmaceutical applications (**Table 8**).

Table 8. Polysaccharide-based probiotic delivery systems: delivery approaches, probiotic characteristics, and applications.

Polysaccharides	Probiotic delivery method	Probiotics	Probiotic characteristics	Applications	References
Hyaluronic acid	Hydrogel	<i>Lactobacillus rhamnosus</i>	Polysaccharide encapsulation enhanced the activity of <i>Lactobacillus rhamnosus</i> in resisting acid and bile salt damage during gastrointestinal transport, and could also prolong the storage time of <i>Lactobacillus rhamnosus</i> under refrigeration and room temperature conditions.	Bacterial enteritis	[157]
Sodium alginate	Hydrogel	<i>Lactobacillus rhamnosus</i>	pH/reactive oxygen species dual-responsive sodium alginate-based hydrogel improved the survival rate of <i>L.rha</i> during storage.	Wound infections	[158]
Hyaluronic acid	Hydrogel	<i>Lactobacillus reuteri</i>	The survival rate of <i>Lactobacillus reuteri</i> under simulated digestion conditions was significantly improved after being encapsulated in hydrogel.	Colitis	[159]
Alginate	Hydrogel	<i>Lactobacillus rhamnosus</i> GG	Exfoliated bentonite/alginate nanocomposite hydrogel enhanced intestinal delivery of probiotics by resistance to gastric pH and on-demand disintegration.	Intestinal delivery	[160]
Fucoidan	Hydrogels	<i>L. rhamnosus</i>	Calcium alginate/fucoidan hydrogels had good swelling property, continuous probiotic release, good storage durability and effective antibacterial ability.	Oral ulcer	[161]
Fucose, Abroma augusta mucilage	Hydrogel	<i>Lactobacillus acidophilus</i> and <i>Lactobacillus casei</i>	Abroma augusta mucilage could protect probiotics and ensure that embedded probiotic cells have a higher survival rate.	Prebiotic function	[162]
Dextran	Hydrogel	<i>L. plantarum</i> LP90	Hydrogel encapsulation could significantly promote the growth and proliferation of probiotics, and protect probiotics from gastric acid, bile salt, reactive oxygen species and antibiotics.	Intestinal delivery	[163]
Carboxylated chitosan and oxidized hyaluronan	Hydrogel	<i>Lactobacillus reuteri</i>	The hydrogel was contributed to the survival of probiotics and supported the continuous secretion of lactic acid to perform biological functions in the environment containing gentamicin.	Wound healing	[164]
Carboxymethyl konjac glucomannan-chitosan, Alginate	Hydrogel	<i>Lactobacillus reuteri</i>	The concentration of alginate in hydrogel beads affected the expansion behavior and structure of hydrogel beads by affecting the hydrogen bond between alginate and CMKGM-CS, thus mediating the release of probiotics.	Intestinal delivery	[165]
Pectin	Hydrogel	<i>Lactobacillus rhamnosus</i> GG	This material maintained the vitality of LGG in vitro and in vivo, thereby extending the shelf life of LGG and enhancing its function in the gastrointestinal tract.	Intestinal delivery	[166]
<i>Momordica charantia</i> polysaccharides	Hydrogel	<i>Lactobacillus acidophilus</i>	MP-WPI successfully increased the survival rate of probiotic <i>Lactobacillus acidophilus</i> after freeze-drying, with a high encapsulation efficiency (98%) and improved storage stability.	Antioxidant	[167]
Alginate	Hydrogel	<i>Bifidobacterium</i>	Multilayer alginate hydrogel beads can be used to continuously release metabolites during the fermentation process to avoid explosive release.	Intestinal delivery	[168]

Alginate-locust bean gum	Microcapsules	<i>Lactobacillus rhamnosus</i>	AGN-LB capsules not only enhanced acid resistance, but also exhibited optimal cell release characteristics.	Intestinal delivery	[169]
Human milk oligosaccharides	Microcapsules	<i>Bifidobacterium animalis</i> F1–7	The addition of HMO exhibited a more stable freeze-drying form and thermal stability.	Intestinal delivery	[170]
<i>Laminaria japonica</i> Polysaccharide	Microcapsules	<i>Lactobacillus plantarum</i>	The addition of LJP could improve the thermal stability of microcapsules.	Intestinal delivery	[171]
Alginate, nanocellulose	Microcapsules	<i>Lactobacillus paracasei</i>	Nanocellulose formed a dense film on the surface of microcapsules through interaction with sodium alginate, isolating harsh external environments and improving the stability of microcapsules	Intestinal delivery	[172]
Alginate	Microcapsules	<i>Lactobacillus rhamnosus</i>	This technology enhanced the tolerance of bacteria to heat treatment at different temperatures, while also enabling them to exhibit metabolic activity under appropriate conditions.	Intestinal delivery	[173]
Rhamnogalacturonan I rich pectin	Microcapsules	<i>Lactiplantibacillus plantarum</i> GDMCC 1.140 and <i>Lactobacillus rhamnosus</i>	This technology enhanced the resistance of probiotics.	Intestinal delivery	[174]
Chitosan-glucose	Microcapsules	<i>K. marxianus</i> VM004	Compared with free yeast, microcapsules had stronger resistance to gastrointestinal diseases and greater stability to refrigeration and room temperature.	Intestinal delivery	[175]
Chitosan hydrochloride-alginate	Microcapsules	<i>Bacillus licheniformis</i>	The prepared microcapsules had good thermal stability.	Intestinal delivery	[176]
<i>Maca</i> polysaccharides	Microcapsules	<i>Bifidobacterium longum</i>	At different temperatures, microcapsules coated with MD-MP exhibited better storage stability than those coated with MD.	Intestinal delivery	[177]
Pectin	Microcapsules	<i>Lactocaseibacillus rhamnosus</i> ZFM231	Double layered microcapsules could significantly enhance the storage and thermal capacity of bacteria.	Intestinal delivery	[178]
Chitosan, Alginate	Microcapsules	<i>Bifidobacteria</i>	Chitosan coated alginate microcapsules could protect <i>Bifidobacteria</i> from gastrointestinal fluids and high temperature environments.	Intestinal delivery	[179]
Alginate	Microcapsules	<i>Lactobacillus rhamnosus</i>	Microcapsules exhibited higher frost resistance, dryness resistance, and heat resistance under humid and hot exposure.	Intestinal delivery	[180]
Chitosan and pullulan	Nanofibers	<i>Lactiplantibacillus plantarum</i> ZJ316	The increase in chitosan concentration enhanced the thermal stability of nanofibers. Compared with free bacteria, the encapsulation of ZJ316 with nanofibers significantly improved its survival rate in simulated gastrointestinal fluid.	Gastritis and colitis	[181]
Fructooligosaccharides	Nanofibers	<i>Lactobacillus. Plantarum</i>	Compared with free cells, encapsulated bacteria had significantly improved resistance to dampness and heat.	Intestinal delivery	[182]
Apple-Pectin	Nanofibers	<i>L. acidophilus</i>	PVA/PEC nanofibers had good thermal stability and excellent barrier properties.	Intestinal delivery	[183]
Alginate	Nanofibers	<i>Lactobacillus paracasei</i> KS-199	Nanofibers could improve the survival rate of bacterial strains in simulated gastric juice.	Intestinal delivery	[184]

5.1 Enhancing gastric acid resistance with polysaccharide-based nanomaterials

Polysaccharide-based nanomaterials have emerged as a powerful tool to enhance the survival of probiotics in the harsh conditions of the gastrointestinal tract, particularly in the strongly acidic gastric environment that often leads to drastic reductions in viable cell counts. Among the various approaches, microencapsulation has proven to be one of the most effective strategies, as it provides a physical barrier around the probiotic cells, reducing their exposure to damaging pH levels, digestive enzymes, and bile salts. Each encapsulation format, however, presents distinct trade-offs. Hydrogel-based systems, typically formed by ionic gelation, offer mild processing conditions but may provide less immediate physical barrier protection in the gastric phase compared to pre-formed microcapsules. Microcapsules excel in creating a defined physical barrier but can be more complex to produce. Nanofibers, produced by electrospinning, offer high surface-area-to-volume ratios for efficient release but may require additional crosslinking to achieve optimal gastric resistance. A critical factor in the success of this technology is the careful selection of wall materials, since the physicochemical properties of the encapsulating matrix directly influence the protective efficacy, release behavior, and overall functionality of the delivery system. By tailoring these materials and structures, researchers aim not only to safeguard probiotic viability during processing and gastric passage but also to ensure their targeted release and functional activity in the intestinal environment.

Cheow and colleagues investigated the effect of incorporating locust bean gum (LB) and xanthan gum (XT) into alginate (AGN)-based capsules on the stress resistance and release behavior of encapsulated cells under simulated gastrointestinal conditions. Compared with single-component AGN capsules, the AGN-LB hybrid capsules exhibited markedly improved resistance to acidic stress and superior release characteristics, demonstrating how the addition of synergistic polysaccharides can strengthen the microcapsule matrix and optimize probiotic delivery ^[169]. This highlights a key advantage of alginate composites: the ability to easily modify and enhance the properties of a widely available, low-cost, and generally recognized as safe (GRAS) material. The trade-off is that the gelation process and final properties can be sensitive to ion concentration and pH, requiring precise process control for industrial scalability. In another study, Huang and co-workers prepared microcapsules containing *Bifidobacterium animalis* F1-7, with and without the inclusion of human milk oligosaccharides (HMOs). The results revealed that the HMO-enriched capsules showed significantly enhanced stability during freeze-drying, improved thermal tolerance, and greater survival rates when exposed to simulated gastrointestinal fluids or during long-term storage, underscoring the importance of selecting biologically relevant oligosaccharides as protective co-materials ^[170].

To further increase the survival of probiotics during gastrointestinal digestion and thermal processing, researchers have explored the use of composite materials derived from natural polysaccharides and proteins. For instance, a system based on *Laminaria japonica* polysaccharides (LJP), sodium caseinate (SC), and gelatin (GE) was developed to encapsulate *Lactobacillus plantarum* using spray-drying. The presence of LJP contributed to the improved thermal stability of the microcapsules, as its negatively charged groups interacted

electrostatically with the positively charged SC/GE components, stabilizing the microstructure and preventing premature disintegration under acidic gastric conditions. Additionally, the inherent carbon and galactose components in LJP further enhanced the thermal resilience of the capsules ^[171]. Such protein-poly saccharide complexes often provide superior functionality but at a higher material cost and with increased formulation complexity compared to single-polymer systems. In a related approach, cellulose nanofibers derived from seaweed were incorporated as crosslinked reinforcements within alginate-based microcapsules. These nanofibers formed a dense surface membrane that effectively isolated the encapsulated *Lactobacillus paracasei* from harsh external environments. As a result, the system achieved superior acid resistance while allowing targeted release of the probiotics upon swelling and rupture in neutral intestinal fluids ^[172].

The concept of multilayered encapsulation has also demonstrated promising results in strengthening acid resistance. Ji et al. designed double-layered microcapsules in which chitosan served as the inner wall material and sodium alginate functioned as the outer protective layer for encapsulating *Bifidobacterium*. Both alginate-only and chitosan-coated alginate capsules exhibited spherical morphology and uniform bacterial distribution; however, the chitosan-coated variants displayed markedly enhanced acid tolerance. This improvement was attributed to the ability of chitosan to adsorb onto the porous alginate surface, thereby sealing structural gaps, reducing the effective contact area between the probiotic cells and gastric acid, and limiting the penetration of bile salts ^[179]. This exemplifies a strategic advantage of chitosan: its ability to form strong, pH-responsive films and coatings that enhance acid resistance. A notable disadvantage, however, is its solubility being limited to acidic conditions, which can complicate processing and may necessitate the use of organic acids, potentially affecting probiotic viability.

More recently, Wang and colleagues developed a core-shell fibrous delivery system for *Lactobacillus plantarum* LP90 using microalgae protein and sodium alginate as core materials. This dual-layer structure showed strong potential in encapsulating probiotics and enhancing their resistance to extreme environmental stresses. The unique pH-responsive characteristics of alginate played a crucial role by enabling the selective release of probiotics under intestinal conditions, further demonstrating the multifunctionality of polysaccharide-based encapsulation systems ^[185].

The survival of specific probiotic strains with clinically relevant health benefits has been another focal point of encapsulation studies. *Lactobacillus plantarum* ZJ316, for example, has been shown to alleviate gastritis and colitis, making its protection during gastric transit essential. Researchers encapsulated this strain using a combination of chitosan and pullulan polysaccharides, forming nanofiber-based structures. Increasing the concentration of chitosan enhanced the thermal stability of the nanofibers, and compared to free bacterial cells, encapsulated probiotics exhibited significantly higher survival rates under simulated gastric conditions. This outcome highlights the ability of chitosan-pullulan nanostructures to form stable, protective environments that preserve probiotic viability during both storage and gastrointestinal exposure ^[181]. Electrospun nanofibers like these offer high encapsulation efficiency and customizable release kinetics, but

the electrospinning process itself can be challenging to scale for industrial food production, and the high voltages used may pose a risk to some sensitive probiotic strains.

Taken together, these studies clearly demonstrate that polysaccharide-based nanomaterials, whether in the form of microcapsules, multilayered matrices, or fibrous nanosystems, can substantially improve the acid resistance and overall survival of probiotics. By carefully selecting and combining wall materials such as alginate, chitosan, pullulan, and marine-derived polysaccharides, researchers have been able to engineer delivery systems with enhanced thermal stability, acid tolerance, and controlled release properties. The choice of system involves critical trade-offs: alginate systems are cost-effective and scalable but may require composite formation for robust acid protection; chitosan offers excellent film-forming and antimicrobial properties but has solubility limitations; while electrospun nanofibers provide superior control over structure and release but face scalability challenges. Moreover, the integration of biologically relevant oligosaccharides or nanofibrous reinforcements offers additional functional advantages, further strengthening the protective barrier against gastric stress. These advances not only expand the potential of probiotics as functional food ingredients and therapeutic agents but also provide a rational basis for the strategic design of delivery vehicles aimed at maximizing probiotic efficacy *in vivo*.

5.2 Polysaccharide-based nanomaterials for stability preservation and transport of probiotics

Ensuring the stability of probiotics during storage and transport remains a major challenge in the field of functional food and biomedical applications. Probiotic cells are extremely vulnerable to environmental stresses such as temperature fluctuations, humidity, oxidative conditions, and even exposure to antibiotics, all of which can drastically reduce their viability before reaching the consumer or clinical site. To overcome these challenges, polysaccharide-based nanomaterials have been increasingly employed as encapsulating and protective carriers. Their natural abundance, biocompatibility, and tunable structural features make them particularly attractive for developing delivery systems that safeguard probiotic viability during long-term preservation and ensure functionality upon administration. The choice between different polysaccharide systems involves important trade-offs. Hydrogel beads, such as those based on alginate, are highly effective for creating a hydrated, protective microenvironment and are relatively simple to produce via extrusion or emulsification, making them suitable for large-scale food applications. However, their porous structure may offer less protection against low-humidity environments during long-term storage compared to denser nanofiber mats. Nanofibers, produced by electrospinning, excel in creating a high-surface-area, dry protective matrix ideal for storage stability but require more specialized equipment and may face challenges in scaling up for high-volume production.

Alginate is one of the most widely studied polysaccharides in this context due to its ability to form ionic gels when crosslinked with multivalent cations such as calcium (Ca^{2+}). For example, calcium alginate/fucoidan hydrogels have been shown to possess excellent swelling capacity, sustained release characteristics, strong storage stability, and notable antibacterial activity^[161]. These properties enable probiotics to be effectively shielded from environmental stress during transport while ensuring a controlled and prolonged release once

the hydrogel reaches the gastrointestinal tract. Such systems not only enhance survival during storage but also contribute to a predictable and efficient release profile *in vivo*. The primary advantage of alginate lies in its gentle, aqueous gelation process, which is highly compatible with probiotic viability. A key disadvantage is its sensitivity to chelating agents and certain ions in the environment, which can lead to premature disintegration if not properly formulated, potentially limiting storage stability under certain conditions.

Building upon these foundations, researchers have developed innovative hydrogel systems that combine multiple protective mechanisms. One notable example involves coating probiotics with a metal–polyphenol complex and integrating them into a hydrogel matrix via Schiff-base reactions. This dual-layer protective network provides both mechanical stability and physiological compatibility, allowing the encapsulated probiotics to maintain normal metabolic activities ^[164]. Importantly, the supramolecular adsorption and separation properties of this hydrogel enable probiotics to survive in environments containing antibiotics such as gentamicin, penicillin, and cephalosporins. This finding significantly broadens the potential application of such systems, particularly in wound-healing contexts where probiotics may need to function in antibiotic-rich conditions. While such advanced hydrogels offer multi-functional protection, their synthesis is more complex and costly compared to simple ionically crosslinked alginate beads. This makes them more suitable for high-value therapeutic applications rather than routine food fortification.

The versatility of alginate is further exemplified by its ability to form multilayer alginate hydrogel beads (MAHBs) when crosslinked with various cations including sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), and iron (Fe^{2+} , Fe^{3+}). In one study, probiotics encapsulated within five-layer MAHBs displayed remarkable performance as oral delivery systems. For instance, *Bacillus subtilis* encapsulated in MAHBs demonstrated not only improved survival but also higher α -amylase production compared to free cells, suggesting that encapsulation did not inhibit metabolic activity ^[168]. Furthermore, the release of metabolites from the encapsulated cells was sustained and stable, avoiding the undesirable burst release that can limit the effectiveness of fermentation or therapeutic processes. These results indicate that MAHBs can be effectively applied to scenarios where continuous metabolite production and controlled release are critical, such as in industrial fermentation or targeted gut health interventions. The multi-layer approach significantly enhances control over release kinetics and mechanical robustness but at the cost of increased production time and complexity. This trade-off may be justified for high-value applications where precise release timing is critical.

In addition to hydrogel systems, nanofiber-based polysaccharide carriers have also attracted increasing attention for probiotic stabilization. Fructooligosaccharides (FOS), for example, have been employed as encapsulating materials to embed *Lactobacillus plantarum* within nanofiber matrices. Compared with free cells, FOS-encapsulated probiotics demonstrated significantly enhanced resistance to moisture and heat, two of the most critical stress factors during storage and global transport ^[182]. This improvement is largely attributed to the dense nanofiber network formed by FOS, which provides a stable microenvironment that minimizes water uptake and thermal damage. The ability of such nanofiber systems to maintain high cell

viability under harsh storage conditions directly translates into extended shelf life and more reliable delivery of active probiotics to consumers. Nanofiber systems are particularly advantageous for creating dry, stable probiotic formulations with long shelf lives, as they form a dense, protective web around the cells. However, the electrospinning process often requires the use of synthetic polymer carriers (e.g., PVA) to achieve good spinnability, which may reduce the overall "natural" polysaccharide content and complicate regulatory approval for certain food applications.

Taken together, these findings underscore the central role of polysaccharide-based nanomaterials in advancing probiotic stability preservation and transport. Hydrogels formed by alginate and other natural polysaccharides provide protective encapsulation, sustained release, and even resistance to antibiotic environments. Multilayered alginate systems enable prolonged metabolite production without compromising bacterial viability, while nanofiber carriers based on FOS ensure superior tolerance to humidity and temperature fluctuations. In practical terms, the selection of an appropriate system depends heavily on the primary stressor: hydrogels are ideal for maintaining a hydrated microenvironment and providing sustained release in the gut; nanofibers are superior for dry storage stability and thermal protection; while complex, multi-functional hydrogels are reserved for challenging therapeutic environments, such as those containing antibiotics. By integrating these material strategies, researchers can design next-generation probiotic delivery systems that guarantee stable preservation during distribution and controlled functionality upon use. Such innovations hold significant promise not only for improving the effectiveness of probiotic-containing foods and supplements but also for expanding their applications into therapeutic and clinical domains where reliable microbial performance is critical.

5.3 Polysaccharide-based biomaterials for reducing oxygen exposure and preserving probiotic activity

Oxygen exposure is one of the major environmental stressors that compromises the viability of probiotics during storage, processing, and gastrointestinal transit. Many probiotic strains are microaerophilic or anaerobic in nature, and their metabolic activity and survival can be significantly impaired under oxidative conditions. In recent years, polysaccharide-based biomaterials have attracted increasing attention as effective protective carriers that reduce oxygen-induced stress while simultaneously enabling targeted delivery and controlled release. The selection of an appropriate polysaccharide system for oxygen protection involves critical trade-offs. Hydrogels offer superior functionality through ROS-scavenging chemical modifications but may have higher oxygen permeability in their swollen state. Microcapsules provide a dense physical barrier ideal for long-term storage but offer less opportunity for active ROS scavenging. Nanofibers create excellent dry-state oxygen barriers but typically require blending with synthetic polymers for electrospinning, which may dilute the bioactive polysaccharide content. Hydrogels, microcapsules, and nanofibers derived from natural polysaccharides not only provide physical barriers that shield encapsulated cells from oxidative damage but also actively participate in scavenging ROS, thereby maintaining probiotic viability and functional activity.

Hydrogels prepared from polysaccharides such as hyaluronic acid and alginate are notable examples. Hyaluronic acid possesses abundant carboxyl and hydroxyl groups, which facilitate chemical modifications and self-crosslinking to form supramolecular hydrogels. Recent studies have designed ROS-responsive hyaluronic acid hydrogels capable of encapsulating *Lactobacillus reuteri* and targeting inflamed colonic tissues. Once the negatively charged hydrogels reach the inflamed sites, they attach to the mucosal surface and release probiotics upon stimulation by excessive ROS in the local microenvironment. Meanwhile, the thiol linkages and the hyaluronic acid backbone impart ROS-scavenging capacity, reducing oxidative stress and extending the residence time of probiotics in the colon ^[159]. The key advantage of hyaluronic acid lies in its innate bioactivity and targeting capability, particularly for inflamed tissues; however, its high cost and complex modification chemistry limit its application to high-value therapeutics rather than bulk food products. Similarly, alginate-based hydrogels have been developed with dual pH and ROS responsiveness. These systems not only improved the survival of *Lactobacillus rhamnosus* during storage but also efficiently removed excessive ROS at wound sites, thereby providing both protective and therapeutic effects ^[158]. Alginate offers a more cost-effective alternative for creating responsive hydrogels, though its oxygen barrier properties in hydrated conditions are generally inferior to those of dry microcapsules or nanofibers. Such multifunctional hydrogel systems highlight the dual role of polysaccharide carriers: passive shielding against oxygen exposure and active detoxification of ROS in pathological environments.

Microcapsule technology further strengthens oxygen protection by embedding probiotics within dense polymeric matrices. By selecting appropriate wall materials such as alginate, chitosan, or pectins, researchers have been able to reduce the permeability of oxygen into the microcapsules, thereby slowing oxidative degradation of cells. Among these, chitosan-based microcapsules offer particularly good oxygen barrier properties due to their dense, film-forming nature, though their application is limited to acidic processing conditions. Alginate microcapsules are more versatile for food applications but may require additional coating or composite formation to achieve optimal oxygen barrier performance. For instance, plant-derived polysaccharides like rhamnogalacturonan-I enriched pectin have been shown to form strong gels that encapsulate probiotics, creating microenvironments where oxidative stress is minimized. Moreover, the incorporation of polysaccharide nanofibers such as seaweed-derived cellulose into alginate capsules can generate dense surface films, further isolating cells from external oxygen exposure ^[172]. Such structural reinforcements not only improve barrier properties but also ensure that probiotics retain metabolic activity and viability until their controlled release in neutral intestinal fluids.

Nanofiber-based systems prepared via electrospinning represent another frontier in oxygen-protective delivery. By embedding probiotics into polysaccharide nanofiber scaffolds, researchers have created lightweight and highly stable matrices with excellent barrier properties. Electrospun nanofibers typically provide the most effective physical barrier against oxygen permeation in dry storage conditions due to their high density and tortuous diffusion pathways. However, this advantage must be balanced against the technical challenges of scaling up electrospinning for industrial food production and the potential viability loss of

sensitive strains during the high-voltage processing. For example, apple pectin combined with polyvinyl alcohol (PVA) was used to prepare composite nanofibers with superior thermal stability and oxygen barrier capacity. Probiotics delivered through PVA/PEC nanofibers exhibited markedly higher survival compared to free cells, confirming the role of nanofiber-based polysaccharides in preventing oxidative stress^[183]. The necessity to blend pectin with PVA exemplifies a common compromise in nanofiber production: enhanced spinnability and mechanical properties at the cost of reduced polysaccharide purity and potential regulatory considerations for food applications. Similarly, fructooligosaccharide (FOS)-based nanofibers provided additional advantages by enhancing moisture and heat resistance while simultaneously reducing oxidative damage, ensuring robust probiotic survival during storage and transport^[182].

Collectively, these findings demonstrate that polysaccharide-based biomaterials play a multifaceted role in reducing oxygen exposure and safeguarding probiotics. Through the combination of physical shielding, ROS scavenging, and structural reinforcement, hydrogels, microcapsules, and nanofibers derived from natural polysaccharides provide an effective means of mitigating oxidative stress. In practical application, the choice between these systems depends on the specific oxygen challenge: hydrogels are preferred for therapeutic applications where ROS scavenging at target sites is crucial; microcapsules excel in providing long-term oxygen barrier protection during storage of food products; while nanofibers offer superior performance in dry powder formulations where minimal oxygen permeability is paramount. By minimizing oxygen penetration and neutralizing ROS, these systems significantly enhance the stability, viability, and therapeutic potential of probiotics across diverse applications, ranging from functional foods to targeted biomedical treatments.

6. Conclusions and Future Prospects

In 2016, the International Scientific Association for Probiotics and Prebiotics (ISAPP) redefined probiotics as bacteria that enhance the balance of intestinal flora and provide benefits to the host. In this context, natural polysaccharides can be selectively utilized and transformed by gut flora, offering potential health benefits. Existing studies have demonstrated that intestinal flora plays a significant role in regulating various conditions, including intestinal diseases, neurodegenerative diseases, diabetes, obesity, immune disorders, malignant tumors, and cardiovascular diseases.

Natural polysaccharides present challenges for human digestion; however, they serve as essential nutritional substrates that facilitate the growth of probiotics. These polysaccharides enhance the competitive ability of probiotics against pathogenic microorganisms, inhibit the proliferation of pathogenic bacteria, and bolster the resilience of probiotics in the adverse conditions of the gastrointestinal tract. Probiotics possess specific enzymes that compensate for the host's deficiency in digestive enzymes. These enzymes are integral to the metabolism of polysaccharides and other substances during digestion, enabling the breakdown of nutrients that the host is unable to metabolize. Furthermore, both the quantity and chemical composition of dietary and endogenous polysaccharides, which are regulated by probiotics, contribute to a dynamic intestinal environment and influence the composition of the intestinal microbiota. Natural polysaccharides play a multifaceted role in modulating human diseases through probiotics; however, their efficacy is often closely

linked to factors such as their relative molecular mass, monosaccharide composition, morphology, and the chemical groups associated with the sugar chain. In the biomodification of polysaccharides, probiotic fermentation can elucidate the polysaccharide-disease conformational relationship, thereby identifying the active centers of polysaccharides. Nonetheless, there is a scarcity of research on the fermentation modification of polysaccharides by probiotics. Future investigations should focus not only on the metabolic and fermentative modification of polysaccharides by probiotics but also employ more precise methodologies such as defined microbial consortia and co-fermentation systems to achieve targeted structural refinement of polysaccharides.

Although probiotics are widely utilized in food and pharmaceuticals, a significant discrepancy exists between their viability and health benefits. This issue arises from the sensitivity of most probiotics to heat, oxygen, acids, enzymes, and bile acids, which leads to reduced viability during processing, storage, and gastrointestinal transport. Previous studies have identified a variety of natural polysaccharides that can serve as encapsulating materials to enhance probiotic viability. Nevertheless, the field continues to confront substantial challenges. Research on natural polysaccharides as encapsulating materials remains in its nascent stages, and there are few studies that utilize natural polysaccharides as the sole encapsulating agent. The majority of existing research has concentrated on the use of natural polysaccharides as supplements. Furthermore, researchers have predominantly employed *in vitro* simulated gastric fluids to assess the encapsulation efficiency and survival of probiotics, resulting in a notable lack of *in vivo* experiments to validate the health effects of natural polysaccharide carriers. It is therefore imperative that future research transitions from *in vitro* models to comprehensive *in vivo* studies utilizing relevant disease models such as colitis, metabolic syndrome, or immune-related disorders to verify the therapeutic efficacy and safety of polysaccharide-based delivery systems. These efforts will be essential to bridge the gap between laboratory findings and clinical applications.

This review has synthesized key mechanisms and synergistic interactions between probiotics and polysaccharides, emphasizing their integrated roles in gut microbiota modulation, bioactivity enhancement, and improved probiotic delivery. Looking ahead, several concrete research directions emerge as critical to advancing the field. Specifically, the application of synthetic biology holds immense potential for engineering next-generation probiotics with tailored carbohydrate-active enzyme (CAZyme) profiles, enabling precise and predictable modification of polysaccharide structures for enhanced functionality. To translate these advances into clinical practice, a major challenge and opportunity lies in developing personalized nutrition strategies that consider an individual's baseline gut microbiota composition and their specific response to polysaccharide-probiotic combinations. Future work should prioritize human clinical trials and longitudinal studies to establish causal health benefits and validate safety profiles. The integration of multi-omics technologies will be essential to elucidate detailed molecular mechanisms and host-microbe interactions. Furthermore, the field would greatly benefit from the establishment of standardized protocols for the probiotic fermentation of polysaccharides, which is crucial for ensuring reproducibility and enabling meaningful

comparisons across different studies. There is also a clear need to develop next-generation intelligent delivery systems responsive to specific gut environments for targeted probiotic release. Furthermore, personalized nutrition strategies based on individual microbiome profiles represent a promising avenue for tailored interventions.

In summary, the interplay between probiotics and polysaccharides constitutes a rapidly evolving research domain with significant potential for therapeutic applications. By deepening our understanding of the underlying mechanisms and addressing current research gaps, we can accelerate the translation of these insights into effective clinical strategies and innovative health solutions.

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Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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