Review Articles

Acupuncture and Herbal Medicine

Action mechanisms of polysaccharides in Chinese herbal decoctions

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Abstract

Water decoction is the main form of traditional Chinese medicine (TCM) administered in clinics. Polysaccharides are major components of decoction. Recent studies reported that polysaccharides possess multiple pharmacological activities. However, the mechanism by which oral Chinese herbal polysaccharides play vital roles in the body remains uncertain. This review discussed the polysaccharides in Chinese herbal decoctions and their effects, direct and indirect. The direct impact of polysaccharides includes being absorbed into the body immunity regulation through Peyer's patches; electrostatic adsorption, hydrophobic interaction, and glycoprotein receptors-induced antibacterial effects; prebiotic functions; gut microbiota structural regulation; and increasing the relative abundance of beneficial bacteria. The indirect effects of the polysaccharides in Chinese herbal decoctions include phytochemical toxicity reduction and activity enhancement. Finally, their clinical and research significance is summarized and future research directions are discussed.

Keywords: Action mechanisms, Decoctions, Gut microbiota, Polysaccharides, Traditional Chinese medicines

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Introduction

Traditional Chinese medicine (TCM) is the cornerstone of Chinese culture and medical practice and has been utilized for the prevention and treatment of diseases for thousands of years[1–2]. Chinese herbal decoction is one of the core applications of TCM and has accumulated rich experience and application cases in clinical practice[3]. Unlike chemical drugs that typically consist of a single chemical component, Chinese herbal decoctions are a mixture of various chemical components. In addition to small molecular compounds, macromolecules, such as polysaccharides, have been shown to be the main components in decoctions[4]. According to Lipinski's rule of five, small molecules including saponins, flavonoids, alkaloids, and polyphenols, have been well studied[5–7]. Small molecules are considered the key active substances responsible for the clinical efficacy of Chinese herbal decoctions[8–9]. The importance of polysaccharides in decoctions has been underestimated because of problems in absorption, bioavailability, and unknown mechanism of action[10].

With the modernization of TCM and their industrial production, polysaccharides are usually removed as impurities in line with the purity and meteorological requirements of TCM final products. Moreover, polysaccharides have also been excluded from pharmacological studies of key chemicals in Chinese herbal decoctions[11]. This deviates from the traditional use of Chinese medicine and is not based on scientific evidence. Essentially, all biological compounds are macromolecules.

Understanding the mechanism of action of polysaccharides is crucial for TCM research and applications, as substantial evidence indicates that the polysaccharides used in TCM exhibit a variety of biological activities[12–14]. Second, the composition and structure of polysaccharides significantly affect the quality of TCM, and an in-depth understanding of their mechanisms of action can help establish a more scientific quality evaluation system and standardization methods[15–16]. Third, studying the mechanism of action of polysaccharides allows for the optimization of TCM formulas, enhancing efficacy and reducing toxicity, thereby improving clinical applications[17] Finally, as natural products, polysaccharides possess potential medicinal values and broad application prospects, and understanding their mechanism of action can inspire and guide the development of new drugs[18–19]. Therefore, the optimal application and innovation of TCM decoctions depends on an in-depth understanding of the

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Table 1

Comparison of the common methods applied to polysaccharide labeling

	Fluorescent labeling	Radioisotope labeling	Immunoassays	Chemical colorimetry
Index	Fluorescence intensity, spectrum, and localization.	Radioactive counting and autography.	Immunofluorescence, enzyme labeling	Colored products
Principle	Fluorescently labeled polysaccharides emit fluorescence upon excitation, with intensity proportional to their concentration.	Radioactive isotope-labeled polysaccharide can be measured by the decay radiation.	The specific antibody binds to polysaccharide, which is labeled with a fluorescent or enzyme-labeled secondary antibody.	The polysaccharides react with chemical reagents to produce colored products and measured through colorimetric determination.
Advantage	Quantitative analysis of polysaccharide content and study of the dynamic process of polysaccharides in organisms.	Extremely high sensitivity to visualize the location and distribution of labeled molecules.	High sensitivity for quantitative and positional analyses.	Simple operation, high sensitivity, and wide range of application
Disadvantage	Affected by photoquenching and photobleaching, sample autofluorescence, and limited penetration depth.	Radiation hazard, short half-life, expensive, and technically demanding.	Specialized equipment and additional operating procedures or optimized conditions are required.	Limited sensitivity and specificity for specific polysaccharides.

mechanisms of action of polysaccharides within TCM. However, understanding the mechanisms of action of oral polysaccharides remains challenging. Previously, we hypothesized five potential mechanisms of action of oral polysaccharides[20]. In this review, we aimed to discuss the current evidence supporting our hypothesis and contribute to an in-depth understanding of the mechanisms of action of polysaccharides in Chinese herbal decoctions, including direct and indirect aspects. The literature search in this article was determined by Web of Science, time range mainly from 2019 to 2024.

Direct effects

The effect of absorbed polysaccharides

The first hypothesis is that a few polysaccharides or oligosaccharides can be directly absorbed into the blood to act on the target. In recent years, polysaccharide pharmacokinetics, the absorption of polysaccharides into the blood stream, has been well elucidated. The absorption entails paracellular transportation, intestinal epithelial endocytosis mediated by the macropinocytosis pathway, and absorption facilitated by clathrin- and caveolin-related pathways.

A key challenge limiting the further development and application of polysaccharides as drugs and biomaterials is the difficulty of detecting polysaccharides *in vivo*, which is attributable to their lack of ultraviolet (UV) absorption and fluorescent groups. To overcome this hurdle, auxiliary methods including fluorescent labeling[21], radioisotope labeling[22], immunoassays[23], and chemical colorimetry[24] (Table 1), have been introduced. Among these, fluorescent and radioactive isotope labeling are the most commonly employed methods. It is vital to carefully control the degree of substitution of the polysaccharide label to ensure that it remains below 2.5%[25], mitigating any potential impact on the physical and chemical properties of the polysaccharide. Among the studies analyzed (Table 2), 60% (9/15) utilized fluorescein isothiocyanate (FITC), 20% (3/15) used biotin p-aminobenzoic ethyl ester (ABEE), and Cyanine 5.5 (Cy 5.5), while the remaining four reports employed instrumental analysis methods, such as high-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD), ultra-performance liquid chromatography-mass spectrometry (UPLC-MS), and liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) to detect polysaccharides, thus, bypassing the need for labeling.

FITC is a highly sensitive fluorescent label commonly employed for *in vivo* pharmacokinetic investigations, particularly for labeling polysaccharides. Zhang et al.[27] studied the pharmacokinetics of FITC-labeled ginseng polysaccharide (GP) and ginseng acidic polysaccharide (GAP) in rats and compared their absorption after oral and intravenous administration. The results indicated superior absorption of GAP following oral administration, with no significant difference after intravenous administration. In parallel, *in vivo* imaging of rats revealed a wider distribution of GAP and GP in the kidneys, liver, and genitals. Furthermore, insights from the Caco-2 cell model have demonstrated that the uptake of GPs by small intestinal epithelial cells is predominantly mediated by lattice proteins and cytosolic cells. Similarly, research conducted by Wang et al.[36] showcased the time-dependent process of FITC-labeled Ganoderma lucidum polysaccharide (GLP) absorption in mouse models. In particular, Wang et al.[36] demonstrated the uptake of GLP by Caco-2 cells through the macropinocytosis pathway, and reported that the Papp value was indicative of a well-absorbed biological macromolecule. Additionally, Shirai et al.[28] administered biotin ABEE-labeled agaro-oligosaccharides (AOSs) orally to rats and detected the presence of AOSs such as agarobiose (Abi), agarotetraose (Ate), and arohexaose (Ahe) in rat plasma *via* LC-MS. These findings revealed intact absorption of AOSs, particularly Abi, *via* the gastrointestinal tract across the intestinal epithelium through the paracellular pathway. Li et al.[32] conducted a study in which pumpkin (Cucurbita moschata Duch) polysaccharides were treated with FITC and Cy5.5. The labeled polysaccharide was detected in the serum and tissues of mice using high-performance gel permeation chromatography with

Table 2

Polysaccharide pharmacokinetics

Polysaccharide/ oligosaccharide	Molecular weight (KDa)	Marking method	Dosing method	Detection sample	Detection method	Whether it can be absorbed and its absorption mechanism	Ref.
Fucoidan	9.5	Nm	ig, iv	Serum, heart, liver, spleen, kidney, lung, stomach, and intestine	HPAEC-PAD detects blood and tissue	Detected in serum and tissues, with the highest concentration in the kidneys	[26]
Ginseng polysaccharide	4.5	FITC	ig, iv	Serum, heart, liver, brain, lung, kidney, and small intestine	Multifunctional enzyme reader and HPLC-MS/MS detection of serum and tissue (heparin treated)	Detected in serum and tissues with high distribution in kidney, liver, and testes, uptake by intestinal epithelial *via* lattice proteins and cytosolic cellar	[27]
AOSs	Nm	ABEE	ig	Serum	LC-MS detects the concentration of AOSs in serum and Caco-2 cells	Detected in serum, the route of transport of AOSs mainly rely on paracellular pathway	[28]
Polygonatum sibiricum polysaccharide	8.64	FITC	ig, iv	Serum, heart, liver, spleen, lung, kidney, stomach, small intestine, and brain	Fluorescence spectrophotometer and CLSM detection of serum and tissue (heparin treated)	Detected in serum and tissues with high distribution in kidney, liver, and lung, mainly excreted by the kidney	[29]
COS	Nm	FITC	ig, iv	Serum	UPLC-MS/MS detects the concentration of COS in serum (heparin treated)	COS can be absorbed by the intestine, and this absorption is mediated by facilitation diffusion and paracellular	[30]
COSs	Nm	Nm	ig, iv	Serum, heart, liver, kidney, lung, spleen, pancreas, cerebellum, and brain	UPLC-MS detects the concentration of COSs in serum and tissue	UPLC-MS was developed to directly detect COSs in blood and tissues, with the highest enrichment in the kidney	[31]
Cucurbita moschata polysaccharide	Nm	FITC and Cy5.5	ig, iv	Serum, heart, liver, spleen, lung, kidney, bladder, MLN, and small intestine	HPGPC-FLD detection of serum and tissue (FITC labeled), NIRF imaging (Cy5.5 labeled)	Detected in serum and tissues with high distribution in kidney, liver, and bladder, absorbed by endocytosis *via* the clathrin-and caveolae-(or lipid draft-) medicated routes	[32]
Lycium barbarum polysaccharides	4.92	FITC	ig	Serum, urine, and feces	HPGPC-FD the fluorescence intensity of sample	Detected in serum and most (92.274%) of LBP-FITC was excreted from urine and feces	[33]
Mulberry fruit polysaccharides	91	FITC	ig	Serum, heart, liver, spleen, lung, kidney, intestine, and stomach	Fluorescence spectrum (sample), and HPGPC (molecular weight)	Absorbed into the blood and with the highest concentration in the intestine, followed by the stomach, liver, and kidney	[34]
Fucoidan	Nm	Nm	Topically applied, iv	Serum, skin, and muscle	Detect anti-Xa activity (amide hydrolysis assay, heparin kit) to reflect the anticoagulant activity of the ointment	Fucoidan in ointments penetrated the skin barrier and accumulated in the striated muscle	[35]
GLP	108	FITC	ig	Duodenum, small intestine, and cecum	Fluorescence spectrophotometer (tissue)	GLP was taken by Caco-2 cells through the pathway of micropinocytosis, in which sugar transporters (SGLT1 and GLUT2) play an important role	[36]
AOs	Nm	Nm	ig	Serum and urine	LC-MS detection of serum (heparin treated) and urine (ammonium formate buffer treated)	AOs are quickly absorbed by the digestive organs and excreted in the urine	[37]

(*Continued*)

Table 2
(Continued)

Polysaccharide/ oligosaccharide	Molecular weight (KDa)	Marking method	Dosing method	Detection sample	Detection method	Whether it can be absorbed and its absorption mechanism	Ref.
Chitooligosaccharides	Nm	ABEE	ig, iv	Serum and urine	HPLC detection of serum (heparin treated) and urine	Chitooligosaccharides are absorbed into the blood	[38]
Arabinogalactan	12.6	FITC	iv	Serum, liver, kidney, lung, spleen, and brain	HPGPC detection of sample (TFA and NAOH treated)	Absorbed into the blood and uptake by parenchymal liver cells *via* the asialoglycoprotein receptor	[39]

ABEE: *p*-Aminobenzoic ethyl ester; AOs: Alginate oligosaccharides; AOSs: Agaro-oligosaccharides; CLSM: Laser scanning confocal microscope; COS: Chito-oligosaccharide; Cy5.5: Cyanine 5.5; FITC: Fluorescein isothiocyanate; GLP: Ganoderma lucidum polysaccharide; GLUT2: Glucose transporter 2; HPAEC-PAD: High-performance anion-exchange chromatography with pulsed amperometric detection; HPGPC-FLD: High-performance gel permeation chromatography with a fluorescence detector; HPLC-MS/MS: High performance liquid chromatography-tandem mass spectrometry; ig: Intragastric; iv: Intravenous; LBP: *Lycium barbarum* polysaccharides; LC-MS: Liquid chromatography-mass spectrometry; MLN: Mesenteric lymph node; NIRF: Near-infrared fluorescence; Nm: Not mentioned; SGLT1: Sodium-glucose linked transporter 1; TFA: Trifluoroacetic acid; UPLC-MS: Ultra-performance liquid chromatography-mass spectrometry.

a fluorescence detector (HPGPC-FLD). Additionally, the distribution of pumpkin polysaccharides labeled with Cy5.5, in mice was observed using near-infrared fluorescence (NIRF) *in vivo* imaging technology. We also investigated the absorption mechanism of pumpkin polysaccharides by Caco-2 and RIN-m5F cells. These findings indicate that the distribution of pumpkin polysaccharides was higher in the liver, kidney, and bladder of mice than in other tissues. Moreover, pumpkin polysaccharides enter the blood stream through clathrin- and caveolin-related pathways. Moreover, Chen et al.[31] developed a sensitive and selective UPLC-MS method for the direct measurement of chitobiose (COS 2) and chitotriose (COS 3) in rat serum and tissues, with the kidney emerging as the primary site of accumulation. Despite these advancements, the aforementioned studies did not examine the bioavailability of polysaccharides or elucidate the specific form in which polysaccharides act within the body (ie, polysaccharides, oligosaccharides, or monosaccharides).

Fluorescence labeling offers the advantage of quantifying polysaccharide content and determining whether polysaccharides are degraded by the HPGPC fluorescence peak[40]. Kaneo et al.[39] investigated the plasma clearance and biological distribution of FITC-labeled arabinogalactan (FA) in rats after intravenous injection. They observed that FA was cleared from the plasma after 30 min and was primarily distributed in the liver and kidneys after 2 h. Specific high-performance size-exclusion chromatography was used to determine the molecular weight (Mw) of the FA in the liver and kidneys. The results indicate that the Mw of FA remained unchanged in the liver but was decreased in the kidneys. Nevertheless, the fluorescence labeling of polysaccharides has limitations as follows[39,41]. 1. Photoquenching and photobleaching: Fluorescent labels may be affected by photoquenching and photobleaching, resulting in signal attenuation or disappearance, limiting long-term observation and quantitative analysis; 2. Autofluorescence: Some samples may exhibit autofluorescence, which may interfere with the detection and analysis of fluorescent labels. 3. Limited penetration depth: The penetration depth of fluorescent signals is limited, which imposes certain limitations when examining deep tissue and *in vivo* research. Additionally, the use of radioactive isotopes for polysaccharide detection offers greater sensitivity than fluorescence, enabling the detection of non-concentrated tissues (eg, muscles, bones, and joints)[22] and excretion, and allows for a detailed analysis of their distribution in organs and blood. With advancements in imaging technology, radioactive isotopes serve as effective imaging probes, particularly for *in vivo* imaging, providing clear visualization of the pharmacokinetics of polysaccharides within living organisms. This method offers unique advantages for revealing the *in vivo* behavior of polysaccharides. However, radioisotope-labeled polysaccharides also have several drawbacks as follows. 1. Radiation hazards: The use of radioisotopes requires strict radiation safety measures and compliance operations involving radiation safety issues; 2. Short half-life: Some radioisotopes have a short half-life, which limits the tracking time; 3. Expensive and technically demanding: The labeling process requires specialized techniques and equipment, and the operator must possess relevant knowledge and skills.

In summary, with the application of modern biochemical technology, the pharmacokinetic absorption of polysaccharides into the bloodstream has gradually been elucidated, encompassing various pathways. Mechanisms, such as paracellular transport, intestinal epithelial endocytosis mediated by the macropinocytosis pathway, and absorption facilitated by clathrin- and caveolin-related pathways are involved (Figure 1). Fluorescent labeling of polysaccharides is both safe and convenient, enabling the quantitative detection of polysaccharides in biological samples and the qualitative exploration of their degradation within the body. This method offers a versatile approach, as allows for the detection of polysaccharides and provides insight into their biological degradation. Radioisotope labeling of polysaccharides offers increased sensitivity in the detection limits of these molecules in biological samples and allows for the visualization of their distribution *in vivo*, making it a valuable tool for research. The choice of the labeling method is crucial for the effective detection of polysaccharides *in vivo*, as it can be tailored for specific experimental purposes and combined with different detection strategies to provide a comprehensive understanding of the pharmacokinetics of polysaccharides and aid in the interpretation of the study results.

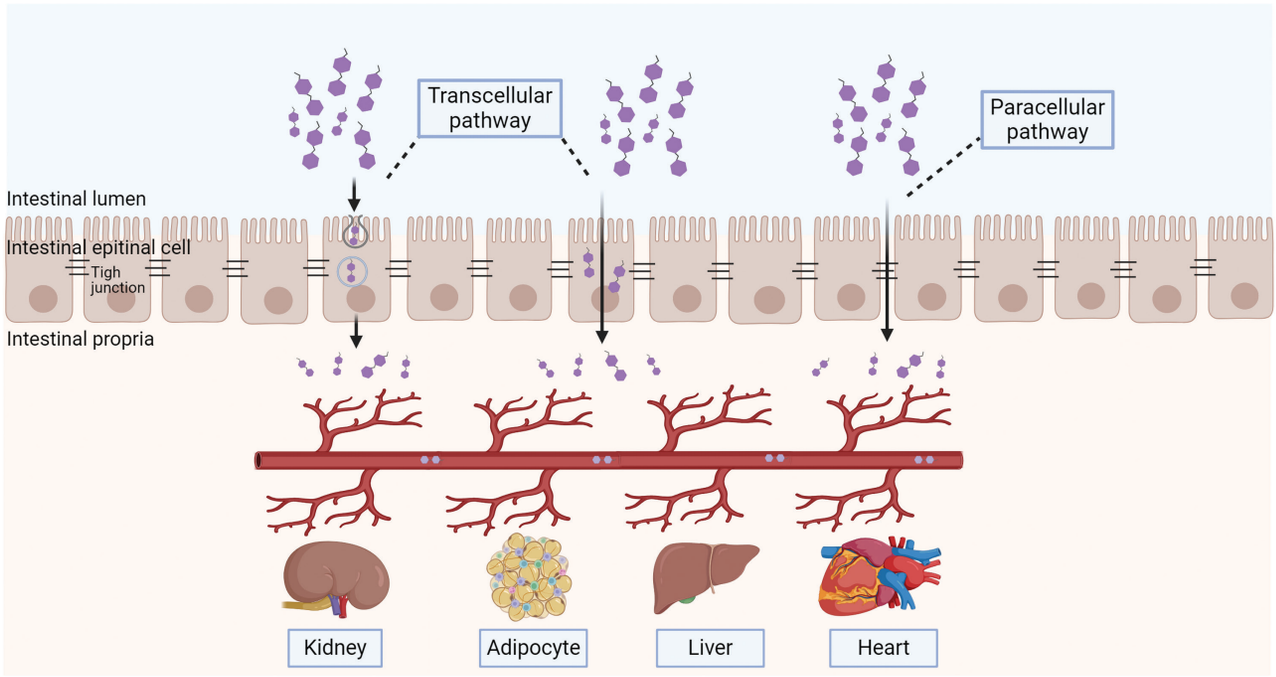


Figure 1. Polysaccharide pharmacokinetics. Polysaccharides can enter the bloodstream through the transcellular and paracellular pathways (eg, micropinocytosis, clathrin- and caveolin-related pathways), binding with target organs to activate the body's immune system.

Immunological regulation of polysaccharides via Peyer's patches (PPs) and mesenteric lymph nodes (MLNs)

The second hypothesis is that polysaccharides or oligosaccharides can initiate an adaptive intestinal immune response *via* PPs or MLNs. Radix Astragali polysaccharides (RAP) have poor bioavailability, but significant anti-tumor activity[42] and can protect against chemotherapy-induced myelosuppression following oral administration[43]. Previous studies have revealed that RAP can rapidly induce immune responses in PPs of the small intestine within one hour, a finding corroborated by *in vitro* experiments with macrophages[44]. Consequently, it is plausible to hypothesize that RAP and other TCM polysaccharides may enter PPs and directly interact with immune cells to initiate immune responses.

The human body is continuously exposed to pathogenic bacteria and viruses but is able to maintain homeostasis through the immune system, which comprises the primary (thymus and bone marrow) and secondary lymphoid systems (spleen, lymph nodes, and mucosa-associated lymphoid tissue [MALT])[45–46]. MALT is a crucial physical and immune barrier against harmful substances and pathogenic bacteria[47]. The largest MALT area is found in the gut-associated lymphoid tissue, which consists of PPs, the lamina propria, and MLNs. PPs, known as induction sites, secrete IgA to the mucosal surface and activate B, T, and dendritic cells (DCs) in response to antigens from the intestinal lumen. This results in IgA secretion, which neutralizes pathogens, and the production of cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6), thus, ultimately contributing to systemic immune activation[48–49]. Additionally, Paneth cells in the intestinal epithelium secrete α-defensin-1 (crytidin; an antimicrobial peptide) in response to bacteria, lipopolysaccharide (LPS), lipid A, and muramyl dipeptides[50–51]. Of note, due to the lack of digestive enzymes, most plant polysaccharides cannot be directly digested or absorbed by the human body[52]. These polysaccharides affect the intestinal microenvironment in two ways. First, the gut microbiota can convert plant polysaccharides into short-chain fatty acids (SCFAs) and carbon monoxide, which further participate in the body's energy metabolism and immune response[53]. Consequently, they influence the abundance, variety, and proportion of the host intestinal microbiota. Second, microfold cells (M cells) cover the surface of the intestine. PPs serve as important immune induction sites in the intestinal mucosal immune system, facilitating the transfer of macromolecular substances to immune cells and the subsequent activation of the intestinal immune response[54]. These intricate processes emphasize the vital role of MALT and its components in immune defense.

After oral administration, many polysaccharides induce rapid immune responses in mice[55–56]. The immunomodulatory effects of these polysaccharides *in vivo* are likely due to their interaction with the lymphatic system in the small intestine in combination with the gut microbiota in the large intestine. However, the rapid immune response induced by oral polysaccharides in the small intestine cannot be solely explained by the interaction between prebiotics (polysaccharides) and the gut microbiota, because such interaction takes time[57]. Consequently, there may be a pathway through which polysaccharides act *in vivo*, independently of blood and gut microbiota.

Understanding how polysaccharides enter the immune system may open opportunities for the future development of oral delivery of polysaccharide-based vaccines or drugs. This hypothesis was explored by Zhang et al.[58] using RAP as an example. The authors first established that the anti-tumor activity of RAP is

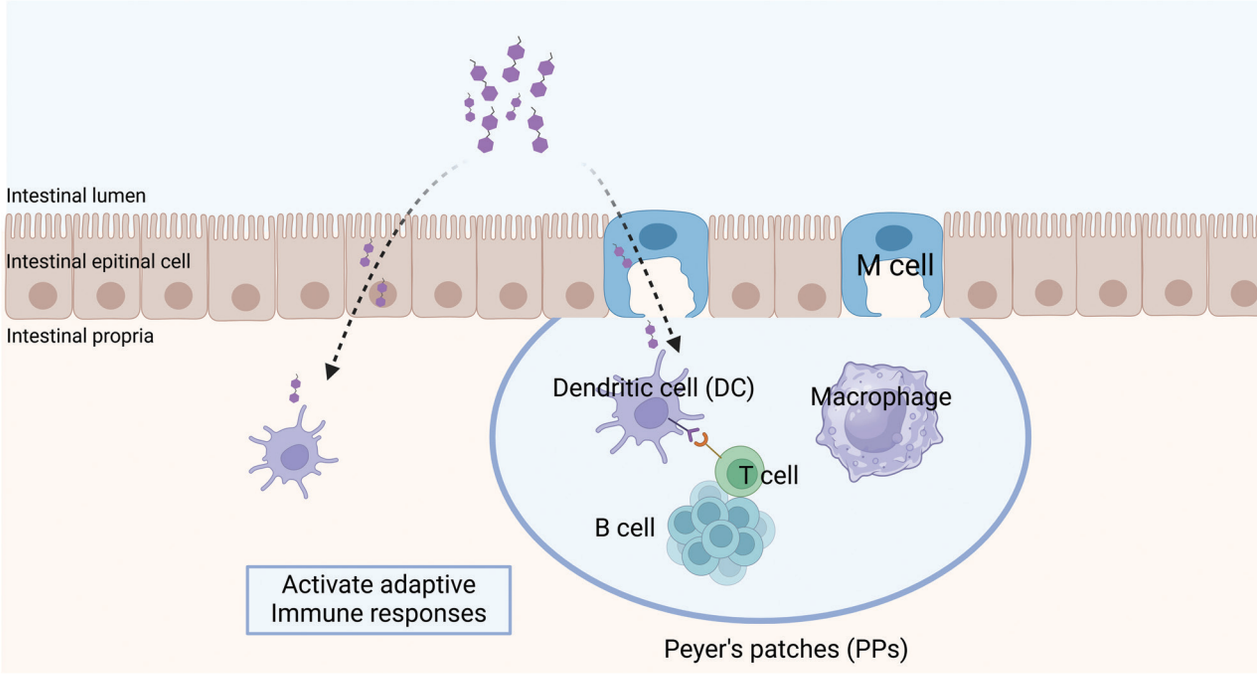


Figure 2. Immunological regulation of polysaccharides *via* Peyer's patches and mesenteric lymph nodes.

immune-dependent. Subsequently, they observed that RAP was not degraded, was not absorbed, and rapidly entered the PPs within one hour of oral administration. RAP directly targets follicular DCs and initiates an anti-tumor immune response. These findings suggest that oral RAP can directly interact with immune cells and trigger an anti-tumor immune response without relying on the selective lymphatic pathway of the blood/gut microbiota. Further research by Zhang et al.[59] indicated that microfold (M) cells located in PPs act as transporter cells that independently transport RAP into the lymphatic system to trigger immune responses. Additionally, the authors hypothesized that the receptor mediating M-cell transversion of RAP is TLR4/GP2[59]. Chen et al.[60] utilized an intestinal perfusion model (jejunum, 10 cm, with only one PP) to explore the immune response of Coptis chinensis Franch polysaccharides (CCP) to PPs. They examined the expression of cytokines in PPs through immunohistochemical staining and found that CCP dynamically promoted the production of cytokines and influenced the ratio of interferon-gamma (IFN-γ)/IL-4 and IL-17/transforming growth factor-beta (TGF-β), indicating its regulatory effect on the intestinal immune microenvironment. Park et al.[61] directly interacted PP cells with Korea Red Ginseng-Derived Polysaccharide (KRG-P) to explore the immunomodulatory effect of KRG-P on PPs. They observed that PPs were stimulated to produce GM-CSF and IgA, and induced bone marrow cell proliferation *in vitro*. Furthermore, oral administration of KRG-P (5 and 50 mg/kg) increased IgA secretion in mouse feces on day 11, suggesting that KRG-P stimulated Peyer's patch immune cells to produce cytokines and IgA to maintain homeostasis in the intestinal cavity.

PPs are lymphatic tissues located in the lower mucosa of the small intestine and constitute a vital component of the intestinal adaptive immune system. Investigations on the activation of the intestinal adaptive immune response by polysaccharides or oligosaccharides through PPs have demonstrated that polysaccharides can serve as antigens for intestinal immunity. Polysaccharides can enter PPs *via* M cells by interacting with specific immune cells within the assembly, thereby stimulating DCs and activating B cells. In the presence of polysaccharides, DCs express costimulatory molecules that facilitate T-cell activation and proliferation. Additionally, B cells interact with polysaccharides to produce antibodies and immunoglobulins that regulate the balance of the intestinal adaptive immune response, while promoting either immune tolerance or an active immune response (Figure 2). Notably, the structure and characteristics of polysaccharides play a pivotal role in determining their antigenicity and immune activity. Table 3 presents evidence of the direct activation of intestinal adaptive immune responses by polysaccharides or oligosaccharides through PPs and MLNs.

Antibacterial effects of polysaccharides by avoiding their invasion

The third hypothesis was that polysaccharides in glycosylated molecules bind specifically to pathogens to reduce the risk of infection in the host. Numerous studies have highlighted the antibacterial properties of the polysaccharides from various sources. These polysaccharides exhibit varying antibacterial activities, which are largely influenced by differences in the bacterial surface structures. The initial step for polysaccharides to exert their antibacterial effects involves their adsorption onto the surface of bacterial cell membranes. The adsorption process relies on the unique structural characteristics of polysaccharides, enabling them to interact with the cell membrane through diverse mechanisms, such as hydrophobic interactions, electrostatic adsorption, or

Table 3

Immune responses by polysaccharides *via* PP and MLNs

Polysaccharide/ oligosaccharide	Molecular weight (KDa)	Marking method	Dosing method	Detection sample	Detection method	Immune response mechanism	Ref.
Astragalus hyperbranched heteroglycan	1334	FITC	ig	Small intestine (mice), PPs (mice), and distal ilea (human)	HPGPC-FLD (cell culture medium), confocal laser microscope (small intestine)	M cells in the follicle-associated epithelial of PPs mediate transcytosis of astragalus polysaccharide	[59]
Astragalus hyperbranched heteroglycan (RAP)	1334	FITC	ig	Intestinal contents, liver, spleen, kidney, stomach, small intestine, MLNs, PPs, cecum, and colon	Phenol-sulfuric acid method (intestinal contents), HPGPC-FLD (serum and tissues)	Intact RAP could quickly enter the lymphatic system after oral administration and directly target FDCs to initiate immune responses	[58]
CCP	Nm	FITC	Intestinal perfusion, ig	Jejunum, intestinal contents, and tissues (jejunum)	Fluorescent labeling (jejunum), ELISA (IFN-γ, IL-4, IL-17, and TGF-β), 16S rDNA sequence	CCP can be absorbed by PPs and promotes the secretion of IFN-γ, IL-4, IL-17, and TGF-β, regulate the diversity, composition, and distribution of gut microbiota	[60]
KRG-P	106	Nm	ig	PPs (mice)	HPSEC (molecular weight of KRG-P), ELISA (GM-CSF, IgA)	KRG-P can stimulate PP immune cells and produce cytokine IgA, activating intestinal immunomodulatory activity	[61]
Lentinan	5	Nm	ig	Spleen, thymus, and intestine	PPs were co-incubated with M cells, ELISA (IgA)	Lentinan can increase the number of PPs, lymphocytes in PPs, intestinal soluble IgA levels, and the number of M-like cells in immunosuppressed mice	[62]
GLP	Nm	Nm	ig	IEL, PBMC, and PPL	GLP was co-incubated with immune cells PBMC, IEL, and PPL. ELISA (IL-10 and IL-2) and RT-PCR (IL-10 and TNF-α)	GLP can stimulate the proliferation of PBMC and PPL, promote the production of IL-2 and IL-10, and stimulate intestinal immune response	[63]
α-D-Glucan (MPG-1)	Nm	pAb	ig, ih	Serum, intestinal tract, MLNs, PPs, spleen, and liver	ELISA (MPG-1 of serum, IL-12 of spleen and liver), immunostaining of tissues	MPG-1 was confirmed to localize in PPs, MLN and the spleen, promotes the production of IL-12, absorbed into the blood and stimulates the systemic immune system	[64]
Spirulina polysaccharide	Nm	FITC	ig	PPs and spleen	ELISA (IgA and IL-6 of PPs, IFN-γ of spleen)	Activates monocytes and NF-κB through CD14- and TLR2-dependent processes, increasing IgA and IL-6 production by PPs and IFN-γ production by splenocytes	[65]
Fructooligosaccharides	Nm	Nm	Feeding	PPs	Immunofluorescence and fluorescence-activated cell sorting	Maintained more lymphocyte subsets (CD19, CD3, CD4, and CD8 cells) in the PP of endotoxemic animals, leading to increased CD4:CD8 ratio during endotoxemia and activation of intestinal immunity receptor	[66]

CCP: Coptis chinensis Franch polysaccharides; ELISA: Enzyme-linked immunosorbent assay; FDC: Follicular dendritic cell; FITC: Fluorescein isothiocyanate; GLP: Ganoderma lucidum polysaccharide; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HPGPC-FLD: High-performance gel permeation chromatography with a fluorescence detector; HPSEC: High-performance size exclusion chromatography; IEL: Intraepithelial lymphocytes; IFN: Interferon; ig: Intragastric; ih: Subcutaneous injection; IL: Interleukin; iv: Intravenous; KRG-P: Korea Red Ginseng-derived polysaccharide; MLN: Mesenteric lymph node; MPG-1: α-D-glucan; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Nm: Not mentioned; pAb: Polyclonal antibody; PBMC: Peripheral blood mononuclear cells; PP: Peyer's patches; PPL: Peyer's patches lymphocytes; RAP: Radix Astragali polysaccharides; RT-PCR: Reverse transcription polymerase chain reaction; TGF-β: Transforming growth factor-beta.

interactions between glycoprotein receptors and the cell membrane[67] (Figure 3).

Some plant polysaccharides contain proteins or polyphenols that impart hydrophobic characteristics, enabling them to bind to the lipid bilayer of bacterial cell membranes through hydrophobic–hydrophobic interactions[68]. This interaction facilitates the passive diffusion of polysaccharides through the lipids of the

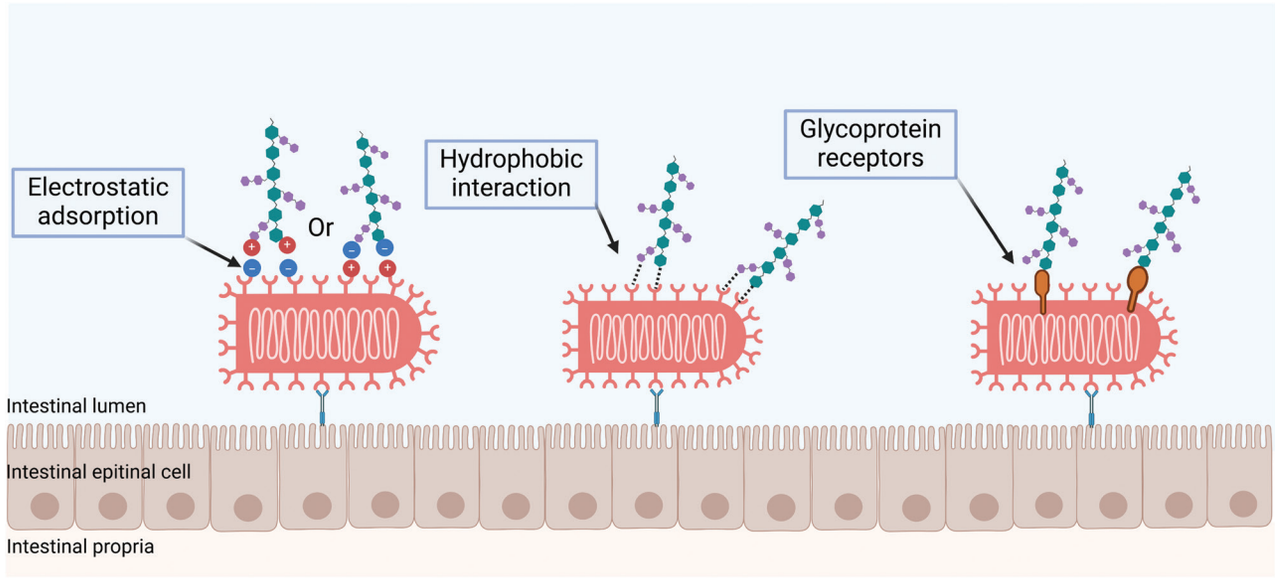


Figure 3. Antibacterial effects of polysaccharides. Polysaccharides can bind pathogenic bacteria through electrostatic adsorption, hydrophobic interaction, and glycoprotein receptors to prevent their invasion into the host.

cytoplasmic membrane bilayer into the bacterial cytosol, causing the escape of intracellular components and disruption of bacterial enzyme systems. Certain polysaccharides interact with the cell membrane surface *via* electrostatic adsorption. For example, chitosan, a cationic polysaccharide, binds to bacterial cell membranes *via* electrostatic adsorption, thereby displaying antibacterial properties[69]. Moreover, glycoprotein receptors present on the surface of some algal polysaccharides aid in their recognition and binding to bacterial surfaces. This interaction alters the permeability of bacterial cell membranes, leads to the degradation of bacterial cell wall structures, triggers cell death, and ultimately inhibits bacterial proliferation[70].

Polysaccharides exhibit antibacterial activity *via* various mechanisms after adsorption onto bacterial cell membrane surfaces *via* hydrophobic interactions, electrostatic adsorption, or glycoprotein receptors. These mechanisms include increasing the permeability of the cell membrane, inhibiting the adsorption of pathogenic bacteria by host cells, blocking transmembrane transport of nutrients or energy substances, and affecting bacterial nucleic acids (Table 4).

Increasing the permeability of the cell membrane

Some plant polysaccharides display antibacterial activity by increasing membrane permeability, which can lead to a rapid increase in the amount of water-soluble proteins in cells, protein dissolution, DNA degradation, leakage of essential molecules, and cell death[87]. The depolymerized fucoidans from *Laminaria japonica* resulted in the collapse of the cell membrane and leakage of the absorbent material at 260 nm; these changes eventually resulted in cell death[88]. Polysaccharides from fresh sarcotesta of *Ginkgo biloba* can reduce polysaccharide intercellular adhesion and secretion by inhibiting the expression of icaA, icaB, icaC, and icaD, thereby inhibiting the biofilm formed by *Staphylococcus aureus*[89].

Inhibition of the adsorption of pathogenic bacteria by host cells

In addition to inhibiting bacterial growth, some plant polysaccharides prevent the adhesion of pathogenic bacteria to the host cells. Polysaccharides extracted from ginseng roots and licorice inhibit the adhesion of *Helicobacter pylori* to the human gastric mucosa. However, ginseng polysaccharides do not inhibit the adhesion of all bacteria to human cells, such as *Lactobacillus acidophilus* and *Escherichia coli*, suggesting that they have selective anti-adhesion activity[90–91]. Several potential mechanisms may explain the anti-adhesive activity of plant polysaccharides. *Panax ginseng* polysaccharides contain a large number of uronic and galacturonic acids, which contain negatively charged groups that play a role in host-bacterial adhesion[90]. The anti-adhesion properties of polysaccharides may also be related to their anti-biofilm formation ability of extracellular polysaccharides. Polysaccharides may alter the physical properties of bacteria. The differences in the cell surfaces of Gram-negative bacteria, such as *E. coli* and *Salmonella enteritidis* might explain the selective adhesion of plant polysaccharides to different bacteria[92].

Blocking the transmembrane transport of nutrients or energy substances

Plant polysaccharides can block the absorption of nutrients by bacteria and affect energy metabolism, leading to inhibition of bacterial growth and death. The antibacterial activities of polysaccharides may stem from their ability to act as a barrier preventing the entry of nutrients[93]. Yerba mate polysaccharides have shown antibacterial activities against various strains, except *E. coli*. The antibacterial activities of the polysaccharides may also stem from their ability to inhibit iron absorption by bacteria. Iron is an important element for bacterial growth. *E. coli* can secrete enterobacteria, which have a high affinity for iron; consequently, the absorption of iron by bacteria

Table 4

Polysaccharides as antibacterial by avoiding their invasion

Polysaccharide/ oligosaccharides	Mechanism of action	Ref.	Polysaccharide/ oligosaccharides	Mechanism of action	Ref.
Chitosan	Biofilm quorum sensing and formation	[71]	Chitosan	Change the permeability of bacterial cell walls	[72]
Pleurotus fanata Mynuk mycelium exopolysaccharide extract	Biofilm adhesion	[73]	Chitosan	Destroy bacterial cell wall	[74]
Chitosan	Biofilm formation	[75]	Chitosan	Change the carbohydrate groups of the bacterial cell wall	[76]
Sulfated acidified polysaccharide extracted from Chlamydomonas reinhardtii	Biofilm formation	[77]	Cicada flower polysaccharide	Increase cell wall permeability	[78]
Xanthan gum oligosaccharide	Biofilm formation	[79]	Chitosan deacetylated	Cell membrane permeability, proteins, mobility, and enzyme activity	[76]
Probiotic extracellular polysaccharide	Biofilm formation	[80]	Chaetomium polysaccharide	Destroy cell membrane integrity	[81]
Cordyceps sinensis polysaccharide	Acting cell membrane protein	[78]	Sulfated polysaccharide extracted from Chlamydomonas reinhardtii	Affects the topology of DNA	[77]
Streptomyces virginia H03 polysaccharide	Change cell membrane potential	[76]	Cicada flower polysaccharide	Inhibits expression of fungal proteins	[78]
Probiotic extracellular polysaccharide	Change cell membrane hydrophobicity	[82]	Low molecular weight chitosan	Inhibits mRNA synthesis to inhibit protein synthesis	[83]
Xanthan gum oligosaccharide	Acts on cell membrane calcium and magnesium ions, affecting ATPase activity	[79]	Chlamydomonas reinhardtii sulfated polysaccharide	Influence metabolic activity and kill bacterial cells	[77]
Chitosan	Block bacterial DNA transcription	[84]	Chitosan	Inhibits phospholipid metabolism in cell membranes	[76]
Streptomyces subtilis H03 polysaccharide	Binding to plasmid DNA molecules	[85]	Amaranth polysaccharide	Interfere with glycolysis and gluconeogenesis processes	[86]

ATP: Adenosine triphosphate.

is inhibited after the addition of plant polysaccharides[94]. Plant polysaccharides can also affect energy metabolism. For example, Quadrupole Time-of-Flight Mass Spectrometry (high performance liquid chromatography [HPLC]/Q-TOF-MS) was used to investigate anti-*E. coli* mechanism of Tetrastigma hemsleyanum Diels et Gilg's polysaccharide (TP). The result showed that TP obstructs *E. coli*'s glycolysis and gluconeogenesis, and therefore, leading to *E. coli*'s death because lacking of adenosine triphosphate (ATP) or nicotinamide adenine dinucleotide (NADH)[86].

The effect of polysaccharides on bacterial nucleic acids

In addition to damaging cell wall and cell membrane integrity, antibacterial polysaccharides can also affect the nucleic acids of foodborne pathogens. Fei Liu et al.[84] reported that FITC-labeled chitosan oligomers (MW = 5,000 and 8,000 Da) could penetrate *E. coli* cells and showed good antibacterial activity by blocking DNA transcription and interfering with RNA molecules. Chitosan can also penetrate bacterial cells *via* binding to DNA molecules and inhibiting RNA synthesis, thereby inhibiting bacterial growth of bacterium[95]. Arpornmaeklong et al.[83] reported that low Mw chitosan could inhibit the mRNA synthesis of bacteria, and Vishwakarma and Vavilala[77] found that sulfated polysaccharides extracted from *Chlamydomonas reinhardtii* could decrease eDNA quantity during the biofilm formation process of *Neisseria mucosa*, *E. coli*, *Streptococcus* sp., and *Bacillus subtilis*. However, polysaccharides are bonded to single-stranded DNA or double-stranded DNA[96], and whether the polysaccharides affect the topology of DNA[97] or degrade DNA or RNA[98] needs to be studied in detail in the future.

The effect of polysaccharides through their intestinal metabolites

The fourth hypothesis proposed is that polysaccharides are metabolized by the gut microbiota into SCFAs to regulate the immune response. SCFAs play a crucial role in providing energy to intestinal cells, reducing the incidence of inflammatory diseases, and regulating the innate

and adaptive immune systems. The human gut microbiome consists of trillions of microorganisms in a complex ecosystem, making it not only the largest organ for digestion and absorption but also a vital defense barrier for the human body. The normal mucosal barrier is designed to protect the host from harmful substances and pathogens while allowing for proper absorption. However, a compromised intestinal mucosa leads to increased intestinal permeability, resulting in the passage of harmful substances and pathogens into the bloodstream, ultimately causing inappropriate immune responses and persistent inflammatory events, such as inflammatory bowel disease (IBD) and obesity[99–101]. Furthermore, the gut microbiota produce various metabolites from dietary products that significantly impact host health and host pathophysiological functions. Notably, the intestinal microorganisms and their metabolites play a critical role in the immune response owing to their close contact with intestinal epithelial cells[102]. Over the past few decades, rapid advancements in microbiomics and metabolomics have confirmed that natural polysaccharides can improve innate and adaptive immunity through their metabolism to SCFAs. SCFAs activate immune-related cells, promote cytokine and chemokine production, and play multiple roles in immune regulation.

Liang et al.[103] conducted a study on the immunomodulatory effects of *Flammulina velutipes* polysaccharide on immunosuppressed mice, focusing on the role of the gut microbiota. The study found that oral administration of *F. velutipes* polysaccharides led to an increase in the relative abundance of SCFA producers, such as *Bacteroide* and *Alloprevotella*, ultimately improving the structure of the gut microbiota and maintaining intestinal homeostasis. Additionally, *Hericium erinaceus* polysaccharides have been shown to possess unique properties in preventing gastritis, ulcers, and diseases of the digestive system diseases[104]. Furthermore, it has been demonstrated to alter the structure of the intestinal flora in immunosuppressed mice, specifically by upregulating the relative abundance of SCFA-producing bacteria, including *Alistipse*, *Uncultured_bacterium_f_Muribaculaceae*, and *Lachnospiraceae_NK4A136*_group and downregulating the relative abundance of *Lactobacillus*, *Bacteroides*, and *Alloprevotella*. This shift results in increased levels of SCFAs, activation of their related receptors, and subsequent activation of the TLR4/NF-κB pathway. These processes stimulate cytokine secretion, ultimately enhancing immunity in immunosuppressed mice[105]. The results indicate that polysaccharides can modulate the composition of the intestinal microbiota in animals to varying extents, leading to an increase in the abundance of SCFA-producing bacteria. Moreover, a significant elevation in the levels of SCFAs can lead to activation of their receptors and enhancement of the immune response (Table 5).

The gut microbiota can metabolize the body's indigestible prebiotic polysaccharides into a variety of primary and secondary metabolites including SCFAs, such as acetic acid, propionic acid, and butyric acid, which regulate the body's immunity[111]. These SCFAs act through G protein-coupled receptors, namely, GPR43, GPR41, and GPR109a. First, SCFAs can stimulate goblet cells to produce mucus and activate inflammasomes, which in turn promote the secretion of IL-18 by intestinal epithelial cells, thereby enhancing the epithelial barrier[112]. Furthermore, SCFAs can inhibit nuclear class I histone deacetylase (HDAC) activity and inactivate the NF-kB signaling pathway, leading to the suppression of proinflammatory factors and nitric oxide (NO) production by DCs and macrophages[113]. SCFAs can also modulate Treg cells and GPR109a to regulate anti-inflammatory cells, resulting in the production of TGF-β and IL-10[114]. Additionally, SCFAs can drive plasma B-cell differentiation by elevating cellular energy and lipid biosynthesis levels[115] (Figure 4).

The effect of polysaccharides as prebiotics

The fifth hypothesis is that the interaction between polysaccharides and intestinal bacteria increases the growth of beneficial bacteria to improve host health. Polysaccharides can act as prebiotics[116] and are mainly sourced from indigestible oligosaccharides. These polysaccharides are absorbed by a specific group of anaerobic beneficial bacteria including *Lactobacillus*, *Bifidobacterium*, *Roseburia*, *Faecalibacterium, Anaerostipes*, and *Coprococcus*[117]. These bacteria possess symbiotic members that produce carbohydrate-active enzymes (CAZymes)[118], enabling the creation of various active metabolites including monosaccharides, oligosaccharides, organic acids (eg, ethanol, lactic acid, and succinic acid), and SCFAs (eg, acetic acid, propionic acid, and butyric acid). The production of these metabolites is beneficial to human health[119]. For example, they can lower the intestinal pH, thereby inhibiting the growth of certain pathogenic bacteria[120]. They can also provide a nourishing growth environment and serve as nutrients for certain beneficial bacteria, ultimately increasing their relative abundance to improve health.

For the evaluation of prebiotics, *in vitro* batch fermentation models have been employed to simulate the anaerobic mixing of intestinal cultures, nutrients, and prebiotics to assess intestinal performance[121–123]. Currently, established prebiotics include inulin-derived fructans (inulin and fructooligosaccharides [FOS]), galactans (galactooligosaccharides [GOS]), and lactulose[124]. These compounds have been found to selectively enhance the populations of *Bifidobacterium* and *Lactobacillus*, which are recognized beneficial bacteria and serve as common prebiotic benchmarks[124]. The prebiotic effect may extend beyond the stimulation of these two microbial targets, potentially offering additional health benefits through a broader range of beneficial bacteria, including SCFA-producing taxa[124]. Furthermore, there is substantial potential for the development of new prebiotic candidates owing to the limited number of available options. In a study by Tian et al.[125], *in vitro* batch fermentation was used to assess the impact of banana powder on the human gut microbial community. These findings revealed that banana powder significantly improved the structure of human gut microbiota, promoted the growth of *Bifidobacterium* and *Bacteroides*, and facilitated the production of beneficial SCFAs (acetate, propionate, and butyrate). Another study investigated the prebiotic activity of barley β-glucan by co-fermenting it with four lactic acid bacteria strains

Table 5

Polysaccharides that regulate immune responses through SCFAs

Polysaccharide/ oligosaccharide	Immunosuppression model	Dosing method	Relative abundance increased	Relative abundance decreased	Increased SCFA	Immune response mechanism	Ref.
Hericium erinaceus polysaccharides	CTX-induced immunosuppression	ig	*Alistipseuncultured_bacterium_f_ Muribaculaceae,Lachnospiraceae_ NK4A136_group, uncultured_bacterium_f_ Lachnospiracea,uncultured_ bacterium_f_Ruminococcaceae and Ruminococcaceae_UCG-014*	*Lactobacillus, Bacteroides,* and *Alloprevotella*	Acetate, propionate, butyrate, and valerate	Changed the composition of gut microbiota, increased the levels of SCFAs, activated their receptors, and ultimately activated the TLR4/NF-κB pathway, improving the immune level of mice	[106]
Astragalus polysaccharides	Nm	Feeding	*Lactobacillus* and *Bacillus*	*Vibrio* and *Aeromonas*	Acetate, propionate, and butyrate	Increase the content of SCFAs and brain neurotransmitter γ-aminobutyric acid, total blood cell count, protein concentration, phenoloxidase activity, serum agglutination titer and lysozyme activity	[107]
Phellinus igniarius polysaccharides	CTX-induced immunosuppression	ig	*Bacteroides acidifaciens, Lactobacillus murinus, Parabacteroides gordonii, Parabacteroides goldsteinii, Bacteroides caecimuris, B. stercorirosoris, Clostridiales bacterium, Clostridium* sp.	*Hepaticus, urinaeequi*	Acetate, propionate, butyrate, and valerate	Affects cell proliferation, stimulates the secretion of IL-2, IL-6, and IFN-γ, and inhibits the expression of TNF-α. In addition, it enhances the immunity of mice with low immune function and significantly affects the gut microbiota and the content of SCFAs	[108]
Rehmannia glutinosa polysaccharides	LPS-induced intestinal inflammation and barrier injury	ig	*Lactobacillus* and *Akkermania*	*Actinomycetes*	Acetate, propionate, and butyrate	Modulates the intestinal structure of LPS mice, produces SCFAs, and increases the expression of proteins ZO-1 and Occludin. Reduced the expression of IL-6, IL-17, IL-1β, and TNF-α	[109]
Lentinan	IHNV-induced microbiota disorder and barrier injury	Feeding	*Carnobacterium* and *Deefgea*	*Mycobacterium* and *Nannocystis*	Acetic acid, butanoic acid, and hexanoic acid	Regulates the autometabolic pathway of intestinal flora induced by hematopoietic necrosis virus IHNV, improves fatty acid metabolism, amino acid metabolism, and SCFAs metabolism, and jointly exerts an antiviral effect on IHNV infection	[110]

CTX: Cyclophosphamide; IFN: Interferon; ig: Intragastric; IHNV: Infectious hematopoietic necrosis virus; IL: Interleukin; iv: Intravenous; LPS: Lipopolysaccharide; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Nm: Not mentioned; SCFAs: Short-chain fatty acids; TLR4: Toll-like receptor 4.

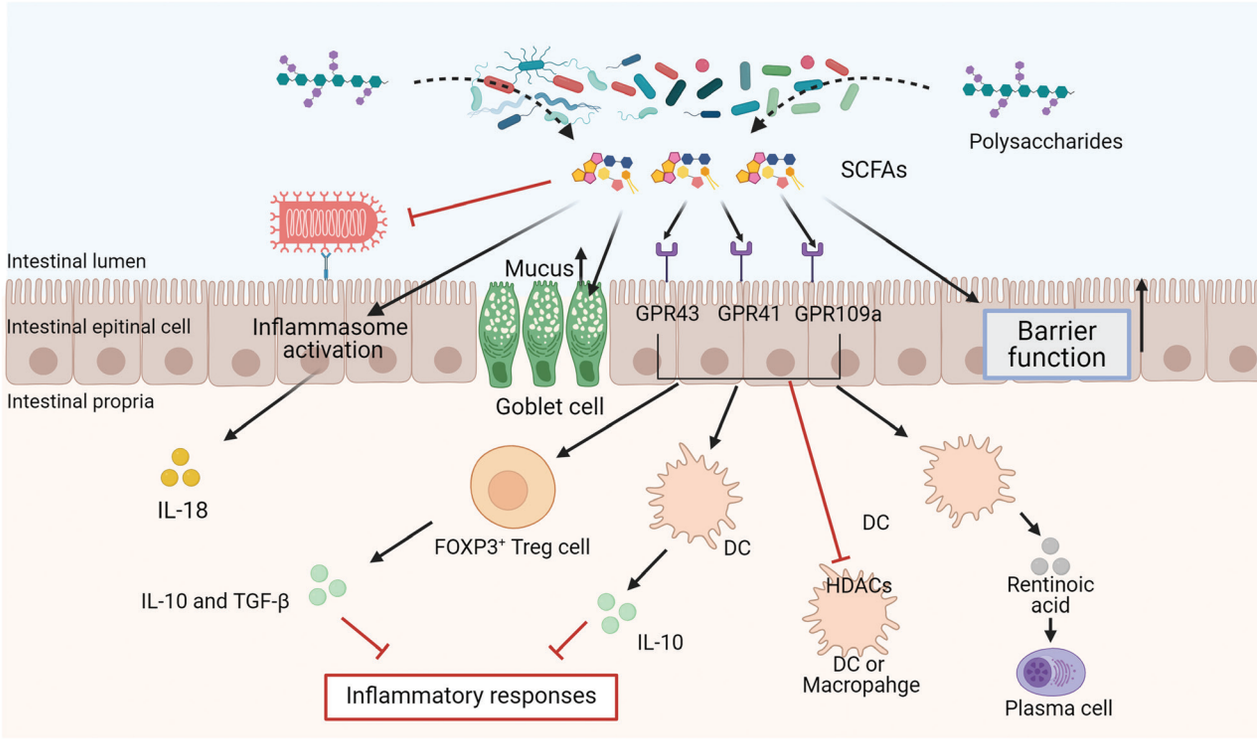


Figure 4. The effect of polysaccharides through their intestinal metabolites of SCFAs. SCFAs can enhance the intestinal epithelial connection function and activate inflammasomes by directly interacting with intestinal epithelial cells but also trigger immune responses by binding to specific receptors on targeted immune cells. DC: Dendritic cells: HDAC: Histone deacetylase; IL: Interleukin; SCFA: Short-chain fatty acids.

(*Lactobacillus acidophilus* LA5, *Lactobacillus plantarum* WCFS1, *Lactobacillus plantarum* CETC 8328, and *Lactobacillus fermentum* CECT 8448) through an *in vitro* digestive tract simulation model. The results indicated that *L. plantarum* and *L. acidophilus* selectively utilized barley β-glucan for growth, highlighting the strain-specific prebiotic activity of barley β-glucan[116].

Polysaccharides act as prebiotics for the gut microbiota, promoting the growth of beneficial commensal bacteria and reshaping the structure of the gut microbiota in pathological states, ultimately improving overall health. *Lycium barbarum* L. oligosaccharide (LBO)[126] has been shown to increase the abundance of the beneficial bacteria *Bacillus*, *Tyzzerella*, *Fournierella*, and *Coriobacteriaceae* UCG-002, leading to reduced serum inflammatory factors and liver hydroxyproline levels, thereby improving liver fibrosis in mice. *Cistanche deserticola* polysaccharide (CDP)[127] has the potential to promote osteoblast differentiation by increasing the relative abundance of SCFA bacteria (*Desulfovibrio* and *Ileibacterium*), while rebalancing the Th17/Treg cell balance and reducing pro-inflammatory factors. *Polygonatum odoratum* polysaccharide (POP)[128] can reduce the abundance of *Klebsiella* and increase the relative abundances of *Muribaculaceae*, *Prevotellaceae* UCG-001, and *Ruminococcus* which inhibit M1 macrophage polarization and pulmonary anti-inflammatory factor production. Polysaccharides from *Angelica sinensis* aboveground parts[129] have been reported to increase *Lactobacillus*, *Akkermansia*, and *Stenotrophomonas* relative abundances, which inhibit TLR4/MyD88/NF-κB pathway resulting in improved colitis symptoms.

The study of the brain-gut axis is a hot topic and further studies are warranted. The gut microbiota is considered the second brain of the human body, with polysaccharides playing pharmacological roles through this axis. Xie et al.[130] proposed that targeting the gut microbiota with polysaccharides could coordinate epilepsy treatment by regulating inflammatory factors, neurotransmitter ion channels, and antioxidant responses. Fecal microbiota transplantation experiments have shown that *Polygonum multiflorum* polysaccharide[131] can exert an antidepressant effect through the gut microbiota *via* the PI3K/AKT/TLR4/NF-κB signaling pathway. Luo et al.[132] proposed that *Polygonatum sibiricum* polysaccharides can reshape gut microbiota, increase the relative abundance of *Akkermansia muciniphila*, decrease the relative abundance of *H. pylori*, and prevent intestinal barrier loss, inflammatory response, and intestinal Aβ deposition, as well as improve pathological behaviors related to memory and cognition in the mouse brain, and prevent the synaptic loss, enhance the microglial phagocytosis of Aβ plaques, ultimately improve Alzheimer disease (Figure 5).

Under certain conditions, the microbes inhabiting the gut can establish beneficial, neutral, or harmful relationships with the host[133]. Prebiotics, which are indigestible and not absorbable by the human body, can promote the growth of beneficial symbiotic bacteria, such as *Bifidobacterium* and *Lactobacillus*, through fermentation within the intestinal flora. This can prevent disorders related to the gut microbiota, restrain the proliferation of tissue pathogens, improve gastrointestinal diseases, enhance systemic immune responses, and ultimately contribute to the overall health of the host. Table 6 provides an overview of current research on polysaccharides as prebiotics that facilitate the growth of beneficial commensal bacteria.

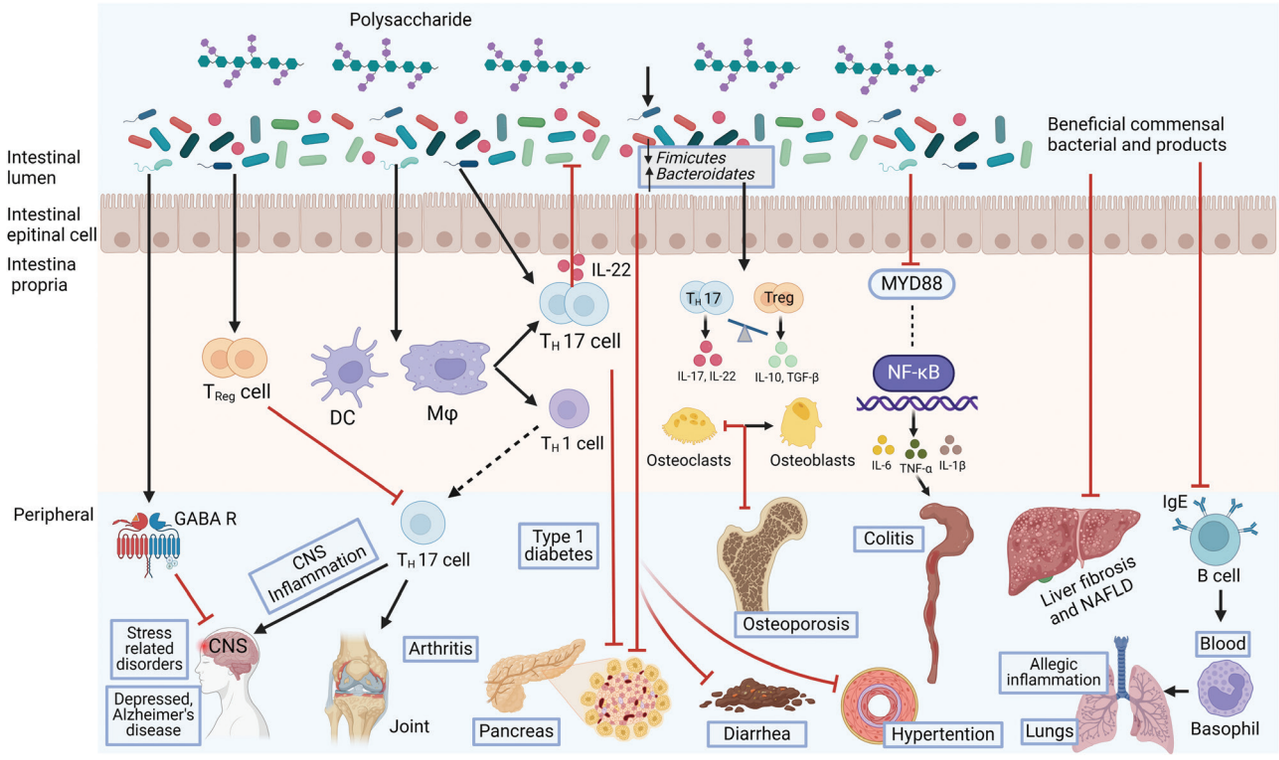


Figure 5. The effect of polysaccharides as prebiotics. Polysaccharides can prevent the development of different diseases after being metabolized by gut microbiota. CNS: Central nervous system; DC: Dendritic cells; GABA: Gamma-aminobutyric acid; IL: Interleukin; NAFLD: Non-alcoholic fatty liver disease; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; TGF: Transforming growth factor.

Indirect effects

The effect of polysaccharides on reducing phytochemical toxicity

The clinical applications of TCM have spanned thousands of years. Compatibility is the essence of all compound formulae. Importantly, the compatibility of TCM not only reduces toxicity and enhances synergy but also dominates the chemical composition in the phase and is closely related to different drug release behaviors. The advent of high-throughput sequencing has greatly enhanced TCM studies on the effects of decoctions. Zhou et al.[149] studied the effect of Du-Shen-Tang on overfatigue and acute cold stress models and explored the synergistic effects of polysaccharides and small molecules. The results showed that ginseng polysaccharides in the decoction can improve intestinal metabolism and absorption of ginsenosides, and at the same time, enhance gut microbiota homeostasis by promoting the abundance of *Lactobacillus* spp. and *Bacteroides* spp., two major bacteria that metabolize ginsenosides. In contrast, *Tripterygium wilfordii* possesses a good therapeutic effect on specific diseases, such as inflammatory lesions associated with leprosy and rheumatoid arthritis[150]. Its two main formulations, ethyl acetate and chloroform methanol extracts, have been commercialized and widely used in China[151]. However, many studies have reported side effects and toxicity, such as leukopenia and thrombocytopenia[152]. The water decoction of *tripterygium wilfordii* seems to be more suitable and its water-soluble ingredients may contribute to its efficacy, while minimizing potential toxicity. Luk et al.[153] indicated that the anti-inflammatory effect of the aqueous extract of *tripterygium wilfordii* was superior to that of the ethanol extract, with a significant anti-inflammatory effect observed in the polysaccharide fraction. In a related study, Shao et al.[154] compared the effects of an ethyl acetate extract and a crude hot water-soluble polysaccharide fraction from *tripterygium wilfordii* on the anti-inflammatory activity and cytotoxicity of macrophages. Both extracts reduced NO accumulation in macrophages in a dose-dependent manner. However, the crude polysaccharide fraction significantly decreased cytotoxicity.

Huanhuan et al.[155] conducted a study on the compatibility and attenuation of toxicity of *Euodiae Fructus-Glycyrrhizae Radix* et *Rhizoma* by employing chemical composition research using fingerprints. The results indicate that *Glycyrrhizae Radix et Rhizoma* polysaccharide serves as the material basis for reducing alkaloids, which are toxic components of *Euodiae Fructus*. This suggests that the alkaloids in *Euodiae Fructus* and the chemical components of *Glycyrrhizae Radix* et *Rhizoma* combine to alleviate the toxicity of *Euodiae Fructus*, possibly through the interaction of polar groups, such as hydroxyl groups. The compatibility of TCM typically leads to pharmacological effects, such as toxicity attenuation and increased efficacy. These effects are usually evaluated by observing the behavior and death of animals after administration, organ index, physiological or pathological morphology of tissues and organs, and biochemical indicators of drug efficacy or toxicity. The attenuating effect of TCM compatibility can be attributed to the antagonism between its components, which enhances the protective effect on the body by reversing the abnormal indicators produced by toxic

Table 6

Polysaccharides as prebiotics for promoting the growth of beneficial symbiotic bacteria

Polysaccharide/ oligosaccharides	Research model	Increased relative abundance of beneficial symbiotic bacteria	Prebiotic activity	Ref.
Xanthan gum, gellan gum, pullulan, and curdlan oligosaccharides	*In vitro* fermentation with human fecal bacteria	*Bifidobacterium, Bacteroides*	More enriched in *Bifidobacterium* and *Bacteroidetes*, respectively, and were accompanied by an increase in SCFA levels	[134]
Banana powder	*In vitro* fermentation with human fecal bacteria	*Bacteroides* and *Bifidobacterium*	Promoting the growth of *Bifidobacterium* and *Bacteroidetes*, and can produce acetate, propionate, and butyrate	[125]
Aalactoglucomannan and arabinoglucuronoxylan	*In vitro* fermentation with human fecal bacteria	*Bifidobacterium, Lactobacillus,* and *Bacteroides*	Increasing the relative abundance of *Bifidobacterium*, *Lactobacillus*, and *Bacteroides*, with levels of butyrate and propionate	[135]
Barley β-glucans	*In vitro* fermentation with human fecal bacteria	*Lactobacillus plantarum* and *Lactobacillus acidophilus*	Increasing the relative abundance of *Lactobacillus plantarum* and *Lactobacillus acidophilus*, enhancing the adhesion ability of probiotics to Caco-2 cells	[116]
Arabino-oligosaccharides	*In vitro* fermentation with human fecal bacteria	*Bifidobacterium adolescentis, Bifidobacterium longum,* and *Bacteroides vulgatus*	Increasing the relative abundance of *Bifidobacterium adolescentis*, *Bi. longum*, and *Bacteroides vulgatus*	[136]
LBO	16Sr RNA gene sequencing	*Bacillus*, *Tyzzerella*, *Fournierella*, and *Coriobacteriaceae* UCG-002	Reducing inflammatory and improving intestinal and liver mitochondrial function, and ameliorated liver fibrosis in mice	[126]
DHP	16Sr RNA gene sequencing	*Bifidobacterium animalis* and *Clostridium disporicum*	Promoting the production of intestinal-derived spermidine, indole, and androsterone and inhibiting hepatic lipid synthesis, and reversing liver damage	[137]
CDP	16Sr RNA gene sequencing	*Desulfovibrio* and *Ileibacterium*	Improving intestinal mucosal damage, increase SCFA levels, rebalance Th17/Treg cell balance, and potentially promote osteoblast differentiation	[127]
OCPs	16Sr RNA gene sequencing	*Muribaculaceae_norank*, *Prevotellaceae*_UCG-001, and *Alloprevotella*	Triggering the PI3K/Akt/GSK-3β signaling pathway and modulating gut microbiota	[138]
POP	16Sr RNA gene sequencing	*Muribaculaceae*, *Prevotellaceae* UCG-001, and *Ruminococcus*	Reducing the abundance of Klebsiella, and inhibits the production of lung pro-inflammatory molecules by inhibiting iNOS M1 macrophages	[128]
Angelica sinensis aboveground part polysaccharide	16Sr RNA gene sequencing	*Lactobacillus*, *Akkermansia*, and *Stenotrophpon*	Improving colitis by regulating intestinal flora and TLR4/MyD88/NF-κB pathway	[129]
Pericarpium Citri Reticulatae "Chachiensis" polysaccharide	16Sr RNA gene sequencing	*Lactobacillus johnsonii*	Enriching *Lactobacillus johnsonii* at the family-genus-species level, exerting anti-obesity effects	[139]
PSP	16Sr RNA gene sequencing	*Bacteroidota*	Improving cognitive function in aged mice and regulate oxidative stress through the "microbiota-gut-brain" axis	[140]
APS	16Sr RNA gene sequencing	*Lactobacillus* and *Akkermansia*	Improving pulmonary fibrosis through the TLR4/NF-κB signaling pathway and intestinal microbiota homeostasis regulation	[141]
DOPS	16Sr RNA gene sequencing	*unclassified_f__Lachnospiraceae*, *Romboutsia*, *Blautia*, *Turicibacter*, and *norank_f__norank_o__Clostridia*_UCG-014	Reversing metabolic hypertension in rats by activating the intestinal SCFAs-GPCR43/41 pathway	[142]

(*Continued*)

Table 6
(Continued)

Polysaccharide/ oligosaccharides	Research model	Increased relative abundance of beneficial symbiotic bacteria	Prebiotic activity	Ref.
QWBZP	16Sr RNA gene sequencing	*Bacteroidales*	Promoting the growth of *Bacteroides* and inhibiting the reproduction of *Enterococci*, thereby effectively treating diarrhea	[143]
GP	16Sr RNA gene sequencing	*Lactobacillus*, *Bacteroides*, and *Akkermansia* spp	Regulating intestinal bacteria changes serum metabolite composition, and improves oxidative stress capacity and inflammation	[144]
PSPs	16Sr RNA gene sequencing	*Akkermansia muciniphila*	Reducing the relative abundance of *Helicobacter pylori* and increases *Akkermansia muciniphila*. preventing intestinal barrier integrity damage, inflammatory response and intestinal Aβ deposition	[132]
CPP	16Sr RNA gene sequencing	*Lactobacillus*	Enriching probiotic lactic acid bacteria and significantly changes amino acids, organic acids, fatty acids, carbohydrates and carnitine, etc, thereby treating spleen deficiency symptoms	[145]
GPS	16Sr RNA gene sequencing	*Bacteroides*	Improving cholestatic liver injury by regulating intestinal flora and inhibiting the TLR4/NF-κB pathway	[146]
Polysaccharide and glycoside (TPG) from *Aralia echinocaulis*	16Sr RNA gene sequencing	*Proteobacteria*, *Acidobacteria*, and *Gemmatimonadetes*	Regulating circulatory system, excretory system, metabolic diseases, signaling molecules and interactions, coenzyme transport and metabolism, and nucleotide transport, thereby improving arthritis	[147]
GCP	16Sr RNA gene sequencing	*Enterorhabdus*, *Odoribacter*, *Ruminococcaceae*, *Ruminiclostridium*, *Lachnospiraceae*	Inhibiting tumor growth *in vivo* and exerts its effect by affecting intestinal flora.	[148]

APS: Astragalus polysaccharide; CDP: Cistanche deserticola polysaccharide; CPP: Codonopsis pilosula polysaccharide; DHP: Dendrobium huoshanense polysaccharide; DOPS: Dendrobium officinale polysaccharide; GCP: Glycyrrhiza polysaccharide; GP: Gracilariopsis lemaneiformis polysaccharide; GPCR: G protein-coupled receptor; GPS: Gardenia jasminoides Ellis polysaccharide; ig: Intragastric; iNOS: Inducible nitric oxide synthase; iv: Intravenous; LBO: Lycium barbarum L. oligosaccharides; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; Nm: Not mentioned; OCP: *Ornithogalum caudatum* Jacq. polysaccharides; PI3K/Akt/GSK: Phosphoinositide 3-Kinase/protein kinase B (Akt)/glycogen synthase kinase; POP: Polygonatum odoratum polysaccharide; PSP: Polygonatum sibiricum polysaccharides; QWBZP: Qiweibaizhu powder crude polysaccharide; SCFAs: Short-chain fatty acids; TLR4: Toll-like receptor 4; TPG: Total polysaccharide and glycoside.

components. Paclitaxel, a complex secondary metabolite of the genus Taxus, promotes microtubule polymerization and stabilizes polymerized microtubules, thus exhibiting high anti-tumor activity. However, its clinical use often results in severe toxic side effects including bone marrow suppression, liver and kidney toxicity, neurotoxicity, allergic reactions, cardiotoxicity, myalgia, and gastrointestinal reactions[156]. In a study by Xiaofang et al.[157], Lycium barbarum polysaccharides were found to have synergistic and attenuated effects on paclitaxel in the treatment of endometrial cancer. The results showed that Lycium barbarum polysaccharides can alleviate side effects caused by paclitaxel including weight loss, immune function, and hematopoietic function. Concurrently, it improves liver and kidney functions, and regulates the oxidative stress response and immunity through the Nrf2 signaling pathway, thereby reducing paclitaxel-induced toxicity. Similarly, Wei et al.[158] found that southern *Taxus mairei* polysaccharide could reduce the toxic side effects of bone marrow transplantation caused by Taxol's anti-tumor effects. Furthermore, the combination of CDP, alginate oligosaccharide (AO), and chitosan oligosaccharide (CO) with Polygoni Multiflori Radix has been shown to regulate the verification reaction and alleviate the immune specificity of Polygoni Multiflori Radix, thus mitigating its hepatotoxicity[159].

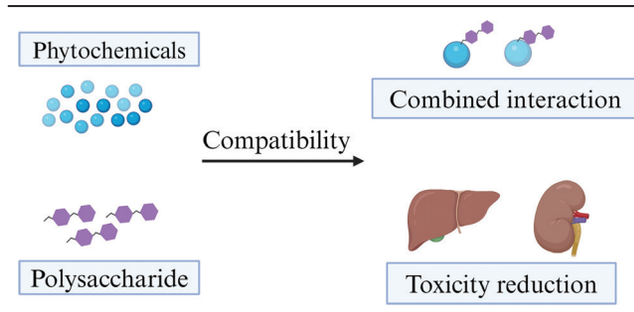


Figure 6. Polysaccharides in TCM decoctions can directly change the molecular structure of toxic components or reverse the abnormal indexes caused by toxic components, thereby reducing phytochemical toxicity. TCM: Traditional Chinese medicine.

These findings demonstrate the role of polysaccharides in enhancing efficacy of TCM decoctions, while minimizing potential toxicity. Specifically, the polysaccharides in TCM decoctions can directly interact with toxic components, thereby altering the molecular structure of the target and reducing its toxicity. Additionally, these polysaccharides can reverse abnormal indicators caused by toxic components to enhance body defense, contributing to the compatibility and attenuation effects (Figure 6). Table 7 provides a summary of research evidence demonstrating how the combination of TCM

Table 7

Polysaccharides that reduce phytochemical toxicity in traditional Chinese medicine

Toxic substance	Attenuating substance	Attenuated form	Attenuation mechanism	Ref.
Polygoni Multiflori Radix	Cistanchedeserticola polysaccharide, alginate oligosaccharide, chitosan oligosaccharide	Compatibility, *in vivo* intervention in mice	The metabolism of anthraquinones (emodin) in Polygoni Multiflori Radix extract causes liver damage. Polysaccharides regulate the inflammatory response and alleviate the immune-specific liver injury caused by Polygoni Multiflori Radix extract	[159]
Euodiae Fructus	*Glycyrrhizae Radix* et *Rhizoma* polysaccharide	Compatibility, *in vitro* composition analysis	It is speculated that the alkaloids in *Euodiae Fructus* may combine with polar groups such as hydroxyl groups in the chemical components of Glycyrrhizae Radix et Rhizoma, thereby mitigating the toxicity of *Euodiae Fructus*	[155]
Paclitaxel	Lycium barbarum polysaccharide	Compatibility, *in vivo* intervention in mice	Lycium barbarum polysaccharide improved the liver and kidney functions of mice, facilitated the metabolic degradation and efflux of excess paclitaxel, and reduced the aggregation and toxicity of paclitaxel in the body	[157]
Taxol	*Taxus mairei* polysaccharide	Compatibility, *in vitro* cell intervention, *in vivo* mouse intervention	*Taxus mairei* polysaccharide can enhance the inhibitory effect of paclitaxel on 4T1 and A549 cells *in vitro*, and reduce the myelosuppressive side effects of taxol in its anti-tumor treatment *in vivo*	[158]
Paclitaxel	*Astragalus* polysaccharide	Compatibility, *in vitro* cell intervention, *in vivo* mouse intervention	Astragalus polysaccharide prolongs the lifespan of tumor-bearing mice induced with paclitaxel. In addition, paclitaxel obviously causes cell cycle arrest mainly in the G2/M phase and produces cytotoxicity to RAW 264.7 cells, while astragalus polysaccharide blocks cell cycle arrest. and protect cells from apoptosis	[42]
Paclitaxel	*Pinus koraiensis* polysaccharide	Compatibility, *in vitro* cell intervention, *in vivo* mouse intervention	*Pinus koraiensis* polysaccharide-loaded gel showed excellent tumor inhibitory effects on 4T1 and MCF-7 breast cancer cell lines *in vitro* and significant tumor growth inhibition and reduced systemic toxicity *in vivo*	[17]

MCF: Michigan Cancer Foundation.

polysaccharides with other TCM ingredients results in toxicity mitigation.

The effect of polysaccharides on improving activities of phytochemicals

Recently, polysaccharides have been widely used as biomaterials for solubilizers, stabilizers, and oral delivery systems because of their low toxicity and high biocompatibility[160].

As solubilizers, they enhance the solubility of the target substance in the solvent and improve its utilization efficiency. Cyclodextrins (CDs), which are cyclic oligosaccharides comprised of 6, 7, or 8 glucose residues linked by α (1–4) glycosidic bonds, have been employed as adjuvants for the extraction of water-insoluble substances such as flavonoids, volatile oils, and glycosides, thereby enhancing the solubility and stability of these water-insoluble substances[161]. Flavonoids exhibit diverse biological activities, including free radical scavenging, antioxidant, anti-cancer, anti-aging, liver protection, anti-inflammatory, and immunity enhancement properties, and thus have significant potential for applications in the health food and pharmaceutical industries[162]. Nonetheless, the pharmaceutical utilization of flavonoids is limited by their low solubility, instability, and remarkably low water solubility, ultimately leading to poor bioavailability[163–164]. To address this issue, CD has been shown to increase the solubility of flavonoids by encapsulating them in the cavities[165]. Moreover, the complex formed by combining Cordyceps militaris polysaccharides with flavonoids, such as dihydromyricetin (DMY), not only contributes to stability and solubility but also enhances the biological activity by forming a new complex[166].

Additionally, research shows that a complex between pectins and tannins can reduce the astringency that develops during persimmon fruit ripening. This is significant because some oligomeric and polymeric alkanols such as condensed tannins have antioxidant, anti-inflammatory, and atherosclerosis-preventing activities[167]. However, these compounds pose a challenge for food applications owing to their strong bitterness and astringency, which negatively affect the sensory quality of the food. Furthermore, when polysaccharides are used as stabilizers, they can enhance the stability of the target substance in the gastrointestinal tract, thereby increasing the flux of the target substance across the intestine and improving their bioavailability[168].

Tea polyphenols[169], anthocyanins[170], and curcumin[171] are the active ingredients of TCM and exhibit promising pharmacological activities, including antioxidant and anti-inflammatory effects. However, their clinical application is hindered by poor oral absorption due to their extremely low water solubility and rapid metabolism. Consequently, the low serum and tissue levels of these compounds, regardless of the route of administration, greatly restrict their bioavailability. To overcome these limitations, chitosan nanoparticles[171], β-glucan,[172] and pectin[173] have emerged as promising drug delivery carrier systems due to their distinctive structural characteristics. Furthermore, compounds such as conjugated linoleic acid (CLA) are susceptible to autooxidation in ambient oxygen. In response, arabinogalactans and β-(1,3)-glucans have been employed as drug delivery carriers to enhance the stability of the complex

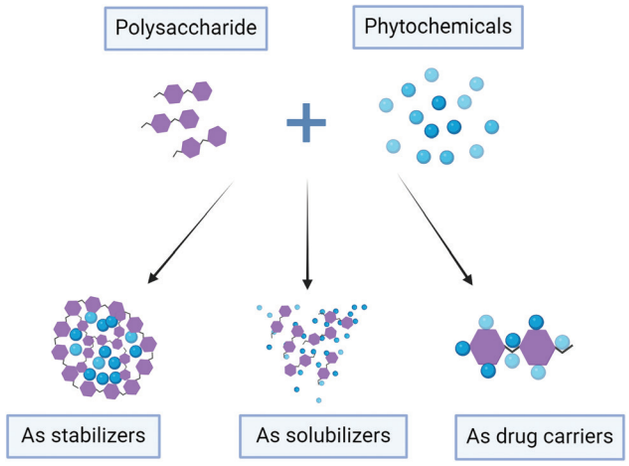


Figure 7. Polysaccharides applications as stabilizers, solubilizers, or drug carriers of phytochemicals into the body.

and effectively shield the CLA from oxidation during processing[174].

Limited solubility, instability, and poor bioavailability hinder the development of numerous natural products with favorable biological activities. Polysaccharides can enhance the solubility and stability of compounds through inclusion, grafting, and covalent polymerization techniques (Figure 7). This not only improves compound bioavailability but also enhances its biological activity during complex formation. Table 8 provides an overview of the applications of polysaccharides as stabilizers, solubilizers, and drug carriers for active ingredients.

Conclusion and perspective

Due to recent advances in biochemical reagents and instruments, a deeper understanding of the absorption and mechanism of action of polysaccharides in Chinese herbal decoctions has been made possible. This understanding is of great significance for the development of polysaccharides as drugs, functional foods, and biological materials. This review discussed the direct and indirect effects of polysaccharides in Chinese herbal decoctions, shedding light on their mechanisms of action. Fluorescent labeling technology has been instrumental in revealing how a small number of polysaccharides can be absorbed into the bloodstream, contributing to regulating immunity *via* PPs and MLNs. Polysaccharides offer various benefits to the host, including antibacterial effects, modulation of gut microbiota metabolism, and structural regulation of the gut microbiota. These suggest that polysaccharides, even those indigestible by the host, could indirectly contribute to the therapeutic effects of Chinese herbal decoctions, including reducing phytochemical toxicity, while also enhancing phytochemical benefits.

Understanding the direct and indirect effects of TCM polysaccharides is crucial for establishing a theoretical foundation and research significance for their clinical applications. Pharmacokinetic studies of these polysaccharides laid the groundwork for subsequent clinical investigations. For example, double-blinded, placebo-controlled clinical trials have demonstrated that gels containing fucose can effectively inhibit erythema and water loss resulting from UV-induced inflammation[184]. Moreover, creams containing 4% fucose have been reported to be effective in treating patients with oral herpes[185]. Furthermore, TCM polysaccharides show promise as vaccine adjuvants[186] owing to their immunoboosting, antibacterial, and antiviral properties. Understanding the dose–effect relationship and mechanisms of action is crucial for innovations. Chinese medicinal herb polysaccharides, such as inulin, can serve as prebiotics to regulate the gut microbiota, thereby, addressing metabolic health issues, such as diabetes and lipid metabolism, as well as contributing to immune regulation and gastrointestinal health[187]. The clinical application of polysaccharide-based coatings within drug delivery systems is another way for them to exert indirect efficacy[188]. However, biointegration remains a significant challenge. TCM polysaccharides have been extensively utilized in various therapeutic domains owing to their safety, cost-effectiveness, stability, biocompatibility, and ease of chemical modification. Despite their proven efficacy in different fields, polysaccharide-based drugs have not garnered the same level of attention as drugs derived from proteins or nucleic acids. For the advancement and broader application of polysaccharide-based therapeutics, it is imperative to elucidate their structure–activity relationships, dose–effect correlations, and mechanisms of action.

Conflict of interest statement

Shaoping Li is an editorial board member of this journal. The other authors declare no conflict of interest.

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Author contributions

Wenfeng Xu: Investigation, visualization, writing of the original draft. Shaoping Li: Conceptualization, supervision, writing, reviewing, editing, and funding acquisition. Jing Zhao: Conceptualization, supervision, writing, reviewing, editing, and funding acquisition.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data availability

All relevant data are within the manuscript.

Table 8

Polysaccharides as natural stabilizers, solubilizers, and natural drug carriers of phytochemicals in traditional Chinese medicine

Polysaccharide/ oligosaccharide	Role	Application object (source)	Function	Ref.
β-(1,3)-Glucan	As a stabilizer for nutritional supplements	Folic acid, boswellic acid, ascorbic acid, coenzyme, quercetin and curcumin (standard)	Increased oxidation, heat, and light stability of nutraceuticals. Improve their stability and bioavailability in systems such as food or nutraceutical formulations	[175]
Oat β-glucan	As a stabilizer of tea polyphenols	Tea polyphenols (standard product 98.38%)	Tea polyphenols and β-glucan form a new complex mainly through hydrogen bonds, which not only improves its stability but also enhances its antioxidant activity	[169]
Polysaccharide collamide	As a drug carrier for anthocyanins	Anthocyanins (bilberry extract)	Capsule systems packaged with polysaccharide collamides encapsulate anthocyanins and protect them from early degradation in the small intestine	[170]
Galactomannoside	As a solubilizer for curcumin	Curcumin (turmeric rhizome crude extract)	Compared with unformulated curcumin, the relative absorption rate of curcumin in the novel fiber formulation was 20 times higher in animals and 15.8 times higher in humans, with maximum absorption also being prolonged	[176]
Sephadex	As a stabilizer for anthocyanins	Anthocyanins (black tea strawberry crude extract)	The complex of blackcurrant anthocyanins combined with dextran gel not only enhances stability but also improves its antioxidant capacity	[177]
Pullulan	As a stabilizer for anthocyanins	Anthocyanins (methanolic extract of hibiscus calyx)	The co-lyophilized pullulan-anthocyanin encapsulation system showed improved stability under all relative humidity environments	[178]
Chitosan	As a solubilizer for gallocatechin	Gallocatechin (standard product 95%)	The administration of chitosan enhanced the plasma exposure of gallocatechin by 1.5-fold, increasing its concentration in the gastrointestinal tract and blood	[179]
Chitosan	As a drug carrier for curcumin	Curcumin (standard product)	The binding of curcumin to chitosan nanoparticles increased their chemical stability and bioavailability, and confocal microscopy detected the nanoparticles in the blood of mice	[171]
Dextran	As a drug carrier for resveratrol	Resveratrol (standard product)	Dextran increases the stability of the complex with resveratrol, and the two have a significant synergistic effect, showing a stronger anti-tumor effect	[180]
Cordyceps militaris polysaccharide	As a solubilizer for dihydromyricetin	Dihydromyricetin (isolated and purified from Vine Tea)	The solubility of Cordyceps militaris polysaccharide-dihydromyricetin complex in water increased by three times and the stability increased by 1.34 times. At the same time, it also improved the free radical scavenging effect	[166]
Arabinogalactan and β-glucan	As a stabilizer for conjugated linoleic acid	Conjugated linoleic acid (standard product)	A small part of the conjugated linoleic acid exists in the form of an inclusion complex, and the rest is adsorbed on the surface of the polysaccharide matrix. The stability of the complexed product against heat stress and oxidative stress is significantly improved	[174]
Cellulose and xylan	As a stabilizer for catechins, caffeic acid, and ferulic acid	Catechin, caffeic acid, and ferulic acid (standard product)	The complex formed is held together by hydrogen bonds, increasing stability	[181]
Cellulose	As a stabilizer for cyanidin-3-glucoside, (+/–)-catechin, and ferulic acid	Cyanidin-3-glucoside, (+/–)-catechin, ferulic acid (standard product)	The complex formed is bound by non-covalent interactions (hydrogen bonds and hydrophobic forces), increasing stability	[182]
Tamarind seed xyloglucan	As a stabilizer for epigallocatechin gallate	Gallocatechin gallate (standard product)	The complex formed is held together by hydrogen bonds and hydrophobic interactions, increasing stability	[183]
Pectin	As a stabilizer for persimmon tannins	Tannin (persimmon pulp extract)	The complex formed is held together by hydrogen bonds and hydrophobic interactions, increasing stability	[168]

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