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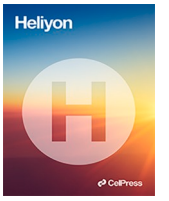

Review article

# Natural polysaccharides regulate intestinal microbiota for inhibiting colorectal cancer

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ABSTRACT

The gastrointestinal tract is an important part of the human immune system. The gut microbiome, which constitutes a major component of the gastrointestinal tract, plays a crucial role in maintaining normal physiological functions and influences the development, diagnosis, and immunotherapy of colorectal cancer (CRC). Natural polysaccharides can be extracted from animals, plants, and traditional Chinese medicines. They serve as an essential energy source for the gut microbiome, promoting probiotic proliferation and regulating the intestinal microecological balance. Moreover, polysaccharides exhibit anti-tumor effects due to their immune regulatory functions and low toxicity. This review focuses on discussing these anti-tumor effects in CRC, along with improving gut microbiome dysbiosis and regulating the tumor immune microenvironment, providing evidence for effective therapeutic strategies against CRC.

## 1. Introduction

Colorectal cancer (CRC) is the most frequently diagnosed malignancy of the digestive system [1–3]. The etiology of CRC is multifaceted and includes epigenetic alterations, familial genetic factors, inflammatory bowel disease (IBD), and environmental susceptibility factors [4–7]. At present, the main ways to prevent the occurrence and development of tumors include inhibiting the proliferation of tumor cells, promoting apoptosis and autophagy, regulating the tumor immune microenvironment (TME), and inhibiting tumor angiogenesis. Emerging evidence has highlighted the significant impact of the gut microbiome on the occurrence and progression of CRC. Recent advancements in high-throughput microbiome sequencing technology have enabled researchers to establish functional relationships among the gut microbiota, immunity, and malignancy. Natural polysaccharides play an indispensable role in modulating and regulating the gut microbiota and have immense potential for CRC prevention and adjuvant therapy.

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Polysaccharides are polymers composed of aldoses or ketoses linked by glycosidic bonds and can be extracted from various food sources [8]. Some studies have suggested that polysaccharides have diverse pharmacological activities, such as anti-tumor, immune regulatory, anti-virus, and hypoglycemic effects [9–13]. As an essential energy source for promoting the growth of gut microbiota, polysaccharides interact with the gut microbiome [14] to promote the proliferation of probiotics. Additionally, polysaccharides enhance organismal immunity and inhibit the growth of tumor cells by regulating intestinal flora imbalance and intestinal bacterial translocation, markedly improving recurrence-free survival (RFS) rates in cancer patients. Owing to their remarkable effects, few side effects, and low toxicity, polysaccharides are widely used as supplementary or alternative therapies for malignant tumors.

In this review, we focus on elucidating how polysaccharides affect CRC progression and TME based on the regulation of gut microbiome. We discuss the relevant intrinsic mechanisms and highlight new approaches that may become potential strategies for CRC adjuvant therapy.

## 2. Role of gut microbiome in CRC

### *2.1. Carcinogenic effects of pathogens in CRC*

The gut microbiome is known as the “human second genome". The main approaches for classifying the composition of the microbiome are 16S ribosomal RNA amplicon sequencing and whole-genome shotgun (WGS) sequencing [15,16]. In healthy individuals, the microbiome is primarily composed of *Firmicutes* and *Bacteroidetes*, with minor components being *Actinobacteria*, *Verrucomicrobia*, and *Proteobacteria*. Recently, several studies have shown that an imbalance in the gut microbiome may play an important role in CRC [17]. Bacteria directly damage the intestinal epithelial cells and induce chronic intestinal inflammatory responses. A growing body of evidence suggests that the abundance of *Bacteroides fragilis, Enterococcus faecalis, Fusobacterium nucleatum,* and other bacteria in the excrement of patients with CRC is higher than that in the healthy population. Dysbiosis contributes to CRC development by promoting tumor cell proliferation, inducing immune evasion, and creating a chronic inflammatory microenvironment [18–21].

It has been reported that *enterotoxigenic B. fragilis* (ETBF) promotes the malignant transformation of colon adenoma to adenocarcinoma. ETBF can induce the activation of signal transducer and activator of transcription 3 (STAT3), interleukin (IL)-17-dependent carcinogenesis, and the expression of spermine oxidase (SMO), leading to increased permeability of the intestinal mucosa, colonic inflammation, and abnormal proliferation of the epithelium. These factors are closely associated with CRC development [22]. In

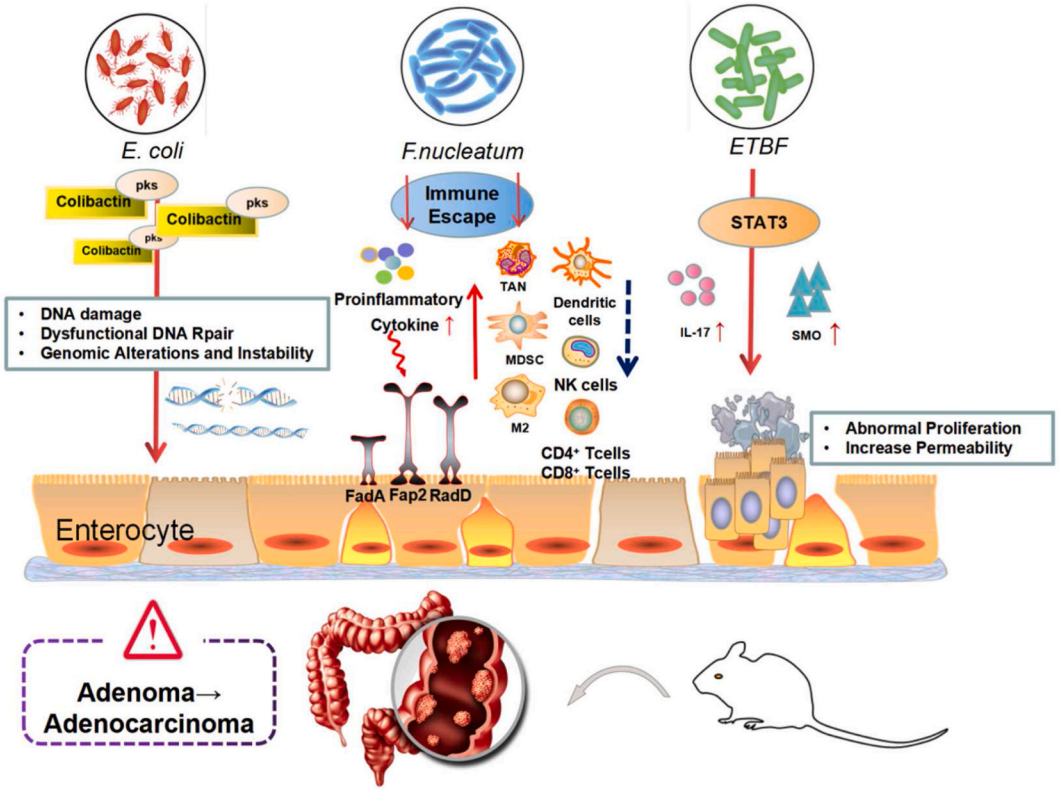


**Fig. 1.** The role of pathogens in CRC and possible mechanisms. Pathogens, such as *ETBF*, *E. coli, F. nucleatum,* and others, can promote CRC development and progress through promoting tumor cells proliferation, inducing immune escape and creating chronic inflammatory tumor microenvironment.

addition, certain species of *Escherichia coli (E. coli)* are considered causative agents of CRC, and studies have shown that *E. coli* increases exponentially in familial adenomatous polyposis and CRC tissues compared to normal mucosa [23–25]. Furthermore, the level of pathogenic *E. coli* in patients with advanced CRC is notably higher than that in patients with early stage CRC [26]. *E. coli* carrying the polyketide synthase (pks) gene synthesizes colibactin, which induces colorectal carcinogenesis by causing DNA damage, dysfunctional DNA repair, genomic alterations, and instability [27,28]. Moreover, the tumor-promoting effect of *E. coli* was also verified *in vivo*, including $Apc^{Min/+}$ mice, azoxymethane (AOM)-treated $IL10^{-/-}$ mice, and $Apc^{Min/+}/IL10^{-/-}$ mice [29–31]. These results also confirmed that IBD in IL-10-deficient mice promoted a specific phenotype of dysbacteriosis, and that mono-colonization with *E. coli* enhanced tumorigenesis in CRC.

*Fusobacterium nucleatum (F. nucleatum)* is another pathogenic bacterium that influences CRC development [32]. On the one hand, *F. nucleatum* promotes CRC proliferation by releasing inflammatory factors in the tumor environment (TME). The cell surface protein FadA can regulate *F. nucleatum* adherence to epithelial cells and immune cells [33], and outer membrane proteins Fap2 and RadD expressed in *F. nucleatum* cause proinflammatory cytokine (including IL-6, CXCL1, IL-8, IL-10, and IL-18) production [34–36]. On the other hand, *F. nucleatum* was shown to lead to immune suppression of the gut mucosa by inducing macrophages to differentiate into the tumor-promoting M2-phenotype, amplifying myeloid-derived suppressor cells (MDSCs) and tumor-associated neutrophils (TANs), suppressing $CD4^{+}T/CD8^{+}T$ helper cells, natural killer (NK) cells, and dendritic cells (DCs) [37–39], all of which could promote tumor growth, immune escape, and resistance to chemotherapy (Fig. 1).

### 2.2. Anti-tumor effects of probiotics in CRC

Probiotics are beneficial to health through playing an anti-inflammatory, anti-cancer, and immune regulation role in body. Probiotics play a significant role in CRC [40] can enhance intestinal mucosal barrier function, and a common feature of CRC is increaProbioticssed tight junction permeability or intestinal mucosal barrier dysfunction, which leads to tumor epithelial-mesenchymal transition (EMT) and metastasis. *E. coli Nissle, Lactobacillus rhamnosus,* and *Lactobacillus plantarum* have been found to improve barrier function by upregulating the expression of tight junction proteins, including zonula occludens protein (ZO)-1, ZO-2, and claudin-1and occludin [41,42]. Probiotics can alleviate the inflammatory microenvironment and promote mucosa

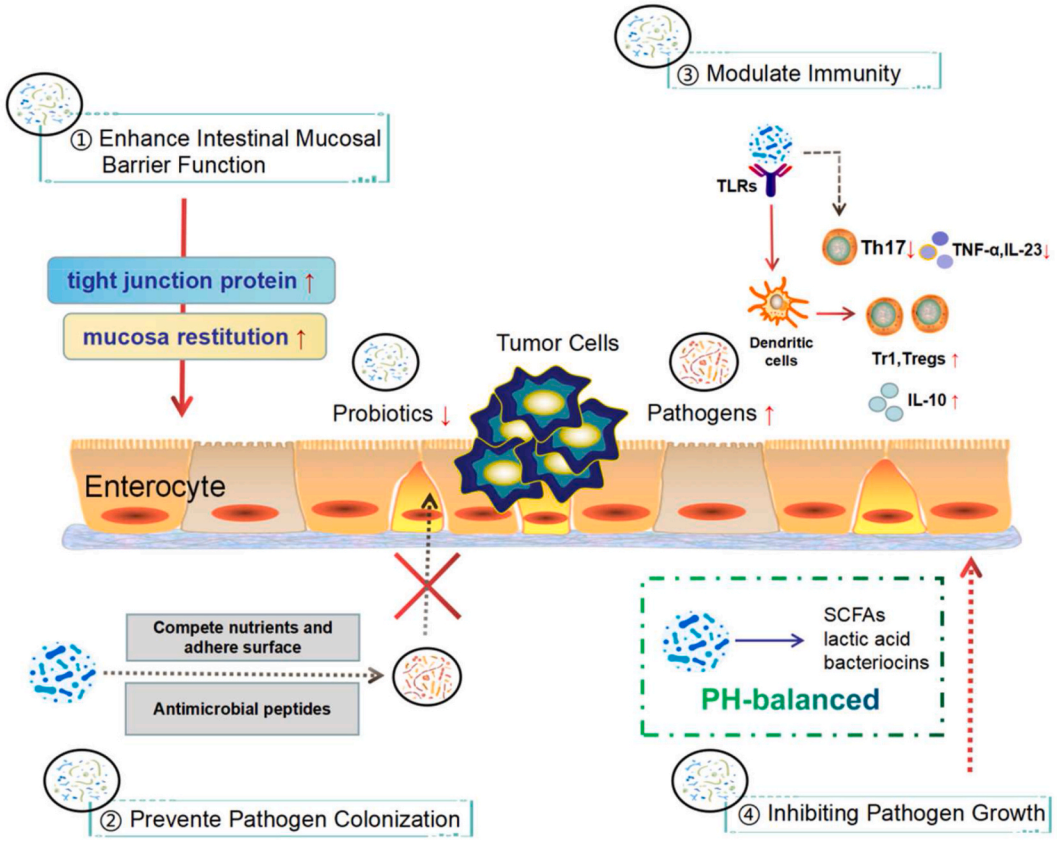


**Fig. 2.** The role of probiotics in CRC and possible mechanisms. Probiotics can intervene in CRC development through enhancing intestinal mucosal barrier function, preventing pathogenic bacteria colonization, modulating immunity directly, and inhibiting pathogen growth indirectly in tumor microenvironment.

restitution [43]. In addition, probiotics can maintain microbial balance by preventing pathogenic bacterial colonization, which could directly prevent intestinal infection [44,45]. In addition to direct interactions, metabolites produced by probiotics, such as acetic acid, lactic acid, and bacteriocins, can regulate intestinal PH to maintain acid-base equilibrium and inhibit pathogen growth [46]. Probiotics can prevent tumor development by excluding pathogenic invasion, lowering the risk of intestinal infection, and reducing complications in patients with CRC.

Probiotics play powerful immunomodulatory roles in the digestive tract. Studies have suggested that *Bifidobacterium breve* and *Bifidobacterium* infantis can bind to Toll-like receptors (TLRs) and activate intestinal dendritic cells (DCs), leading to IL-10 secretion and the increase of the number of type 1 regulatory T cells (Tr1) and Foxp3$^{+}$ regulatory T cells (Tregs) [47,48]. *Lactobacillus acidophilus* can inhibit Th17 cells differentiation, expansion, and function by suppressing IL-23 and TGFβ1 secretion, which can lead to decreasing of proinflammatory cytokine IL-17 and TNF-α secreted by Th17 cells. The expression and phosphorylation of Signal Transducer and Activator of Transcription 3 (STAT3) can upregulate Th17 cell numbers and IL-23 secretion, while *L. acidophilus* inhibits the Th17 cell response to IL-23 and TGF-1 by suppressing STAT3 expression [49]. (Fig. 2). These data suggested that the function of probiotics in suppressing inflammatory microenvironment, and it is considered that regulation of the immune cells and cytokines of TME is beneficial for CRC prevention.

### 2.3. Microbiome as non-invasive diagnostic markers in CRC

The causative relationship between the gut microbiome and CRC development is complex. However, significant progress has been made in identifying the relationship between microbiome signatures and CRC. Studies have shown that the gut microbiome can be used as a potential biomarker for early diagnosis and prognosis for patients with CRC. Researchers analyzed the metagenomic data of excrements from 526 patients with CRC, several enrichment bacteria were found, including *Bacteroides fragilis, Fusobacterium nucleatum, Parvimonas micra, Prevotella intermedia, Alistipes finegoldii,* and *Thermanaerovibrio acidaminovorans.* what is more, *clostridiales cluster* was more prevalent in female patients with CRC [50,51]. In addition, *Firmicutes, Bacteroidetes,* and lactic acid bacteria were markedly decreased in patients with CRC compared with the healthy population [52]. Besides, another large-scale integrated analysis of gut microbiome in patients with late-onset CRC (LO-CRC) and early-onset CRC (EO-CRC), data showed the diversity of gut microbiota was significantly reduced in patients with CRC. Meanwhile, they found that *Fusobacterium nucleatum* enrichment characterises LO-CRC, while multiomics signatures of EO-CRC tended to be related to enrich Flavonifractori plauti. Researchers considered microbiome-derived biomarkers as non-invasive tool to detect and distinguish individuals with EO-CRC [53].

Furthermore, Yu et al. [54] demonstrated that *F. nucleatum* might lead to CRC chemotherapy resistance using bioinformatic and functional studies. Moreover, they found that *F. nucleatum* can target TLR4, and myeloid differentiation factor 88 (MyD88) innate immune signaling activates the autophagy pathway, which leads to treatment failure and recurrence. What is more, Wang et al. [55] also considered that *F. nucleatum* could use as diagnostic biomarker. All these data indicated that gut microbiome feature could considered as an effective non-invasive biomarker to predictive of clinical outcomes, prognosis, and responses to immunotherapy.

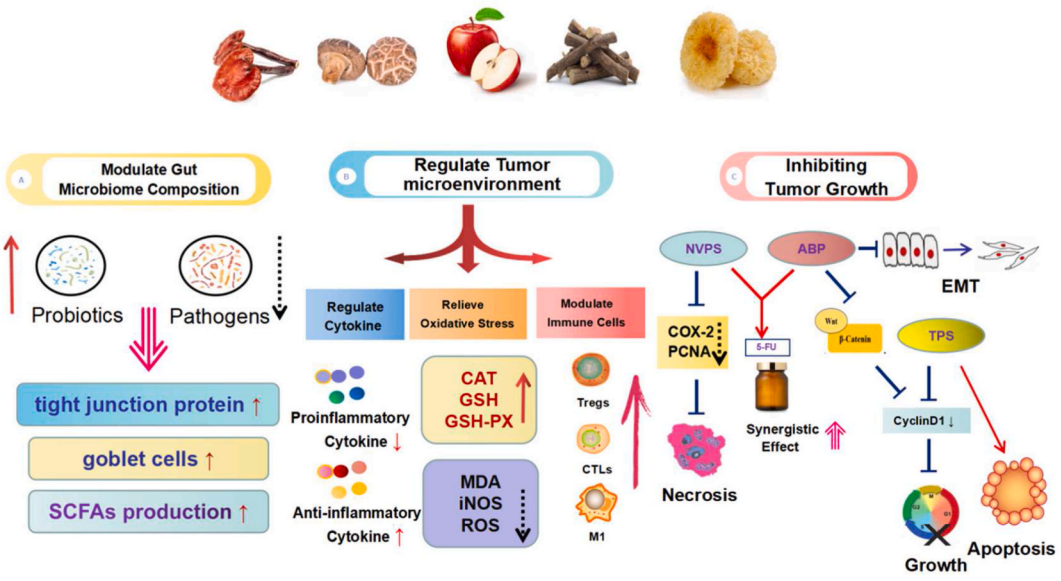


**Fig. 3.** The role of natural polysaccharides in CRC and possible mechanisms. Polysaccharides play an anti-tumor effect in CRC through modulating composition of gut microbiome, regulating tumor microenvironment, and inhibiting tumor growth and proliferation.

## 3. Anti-tumor effect of natural polysaccharides in CRC

As previously mentioned, microbial dysbiosis may be an important pathogenic factor in CRC progression. In recent years, there has been a growing body of evidence showing the antitumor bioactivity of natural polysaccharides in adjuvant therapy and chemoprevention is very notable [56,57]. Natural polysaccharides are widely present in animals, plants, and traditional Chinese medicines [58–62]. They are high-molecular-weight polymers formed by the linkage of aldehyde and ketone groups through glycosidic bonds. Studies showed that polysaccharides possess health care and medicinal value, including immune regulation, antiviral, hypoglycemic, antioxidant, and so on [63]. For the past few years, studies indicated that polysaccharides could inhibit CRC development through several pathways, which has potential development value in CRC adjuvant therapy.

First, the gut microbiome degrades polysaccharides into monosaccharides, oligosaccharides, and short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate [64,65]. They provide energy to colonocytes and regulate the intestinal microenvironment. SCFAs are modulators of host–microbiome interactions, and changes in SCFAs are thought to reflect dynamic changes in the gut microbiome composition [66]. Second, accumulating data indicate that polysaccharides have notable anti-cancer effects by regulating gut microbiome composition, metabolism of the microbiome, remodeling immune function, inhibiting inflammatory TME [67,68], inhibiting tumor growth and proliferation, inhibiting the metastasis, inducing apoptosis and autophagy, and exerting a synergistic effect with chemotherapeutic drugs [56,57] (Fig. 3).

### *3.1. Natural polysaccharides modulate composition of gut microbiome*

As mentioned above, dysbiosis is one of vital pathogenic factors of CRC. In addition, dysfunction of the intestinal barrier and an increase in intestinal permeability lead to the translocation of bacteria and/or the cytoplasmic component lipopolysaccharides (LPS) into the blood circulation, thus increasing the risk of CRC development [69,70]. In recent years, growing evidence has shown that natural polysaccharides exert anti-tumor effects by regulating the composition of the gut microbiome and repairing the intestinal mucosal barrier (Fig. 4).

It has been reported that *Ganoderma lucidum* polysaccharide (GLP) can ameliorate microbiome dysbiosis in an AOM/DSS mouse model and increase SCFAs production. In addition, GLP can effectively repair the barrier function of the intestinal mucosa by promoting the proliferation of goblet cells, mucoprotein 2 (MUC2) secretion, and tight junction (TJ) protein (occludin and ZO-1) expression, and by decreasing circulating LPS levels [71]. Furthermore, *Dendrobium officinale* polysaccharides (DOPS) similarly increases occludin and ZO-1 expression [72]. *Tremella fuciformis* polysaccharides (TPs) can increase the gut microbiome diversity and influence tyrosine biosynthesis and tryptophan and bile acid metabolism [73]. In addition, *Lachnum* sp. polysaccharides (LEP) [74],

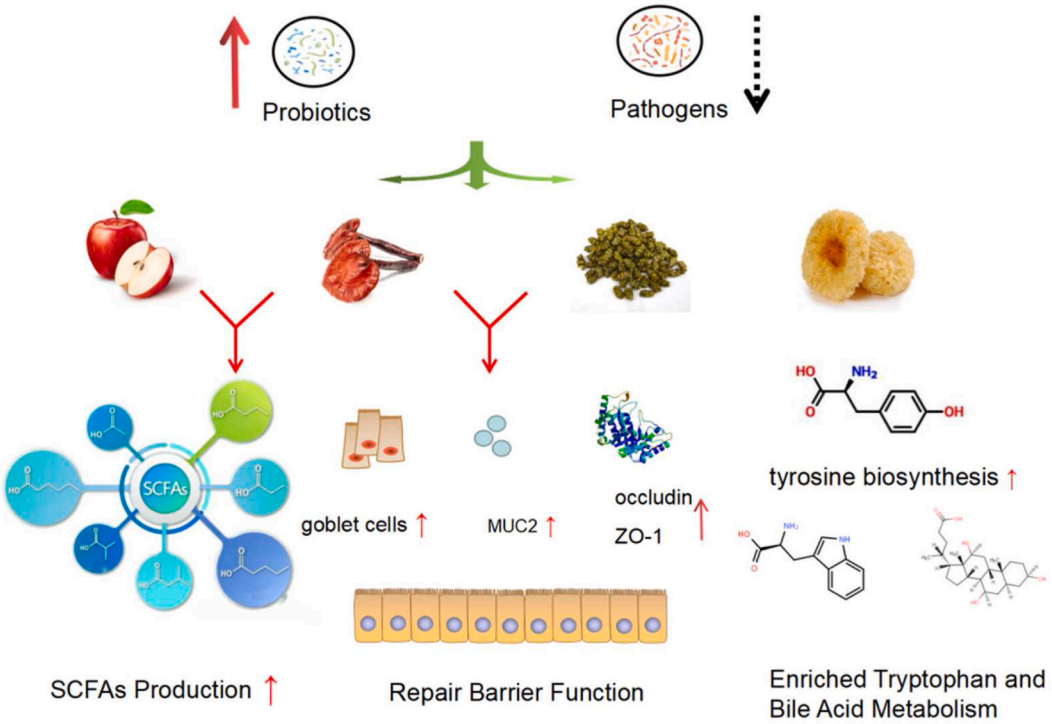


**Fig. 4.** The role of natural polysaccharides in gut microbiome composition. Polysaccharides can modulate composition of gut microbiome by enriching SCFAs production, tyrosine biosynthesis, and tryptophan and bile acid metabolism. Besides, polysaccharides can also repair barrier function of the intestinal mucosa.

apple polysaccharides (AP) [75], and polysaccharides from *N. commune* (NVPS) [76] strongly inhibited the CRC incidence rate by markedly altering the structure and community of the gut microbiome in an ADM/DSS mouse model and increasing SCFAs production (Table 1 and Fig. 5).

### 3.2. Natural polysaccharides regulate tumor microenvironment

Chronic inflammation is considered a predisposing condition for tumorigenesis and continuously promotes a protumor microenvironment [82]. Chronic IBD, including Crohn's disease and ulcerative colitis (UC), are recognized risk factors for CRC [83–85]. Oxidative stress is another factor that contributes to the development of CRC. Reactive oxygen species (ROS), production of oxidative stress process, can increase the secretion of pro-inflammatory cytokines [86]. Both these factors lead to immune disorders and promote the development of CRC. Moreover, immune cells infiltrate tumor tissues and influence tumor progression [87]. Accumulating evidence has revealed that natural polysaccharides have an important effect on the regulation of human immunity, especially in maintaining the immune balance in the tumor inflammatory microenvironment.

It was reported that Albuca Bracteate Polysaccharides (ABP) can increase the secretion of IL-10 (an anti-inflammatory cytokine) and decrease secretion of TNF-α, IFN-γ, and IL-6 (pro-inflammatory cytokine) in the AOM/DSS mice model. Through this mechanism, ABP is able to suppress IL-6/STAT3 signaling pathway activation and reduce inflammatory responses in CRC, treatment with a combination of ABP and 5-FU resulted in enrichment of *Ruminococcus*, *Anaerostipes*, and *Oscillospira* in gut microbiota [88]. Analogously, DOPS can also regulate secretion of IL-10, TNF-α, and IL-1β. Furthermore, DOPS can improve the metabolic activity of tumor infiltrating $CD8^+$ cytotoxic T lymphocytes (CTLs), increasing the levels of ATP and Glu in CTLs to provide energy for effector functions and inhibiting the expression of programmed cell death protein 1 (PD-1) in CTLs to enhance the anti-tumor immune response in the TME [72]. Ayeka et al. [89] suggested that licorice polysaccharide (*Glycyrrhiza uralensis* Fisch.) show immunomodulatory activities via promoting the secretion of IL-2, IL-6, and IL-7, and inhibiting TNFα in CT 26 tumor-bearing mice. Furthermore, LP may activate of $CD4^+$ and $CD8^+$ T lymphocytes to achieve immune regulation effect. However, the mechanism by which LP regulates TME has not yet been elucidated. TPs could activate $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs) to suppress the inflammatory response by increasing IL-10 and decreasing TNF-α, IFN-γ, and immunoglobulin A (IgA) [73].

Khan et al. [90] found that GLP and *Gynostemma pentaphyllum* (GpS) can remodel the inflammatory microenvironment by reducing expression of IL-1β, IFN-γ, FOXP3, and TNF-α, and increasing expression of IL-4, IL-10, IL-12, and IL-13. In addition, in $Apc^{Min/+}$ mice treated with GLP and Gps, the trend of M1 phenotype to M2 phenotype polarization was reversed, and iNOS was downregulated. In addition, GLP and GpS down regulated relative abundance of harmful bacteria especially *Bacteroidetes*. Moreover, GLP exerts immunomodulatory effects [71] and can downregulate expression of TLR4 and MyD88, and NF-κB p65 phosphorylation. In the meantime, GLP can downregulate expression of IL-1β, iNOS, and COX-2 both at the mRNA and protein level and inhibit macrophages infiltration in the AOM/DSS mice model, which leads to the inhibition of inflammatory responses in the TME. Similarly, AP reduces the numbers of T cells and macrophages, inhibiting the activation of the Wnt signaling pathway by suppressing nuclear aggregation of β-catenin [75]. In addition, carboxymethyl pachyman (CMP) has been shown to have anti-inflammatory, immunoregulatory, and antioxidant activities that reduce damage to the intestinal mucosa induced by 5-fluorouracil (FU) treatment in an AOM/DSS mouse model. Research found that CMP can reduce the production of ROS in the mesenteric lymph nodes (MLN) and increase the levels of

**Table 1**
Natural polysaccharides modulates composition of gut microbiome.

| Sources of Polysaccharides | Common name | Microecological change (up-regulation) | Microecological change (down-regulation) | Composition and Proportion | Molecular weight |
|---|---|---|---|---|---|
| Ganoderma lucidum polysaccharide [71] | Ganoderma lucidum | Lactobacillus<br>Bifidobacterium | Oscillibacter<br>Desulfovibrio<br>Alistipes<br>Lachnoclostridium<br>Parasutterella | fucose, mannose, glucose and galactose<br>0.13: 0.05: 0.72: 0.10 | $3.98 \times 10^3$ kDa [77] |
| Tremella fuciformis polysaccharide [73] | Tremella fuciformis Berk. | Lactobacillus<br>Lactobacillaceae | Odoribacter<br>Ruminococcaceae<br>Marinifilaceae<br>Helicobacter | mannose, xylose, fu-cose, glucose, glucuronic acid<br>1.91: 0.1: 2.49: 6.23: 0.95 | $1.14 \times 10^3$ kDa [78] |
| Lachnum sp. polysaccharides [74] | Lachnum | listipes<br>Alloprevotella<br>Ruminiclostridium | Parabacteroides<br>Escherichia_Shigella<br>Desulfovibrio<br>Helicobacter | _ | $3.22 \times 10^4$ kDa [79] |
| Apple polysaccharide [75] | Apple | Lactobacillus | Fusobacterium | mannose, rhamnose, glucuronic acid, galacturonic acid, glucose, xylose, galactose, arabinose<br>7.19:4.42:0.90:6.57: 6.55: 7.97:20.58:45.82 | 403 kDa [80] |
| Nostoc Commune polysaccharide [76] | Nostoc commune Vauch. | Phyla Firmicutes<br>Cyanobacteria | Bacteroidetes<br>Actinobacteria | Glc, Gal, Xyl, GlcA, Man<br>1:0.4:0.90:0.14:0.08 [81] | _ |

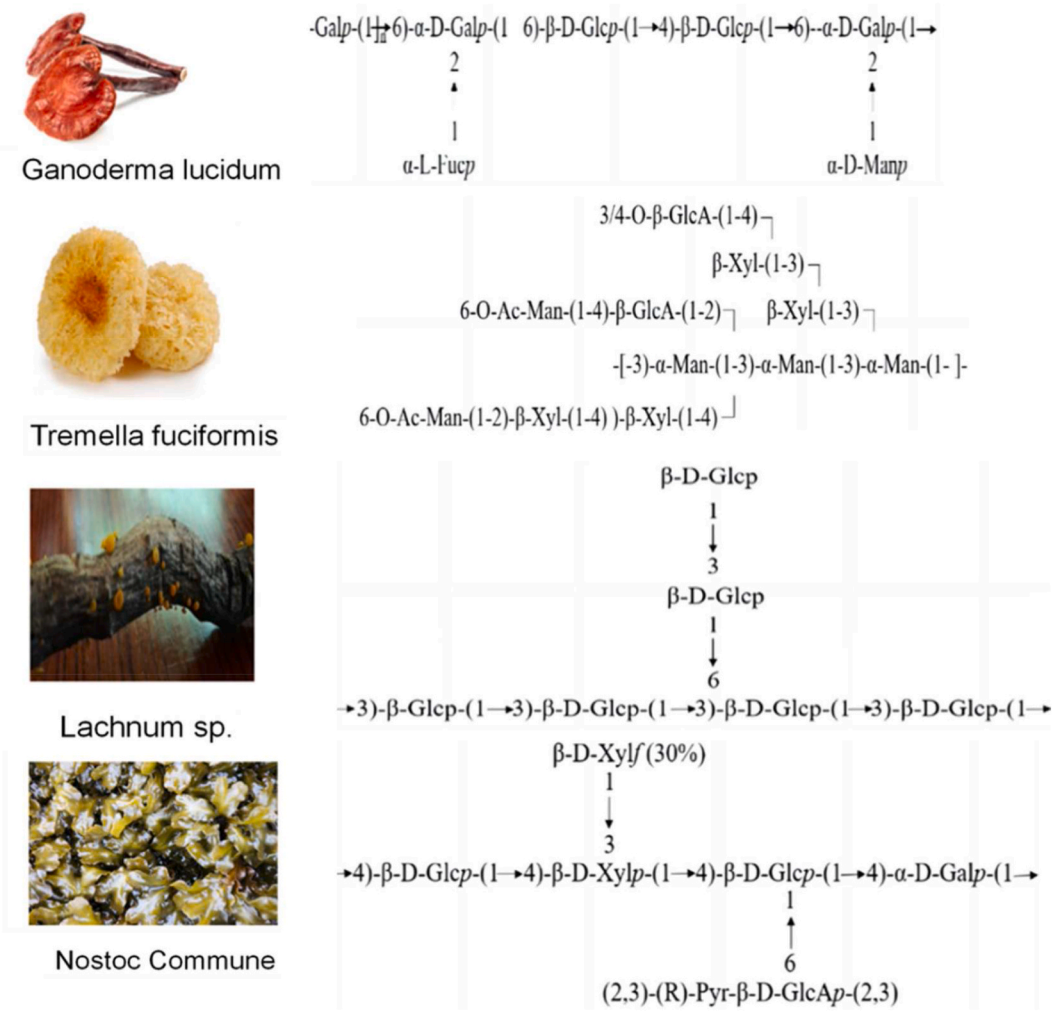


**Fig. 5.** The Structural characterization of Ganoderma lucidum polysaccharide, Nostoc Commune polysaccharideTremella fuciformis polysaccharides, Lachnum sp. Polysaccharide and Nostoc Commune polysaccharide.

glutathione, peroxidase (GSH-Px), GSH, and catalase (CAT). Moreover, it was revealed that CMP alleviates intestinal injury by regulating NF-κB, Nrf2-ARE, and MAPK/P38 signaling pathway, also promoting the restoration of gut microbiome, the probiotics obviously increased (*Bacteroides*, *Lactobacillus*, butyric acid-producing bacteria, and acetic acid-producing bacteria). all the data suggested that CMP played a synergistic role in the treatment of CRC [91] (Table 2).

### 3.3. *Natural polysaccharides inhibit CRC growth*

Studies have found that natural polysaccharides exert a direct inhibitory effect on tumors by reducing tumor weight and increasing the tumor inhibition rate. Guo et al. [76] suggested that polysaccharides from N. commune (NVPS) considerably decrease the number and weight of tumors formed in AOM/DSS-induced CRC models. In addition, NVPS plays a protective role against dysplasia/adenocarcinoma and surface tumor necrosis induced by AOM/DSS. Mechanistically, NVPS downregulates the expression of Cyclooxygenase-2 (COX-2) and proliferating cell nuclear antigen (PCNA). A similar pathomechanism was found by Yuan et al. [88], who revealed that ABP can suppress the proliferation of CRC cell lines in a dose- and time-dependent manner through suppression of the Wnt/β-catenin pathway (including β-catenin, c-Myc, CyclinD1, COX-2, and PCNA downregulation). In addition, ABP can also suppress tumor migration and invasion *in vitro* by inhibiting expression of epithelial mesenchymal transformation (EMT) related markers Vimentin and E-cadherin. Meanwhile, both NVPS and ABP play a vital synergistic role in the 5-FU treatment of CRC. Besides, Tea polysaccharide (TPS) can reduce the morbidity of AOM/DSS mice, promote tumor cell apoptosis, and inhibit cell proliferation, as well as interfere with cell cycle progression through inhibiting CyclinD1 expression both *in vitro* and *in vivo* [56]. Besides, low-molecular-weight chondroitin sulfate from hybrid sturgeon cartilage could inhibit cancer cell HCT-116 *in vitro* and HT-29 *in vivo* through activation of p53 signaling pathway [62] (Table 3).

**Table 2**
Natural polysaccharides regulate the Tumor Microenvironment.

| Sources of Polysaccharides | Common name | Regulation of Cytokines (up-regulation) | Regulation of Cytokines (down-regulation) | Modulate Immune Cells | Composition and Proportion | Molecular weight |
|---|---|---|---|---|---|---|
| Albuca Bracteate polysaccharide [88] | Albuca Bracteate | IL-10 | TNF-α<br>IFN-γ<br>IL-6 | _ | glucose, mannose, galactose, xylose, galacturonic acid, glucuronic acid 37.8:8:2.5:1.7:1:1 | 18.3 kDa [88] |
| Dendrobium officinale polysaccharide [72] | Dendrobium officinale Kimura & Migo | IL-10 | TNF-α<br>IL-1β | CTLs ↑ | Glucose, mannose 1.00:5.78 | $4.56 \times 10^3$ kDa [77] |
| Glycyrrhiza uralensis Fisch. polysaccharide [89] | Glycyrrhiza uralensis Fisch. | IL-2<br>IL-6<br>IL-7 | TNF-α | $CD4^+$T cells ↑<br>$CD8^+$T cells ↑ | Ara, Man, Glc, Gal 1:5.33:1.91:5.97 | $14.9 \times 10^3$ kDa [92] |
| Tremella fuciformis polysaccharide [73] | Tremella fuciformis Berk. | IL-10 | TNF-α<br>IFN-γ<br>IgA | $CD4^+CD25^+FOXP3^+$ Tregs↑ | mannose, xylose, fu-cose, glucose, glucuronic acid 1.91: 0.1: 2.49: 6.23: 0.95 | $1.14 \times 10^3$ kDa [73] |
| Gynostemma pentaphyllum polysaccharide & Ganoderma lucidum polysaccharide [90] | Gynostemma Blume& Ganoderma lucidum | IL-4<br>IL-10<br>IL-12<br>IL-13 | IL-1β<br>IFNγ<br>FOXP3<br>TNFα | M1 phenotypes ↑ | rhamnose, arabinose, galactose, glucose, xylose, mannose, galacturonic acid 4.11: 7.34: 13.31: 20.99: 1.07: 0.91: 4.75: 0.36 | $4.07 \times 10^4$ kDa [93] |

**Table 3**
Natural polysaccharides Inhibit Tumor Growth.

| Sources of Polysaccharides | Common name | Composition and Proportion | Regulation Target | Molecular weight |
|---|---|---|---|---|
| Nostoc commune Vaucher polysaccharides [76] | Nostoc commune Vaucher | glucose, arabinose, xylose, mannose, galactose 1:4.96:182.02:0.97:3.15 | COX-2<br>PCNA | _ |
| Albuca Bracteate Polysaccharides [88] | Albuca Bracteate | _ | β-catenin c-Myc<br>CyclinD1<br>COX-2<br>PCNA | 18.3 kDa [88]. |
| Camellia sinensis L.O. Kuntze Polysaccharides [56] | Camellia sinensis (L.) Kuntze | rhamnose, ribose, arabinose, mannose, glucose, galactose 1.26:3.18:4.08:1.00:1.52:3.29 | CyclinD1 | $26.8 \times 10^4$ kDa. |
| Chondroitin sulfate [62] | – | _ | p53<br>p21<br>Caspase-9<br>Caspase-6<br>Caspase-3<br>Bax | 19.7 kDa |

## 4. Current challenges

Currently, most studies on the gut microbiome and the adjuvant therapeutic effects of polysaccharides on CRC are still in the exploratory stage. Although microbiome components can be detected in excrement, bile, saliva, and other samples, identifying a consensus among these samples is difficult due to inconsistent microbiome compositions. This inconsistency has led to controversy regarding the efficacy of probiotic therapies. Additionally, different types of natural polysaccharides have varying compositions, structures [94], and relative molecular weights [10,95,96] that can affect the recognition and glycometabolism between polysaccharides and the gut microbiome. Furthermore, considering the dysfunction of the gut microbiome in patients with CRC, it is important to consider the capacity for indigestible polysaccharide loads. Although the anti-tumor effects of polysaccharides have been observed in animal experiments, relevant clinical trials are scarce. Therefore, further research is needed to elucidate how the human body benefits from interactions between polysaccharides and the gut microbiome.

## 5. Conclusions and perspective

With a comprehensive understanding of the influence of the gut microbiome on CRC and its related mechanisms, the rational utilization of natural polysaccharides to manipulate the gut microbiome may serve as an effective adjuvant therapy for CRC. Currently, the modulation of the gut microbiome is recommended to prevent CRC incidence, alleviate treatment side effects, and enhance the efficacy of chemotherapy. The potential anti-tumor effects of polysaccharides targeting the gut microbiome can be achieved through the inhibition of inflammation in the TME, restoration of mucosal barrier function, suppression of tumor growth, and correction of

dysbiosis. Considering that natural polysaccharides play pivotal roles in regulating both the gut microbiome and CRC tumor microenvironment, it is worth exploring comprehensive therapeutic strategies that integrate microbiome modulation with immune checkpoint blockade and chemotherapy. The use of natural polysaccharides to restore homeostasis in the gut microbial communities has emerged as a promising approach for CRC prevention and adjuvant treatment, as cancer management often requires multifactorial intervention rather than monotherapy.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## CRediT authorship contribution statement

**Lili Liu:** Writing – original draft. **Yinan Li:** Writing – original draft. **Xiaoting Zheng:** Writing – review & editing. **Rong Huang:** Writing – review & editing. **Xiaoli Huang:** Conceptualization. **Yonghui Zhao:** Conceptualization. **Wenjing Liu:** Supervision. **Yanli Lei:** Supervision. **Qiu Li:** Funding acquisition. **Zhangfeng Zhong:** Project administration. **Ziyun Zhao:** Project administration.

## 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.

## Acknowledgements

Not applicable.

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