Journal of Food Bioactives

International Society for Nutraceuticals and Functional Foods

Review

J. Food Bioact. 2024;28:24–30

Research progress on the regulation of gut microbiota by Chinese yam polysaccharides

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DOI: 10.26599/JFB.2024.95028392

Received: December 15, 2024; **Revised received & accepted:** December 26, 2024

Abbreviations: AAD, Antibiotic-associated diarrhea; Ara, arabinose; CD, Crohn's disease; CHOP, C/EBP-homologous protein; Cy or CTX, Cyclophosphamide; CYPs, Chinese yam polysaccharides; DSS, Dextran sodium sulfate; ET, Endotoxin; GC, Gas chromatography; GC-MS, GC-mass spectrometry; Gal, Galactose; GalA, Galacturonic acid; Glu, Glucose; GluA, Glucuronic acid; GM, Gut microbiota; GPC-MALLS-IR, Multi-angle laser light scattering detector and differential refractive index detector combined with gel permeation chromatography; GRP78, Glucose regulatory protein 78; HFD, High-fat diet; HPGPC, High-performance gel permeation chromatography; HPLC, High performance liquid chromatography; IBD, Inflammatory bowel disease; IL-6, Interleukin-6; IL-10, Interleukin-10; IL-1β, Interleukin-1β; IR, Infrared spectroscopy; LBP, Lipopolysaccharide binding protein; LDL, Low-density lipoprotein; LPS, Lipopolysaccharide; Man, Mannose; MMP-3, Matrix metalloproteinase-3; MPO, Myeloperoxidase; MUC-2, Mucin-2; NF-κB, Nuclear factor κB; NLRP3, Nucleotide-binding oligomerization domain-like receptor protein 3; NMR, Nuclear magnetic resonance; NO/iNOS, Nitrogen monoxide/Inducible nitric oxide synthase; Rha, Rhamnose; Rib, Ribose; SCFAs, Short-chain fatty acids; SCYP, Sulfated yam polysaccharides; TNBS, 2,4,6-trinitrobenzene sulfonic acid; TNF-α, Tumor necrosis factor-α; UC, Ulcerative colitis; UHPLC-ESI-MS, Ultrahigh performance liquid chromatography-electrospray ionization mass spectrometry; Xyl, Xylose; YP, Yam polysaccharide; ZO-1, Zonula occludens-1

Citation: Hu, T., Wu, P., Zhan, J., and Wang, W. (2024). Research progress on the regulation of gut microbiota by Chinese yam polysaccharides. J. Food Bioact. 28: 24–30.

Abstract

Chinese yam is a traditional medicinal herb with a long history of medicinal and edible use in China. Polysaccharides are one of its main active components, possessing biological activities such as immune regulation, anti-tumor, hypolipidemic, hypoglycemic, antioxidant, anti-inflammatory, and antibacterial properties. Recent research has indicated that Chinese yam polysaccharides (CYPs) play a significant role in promoting intestinal health and balancing gut microbiota. The gut microbiota has a direct impact on human digestion, nutrient absorption, energy levels, fat metabolism, and immune system regulation. Moreover, its imbalance can lead to the occurrence of various diseases such as enteritis, diabetes, obesity, tumors, and more. This review provides a brief overview of the extraction, isolation, purification, and structural characteristics of CYPs, with a particular emphasis on their prebiotic benefits, including anti-inflammatory bowel disease, anti-obesity, immune modulation, and anti-inflammatory effects, laying a foundation for future applications of CYPs in the treatment of related diseases.

Keywords: Chinese yam; Polysaccharides; Structural characteristics; Gut microbiota; Probiotic benefits.

1. Introduction

Yam (*Dioscorea opposita* Thunb) belongs to the *Dioscorea* genus and is the world's third largest tuber crop, consisting of over 600 different species, primarily grown in tropical and subtropical regions of Africa, Americas, and Asia. Due to its advantages such as abundance, affordability, and ease of storage, yam is a popular food known for its high nutritional value and unique flavor. The

"Compendium of Materia Medica" states that it has the ability to "enhance kidney energy, promote a healthy spleen and stomach, halt diarrhea and dysentery, convert phlegm and saliva, and moisturize the skin and hair". Modern medical research has shown that yams contain a variety of bioactive components, including polysaccharides, starch, fiber, protein, sapogenins, dioscorin, flavonoids, polyphenols, allantoin, and other nutrients (Li et al., 2023; Guo et al., 2024). The primary active component in yam is polysaccharides, which have various functions including hypoglycemic (Yang et al., 2010), hypolipidemic (Yu et al., 2020), antioxidant (Zhou et al., 2021), anti-inflammatory (Niu et al., 2020), antibiotic (Yu et al., 2014), immune regulation (Huang et al., 2020; Hao and Zhao, 2016), anti-tumor, anti-aging (Wang et al., 2020), and prebiotic activities (Chang et al., 2024).

As is well known, the intestines are the digestive and immune organs of the human body, responsible for digestion and absorption of food. The 100 trillion bacteria living in the gastrointestinal tract make up the gut microbiota (GM), which includes *Proteobacteria*, *Firmicutes*, *Fusobacteria*, *Bacteroidetes*, and *Verrucomicrobia* (Eckburg et al., 2005; Hollister et al., 2014). Among them, the *Bacteroidetes* and *Firmicutes* are the predominant groups (Tap et al., 2009). The composition and function of GM are closely related to human health, playing a crucial role in maintaining physiological balance. The alteration of GM may disturb the metabolism of nutrients, potentially resulting in diseases like obesity (Jones et al., 2008), diabetes (Chen et al., 2020), colon cancer (Kostic et al., 2012), as well as liver disease (Li et al., 2024). GM plays a crucial role in protecting the intestines from harm, as the stability and dynamic balance of the gut microbiota can assist in maintaining overall health and preventing disease by resisting the colonization of pathogens.

Research has shown that the gut microbiota plays a role in the utilization and degradation of large molecular polysaccharides, possessing physiological functions that some human organs do not have. The active enzymes produced by the gut microbiota degrade polysaccharides into short-chain fatty acids (SCFAs) and other metabolic byproducts like acetic acid, propionic acid, and butyric acid, which play a role in regulating gut integrity, glucose levels, lipid metabolism, and inflammatory responses (Le Poul et al., 2003). Research has found that many diseases in the human body, such as obesity (Tremaroli and Bäckhed, 2012), diabetes (Upadhyaya and Banerjee, 2015), coronary heart disease (Jie et al., 2017), and Parkinson's disease (Perez-Pardo et al., 2017), are closely related to the gut microbiota. The involvement of intestinal microbiota in the metabolism of polysaccharides can alter the bioactive components of polysaccharides, thereby playing a mediating role in the mechanism of polysaccharide therapy. In recent years, plant polysaccharides from natural sources have been proven to be beneficial for gut health, with the advantages of being safe, highly effective, non-toxic, and biocompatible (Niu et al., 2021).

Yam has been used in traditional folk medicine for thousands of years to treat gastrointestinal diseases. Recent research has shown that the beneficial effects of yam on improving gastrointestinal health are mainly attributed to CYPs. CYPs can act as prebiotics, treating gut dysbiosis by regulating the composition and metabolism of intestinal flora. In recent years, there has been a multitude of research conducted by scholars from both domestic and international backgrounds on the regulation of intestinal flora activity by CYPs, leading to significant advancements in the field. Based on the review of a large number of literatures, a brief overview was provided on the extraction, separation, purification, and structural features of CYPs, and the research progress in recent years on the prebiotic benefits of CYPs by regulating gut microbiota and enhancing of intestinal immunity were summarized, providing a basis for the research and development of CYPs as targeted probiotics regulators.

2. Extraction, separation, purification, and structural characteristics of CYPs

Currently, CYPs are primarily extracted using the water extraction with different temperature and alcohol precipitation method (Shao et al., 2022; Zhao et al., 2017). Additionally, enzymatic extraction (Liu et al., 2022), alkali extraction (Hu et al., 2024; Guo, et al., 2024), ultrasound-assisted extraction (Bu et al., 2022), ultrafiltration-assisted extraction (Xue et al., 2019), deep eutectic solvent extraction (Ouyang et al., 2021; Zhang and Wang, 2017) are also used. Generally, CYPs obtained through various extraction methods such as water extraction and alcohol precipitation usually contain a large amount of impurities such as proteins, pigments, and small molecules, which require separation and purification operations to remove proteins, decolorize, and eliminate small molecules. The Sevage method, enzyme method, trichloroacetic acid method, or a combination of two of these methods are commonly used for deproteinization, while methods for decolorization include the hydrogen peroxide method, ion exchange resin method, activated carbon adsorption method, etc. Dialysis is frequently employed for removing small molecular impurities. After the removal of proteins and pigments, followed by dialysis and vacuum freeze-drying, the refined polysaccharides are obtained. These polysaccharides are typical mixtures that need to be further separated into individual polysaccharides. Popular techniques for this process include DEAE cellulose column chromatography and Sephadex gel column chromatography (Figure 1).

Although there have been numerous literatures report on the structure of CYPs, the research in this field is still at a preliminary stage. Most studies have concentrated on the primary structure, specifically on the monosaccharide composition, glycosidic bonds, and main chain structure of CYPs. Nevertheless, the study of the high-level structure of CYPs, such as molecular weight, molecular size, and chain conformation, has only preliminarily determined the average molecular weight of CYPs, without fully clarifying their molecular size and chain conformation. The analysis methods or instruments for characterizing the structure of CYPs mainly include infrared spectroscopy (IR), high performance liquid chromatography (HPLC), gas chromatography (GC), GC-mass spectrometry (GC-MS), periodate oxidation, Smith degradation analysis, partial acid hydrolysis, methylation analysis, nuclear magnetic resonance (NMR), ultrahigh performance liquid chromatography-electrospray ionization mass spectrometry (UHPLC-ESI-MS), high-performance gel permeation chromatography (HPGPC), and multi-angle laser light scattering detector and differential refractive index detector combined with gel permeation chromatography (GPC-MALLS-RI) among others. According to the literature, yam polysaccharides are mainly composed of seven monosaccharides and two uronic acids (Li et al., 2020; Guo, et al., 2024). The seven monosaccharides include glucose (Glu), mannose (Man), rhamnose (Rha), galactose (Gal), xylose (Xyl), ribose (Rib), and arabinose (Ara), with higher contents of Gal, Glu, Rha, and Ara in the CYPs. The two uronic acids identified are galacturonic acid (GalA) and glucuronic acid (GluA). The molecular weight of yam polysaccharides ranges from 3 to 100 kDa, with various linkage patterns including (1→), (1→2), (1→3), (1→4), and (1→6) being the main forms (Zhang et al., 2024).

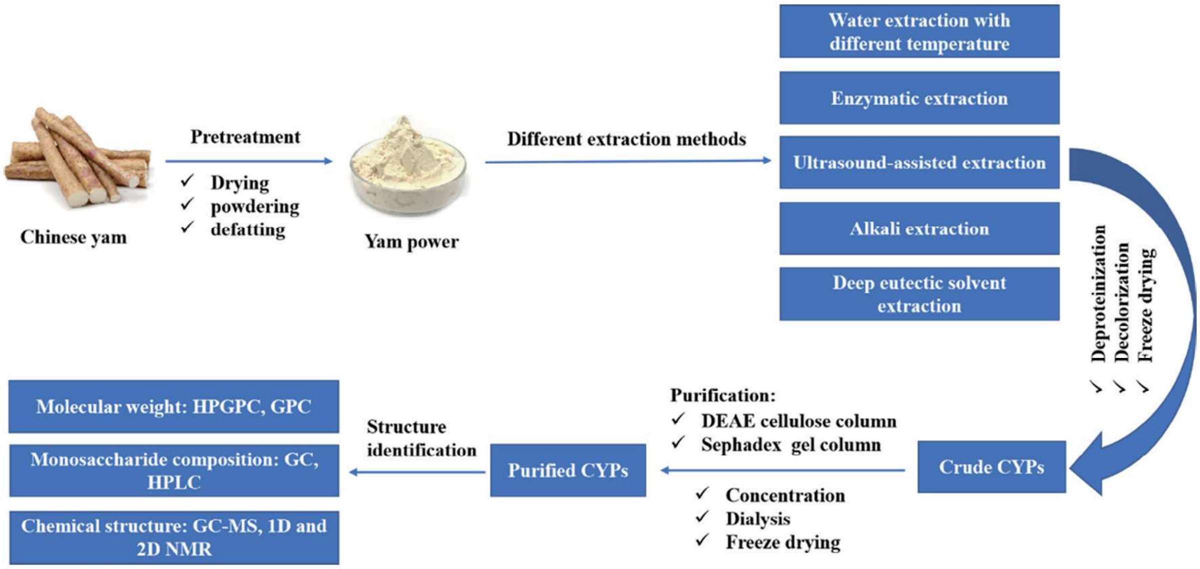

Figure 1. The extraction, separation, purification and structure identification of CYPs.

3. Prebiotic effects of CYPs in modulating the gut microbiota

CYPs can exert multiple health-promoting effects by modulating the composition and metabolism of the host gut microbiota. Their prebiotic benefits encompass anti-inflammatory bowel disease (IBD) (Li, et al., 2020), anti-obesity (Feng et al., 2024), immune regulation (Li et al., 2024), anti-inflammatory (Bai et al., 2023), and alleviating antibiotic-associated diarrhea (AAD) effects (Zhang et al., 2019). The function of CYPs is manifested through promoting the proliferation of beneficial gut bacteria, inhibiting the growth of pathogenic bacteria, increasing the production of SCFAs, enhancing intestinal immunity, and activating specific signaling pathways. Herein, we summarize the prebiotic effect and mechanism of CYPs in Table 1.

3.1. Anti-inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the intestines, including ulcerative colitis (UC) and Crohn's disease (CD), and its precise cause is still unknown. According to statistics, the incidence of IBD shows an upward trend. The primary treatment for IBD includes immunosuppressants and antibiotics, which can result in a compromised immune system in patients as a result of prolonged use of these drugs. Therefore, it is of great significance to find natural products that possess efficient, no or low-toxic, and anti-IBD effects. In recent years, natural polysaccharides derived from plants have been proven to be beneficial for gut health, showing great potential in preventing IBD (Li, et al., 2024). It is worth noting that an increasing amount of animal research have shown that CYPs could be a viable treatment option for preventing or reducing IBD. Li et al. isolated a water-soluble mannoglucan from yam, CYP-1, which showed beneficial effects in DSS-induced colitis mice. CYP-1 could improve gut dysbiosis, inhibit the activation of inflammatory signaling pathways such as NF-κB and NLRP3 inflammasome, and upregulate the expression of mRNA for colon tight junction proteins such as ZO-1, claudin-1, occludin, and connexin-43, and adjust gut microbiota by decreasing the abundances of *Alistipes*, *Helicobacter*, and *Enterobacteriaceae* (Li, et al., 2020). Zhang and his team utilized the three-phase partitioning (TPP) method to extract and purify a refined *Dioscoreae persimilis* (*D. persimilis*) polysaccharide (DP), and found that it could alleviate colonic tissue pathological changes in colitis mice, enhance colonic antioxidant capacity, and improve inflammatory response. In addition, DP could restore the diversity and composition of the intestinal microbiota, particularly by increasing the abundances of *Acetatifactor*, *Lachnospiraceae*, *Lactobacillus*, and Proteobacteria, as well as enhancing the ratio of *Firmicutes* to *Bacteroidetes* (Zhang et al., 2023). Lu et al. also discovered that Chinese yam polysaccharide (CYP) reduced intestinal inflammation by regulating the expression of inflammatory factors, restoring intestinal barrier integrity, regulating gut microbiota and SCFAs metabolites, reversing microbiota dysbiosis, and exhibiting a palliative effect on DSS-induced mice UC model (Lu et al., 2023). Furthermore, Cai et al. discovered that the combination of CYPs and inulin not only significantly restored the balance of intestinal microbiota structure and function, but also increased SCFAs-producing bacteria, lactic acid-producing bacteria and decreased *Bacteroides*, *Proteobacteria* and sulfate-reducing bacteria, leading to an improvement in experimental colitis induced by 2,4,6-trinitrobenzene sulfonic acid (TNBS) in rats. (Cai et al., 2019).

3.2. Anti-obesity

Obesity is a chronic multifactorial disease characterized by an increase in body fat mass, affecting over 600 million people worldwide. Research has shown that obesity is closely linked to an imbalance in the gut microbiota. The gut microbiota plays a crucial role in regulating host energy metabolism and fat accumulation. In recent years, studies have found that polysaccharides can play a role in treating obesity by regulating gut microbiota (Ren et al., 2021; Zhu et al., 2024). Feng and colleagues isolated and purified a novel acidic polysaccharide component (CYP) from Chinese yam. CYP may affect the composition and abundance of intestinal flora, thereby influencing the types of metabolites in the gut and improving the deposition of fat around the liver and kidneys, lead-

Table 1. The prebiotic benefits of CYPs in modulating the gut microbiota

Prebiotic benefits	Polysaccharide names	Experimental model	Polysaccharide doses	Mechanism	References
Anti-IBD	CYP-1	LPS-induced Raw 264.7 cells and DSS-induced colitis mice	31.25 μg/mL, 62.5 μg/mL, 125 μg/mL, 250 μg/mL, 500 μg/mL, and 300 mg/kg	Colonic pathological damage↓, NF-κB signaling pathways and NLRP3 inflammasome↓, mRNA expression of junctional proteins (claudin-1, occludin, ZO-1, connexin-43) ↑, *Alistipes*, *Helicobacter*, Enterobacteriaceae↓	(Li, et al., 2020)
	CYP	DSS-induced mice UC model	200 mg/kg	Colitis symptoms, IL-10, mucin MUC-2, ZO-1 and occludin, SCFAs↑, IL-1β, TNF-α, MPO activity, LBP and ET in serum, oxidative stress in liver↓, *Alistipes*, *Bacteroides*↑	(Lu, et al., 2023)
	DP	DSS-induced UC in mice	400 mg/kg	Colonic antioxidant capacity↑, *Acetatifactor*, *Lachnospiraceae*, *Lactobacillus*, and Firmicutes/Bacteroidetes↑	(Zhang, et al., 2023)
	CYP-3a	DSS-induced Caco-2 cells	50 μg/mL, 100 μg/mL, and 200 μg/mL	Number of DSS-induced Caco-2 cells↓, Endoplasmic reticulum stress-mediated apoptotic pathway↓, TNF-α, IL-6, GRP78, CHOP and NF-κB↓	(Ren et al., 2024)
	CYP and inulin	TNBS-induced colitis rat model	300 mg/kg	Colitis inflammation, oxidative stress, cell motility, and signal transduction↓, Basic metabolism↑, SCFAs-producing bacteria, lactic acid-producing bacteria↑, Bacteroides, Proteobacteria and sulfate-reducing bacteria↓	(Cai, et al., 2019)
Anti-obesity	CYP	High-fat diet (HFD)-induced obese C57BL/6J mice	100 mg/kg, 200 mg/kg and 400 mg/kg	SCFA-producing bacteria *Lachnospiraceae*, *Lachnospiraceae_NK4A136_group*, and *Ruminococcaceae_UCG-014*↑, *Desulfovibrionaceae* and *Ruminococcus*↓, Arginine, propionylcarnitine, and alloisoleucine↓	(Feng, et al., 2024)
	CYP	HFD-induced obesity C57BL/6 mice	10 mg/kg,20 mg/kg	LDL, total cholesterol↓, IL-10, IL-1β, leptin in serum, MMP-3 and NF-κB (*P65*)↓	(Cheng, et al., 2019)
Immune regulation	DOP-2	LPS-induced RAW264.7 cells and Cyclophosphamide (CTX)-treated mice	10 μg/mL, 50 μg/mL, 100 μg/mL, 250 μg/mL, 500 μg/mL, 200 mg/kg, 400 mg/kg, and 800 mg/kg	NO, IL-6, TNF-α, body weight, the degree of injury to the immune organ index, and SCFAs↑	(Li, et al., 2024)
	SCYP	Cyclophosphamide (Cy)-treated mice	50 mg/kg,100 mg/kg and 200 mg/kg	Colon contents digestive enzyme activities↑, SCFAs↑, *Lactobacillus*, *Bacteroidetes*, *Akkermansia*↑, *Proteobacteria*, *Verrucomicrobia*↓	(Huang, et al., 2021)
Anti-inflammatory	CYP	LPS-stimulated coculture Caco-2/Raw264.7 cells	100 μg/mL	SCFAs↑, *Bifidobacterium*, *Megasphaera*↑, Intestinal tight junction *ZO-1* and *Occludin*↑, NO/iNOS, TNF-α, and IL-1β↓	(Bai, et al., 2023)
	CYP, SCYP	LPS-induced acute Inflammation in male C57BL/6J mice	100 mg/kg	Plasma IL-6, TNF-α↓, hepatic IL-6, IL-1β, TNF- α↓*Bacteroidetes*, *Firmicutes*↑, *Proteobacteria*, *Desulfovibrio*↓CYP increased *Prevotella*, SCYP increased *Coprococcus*	(Wu, et al., 2023)
Anti-AAD	YP	Ampicillin antibiotic-associated diarrhea (AAD) Balb/c mice	–	Severe diarrhea↑, body weight loss, cecum expansion↓, *Bifidobacteria, Lactobacilli*↑, *Clostridium perfringens, Enterococcus*↓	(Zhang, et al., 2019)

ing to a lipid-lowering effect. Additionally, proteins related to lipid synthesis and breakdown are also regulated by CYP intervention. According to this research, CYP has the potential to serve as a lipid metabolism regulator (Feng, et al., 2024). In Cheng's study, it has been demonstrated that CYP could play a role in inducing insulin resistance and hyperlipidemia in obese mice by reducing low-density lipoprotein (LDL) and cholesterol levels, producing fewer SCFAs, lowering serum leptin, IL-10 and IL-1β levels, and downregulating MMP-3 and NF-κB expression in visceral adipose tissue. Therefore, CYPs can improve insulin sensitivity by reducing inflammatory protein products, thus increasing insulin sensitivity, providing evidence that CYPs are effective compounds in yam functional foods for preventing hyperlipidemia and type 2 diabetes (Cheng et al., 2019).

3.3. *Immune modulation*

Polysaccharides, a natural type of large molecule, have been extensively studied for their ability to modulate immunity, especially in the gut. The purified polysaccharides fraction, DOP-2, was prepared from *Dioscorea opposita* Thunb (*D. opposita*), could promote the production of SCFAs in immunosuppressed mice and regulate the composition of their gut microbiota, thereby restoring the immune regulatory activity of the intestines. This finding provides a theoretical basis for the application of DOP-2 in improving immune function and gut health (Li, et al., 2024). Additionally, it is worth noting that sulfated yam polysaccharides (SCYP) exhibit significant immunomodulatory activity in the intestines, which is mainly attributed to the sulfation modification. Huang and colleagues successfully obtained sulfated derivatives of yam polysaccharides. Compared to unmodified yam polysaccharides, these derivatives exhibit a more pronounced regulatory effect on the intestinal microbiota of mice treated with cyclophosphamide (Cy), contributing to maintain the balance of the gut microbiota affected by Cy- treatment. These findings suggest that SCYP has stronger immune-regulating activity than CYP (Huang et al., 2021).

3.4. *Anti-inflammatory*

Inflammation is a typical defense response to infection, tissue damage, or harmful stimuli. However, excessive inflammation can lead to the occurrence and progression of chronic diseases. It is worth noting that polysaccharides demonstrate good performance in protecting the body from attacks by inflammatory cytokines. Wu et al. discovered that SCYP can effectively reduce plasma levels of TNF-α and IL-6 compared to CYP, demonstrating significant anti-inflammatory capabilities (Wu et al., 2023). SCYP reversed the gut microbiota dysbiosis by decreasing *Desulfovibrio* and increasing *Coprococcu* (Wu, et al., 2023). In addition, it has been found that fecal fermentation improved the anti-inflammatory effects. Compared to digested CYP, fecal fermentation CYP significantly inhibited the levels of anti-inflammatory mediators such as NO/iNOS, TNF-α, and IL-1β, while increasing the production of SCFAs and promoting the growth of *Bifidobacterium* and *Lactobacillus,* demonstrating good anti-inflammatory and intestinal barrier protective effects (Bai, et al., 2023).

3.5. *Alleviate AAD*

Antibiotic-associated diarrhea (AAD) is a common complication of antibiotic treatment. In Zhang's research, yam polysaccharide (YP) could facilitate the recovery of acute diarrhea by enhancing the relative abundance of beneficial bacteria such as *Bifidobacteria* and *Lactobacilli*, while decreasing the levels of harmful pathogens like *Enterococcus* and *Clostridium perfringens*. This reversal of gut microbiota imbalance and increase in SCFA levels may be attributed to the polysaccharides in Chinese yam that regulate gut microbiota. The detailed mechanism of YP in alleviating AAD remains to be further explored (Zhang, et al., 2019).

4. Conclusions

CYPs have beneficial effects on IBD, obesity, inflammation, and AAD, as they stimulate the secretion of anti-inflammatory cytokines, reduce the production of pro-inflammatory cytokines, repair damaged intestinal mucosal barriers, increase the production of beneficial bacteria, enhance the production of SCFAs, maintain the intestinal microenvironment, and strengthen immune function. However, due to the complexity of the structure of CYPs and their mechanism of regulating gut bacteria, the basic research on CYPs is not thorough enough. Further studies are needed to determine the optimal therapeutic effects, accurate targets, and structure-activity relationship. The aforementioned research primarily focuses on animal experiments, lacking support from clinical studies. In addition, the activity of CYPs can be increased by altering their structure through chemical modifications and fermentation techniques. Hence, a comprehensive analysis of the molecular composition and chemical modifications of CYPs is essential in order to understand the correlation between CYPs molecular structure and their biological effects.

Acknowledgments

This work was supported by the Grant from Hubei Province, China (GRANT number 2019ABA100), Assessment and Comprehensive Utilization of Characteristic Biological resources in Dabie Mountains (4022019006).

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