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A review of food-derived polysaccharides in intervening in disorders of glucose and lipid metabolism: an inter-organ crosstalk between gut, liver, adipose tissue, and nervous system

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ABSTRACT

The diseases caused by disorders in glucose and lipid metabolism have become one of the prevalent health issues, posing a serious threat to human health. Previous studies have shown that food-derived polysaccharides have a certain intervention effect on disorders in glucose and lipid metabolism. This article reviewed the structure-function relationship of food-derived polysaccharides and elucidated their role in regulating glucose and lipid metabolism. Some new evidence suggests that secondary metabolites such as short-chain fatty acids, secondary bile acids, and lipopolysaccharide act as signaling molecules, activating pathways related to glucose and lipid metabolism, alleviating oxidative stress, inhibiting inflammation in the body, and regulating the homeostasis of glucose and lipid metabolism. These results indicated that food-derived polysaccharides have a positive impact on the regulation of glucose and lipid metabolism by improving the gut microbiota environment. On the other hand, gut microbiota disturbance can affect the host's health through the gut-liver, gut-brain and gut-adipose tissue axes. Therefore, it is speculated that food-derived polysaccharides may intervene in glucose and lipid metabolism through the inter-organ crosstalk between gut, liver, adipose tissue, and nervous system. This essay provides a theoretical basis for the development and utilization of food-derived polysaccharides as prebiotics in intervening disorders in glucose and lipid metabolism.

1. Introduction

In recent years, the increasing high-sugar and high-fat diet intake has led to a series of diseases caused by glucose and lipid metabolism disorders, such as hyperlipidemia, diabetes, obesity, hypertension, cardiovascular and cerebrovascular diseases. Diseases caused by glucose and lipid metabolism disorder have been among the epidemic diseases, which often induce to damage of various organs, posing a serious threat to human health[1].

A primary cause of glucose and lipid metabolic disorders may be the inability to promptly decompose and utilize excess calories, leading instead to their accumulation as fat in the liver, and this process contributes to increased hepatic oxidative stress and the overexpression of peroxisome proliferator-activated receptor alpha (*PPAR-α*)[2], resulting in the intensified oxidative stress, liver damage, and the insulin resistance. Clinical treatment is generally chemotherapy to simply reduce blood sugar, which has side effects. This leads to a marked deterioration of the energy accumulation mechanism in the body[3]. Previous studies have shown that food-derived polysaccharides can enhance the body's antioxidant defense system, suppress the inflammation, and regulate the homeostasis of glucose and lipid metabolism[4].

Food-derived polysaccharides are naturally occurring carbohydrates extracted and prepared from edible sources, which exhibit complex

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structures and diverse functional activities. These polysaccharides are obtained from a wide range of common dietary components including fruits, vegetables, grains, aquatic products, and certain meat products, as illustrated in Fig. 1. Studies have shown that food-derived polysaccharides exhibit promising applications in immune regulation, anti-tumor activities, antiviral properties, antioxidant effects, and blood sugar reduction. Due to their natural origin and low toxicity, they are considered ideal materials for pharmaceuticals and health food products[5]. Research on dietary polysaccharides can be dated back to the early 19th century. In 1825, Braconnot extracted a substance from carrots that could form a gel, naming it pectin[6]. Given the diverse physiological functions and physicochemical properties, dietary polysaccharides have been widely used in pharmaceuticals, health products, material sciences, and the food industry[7]. Many researchers and companies are paying attention to this valuable macromolecular compound.

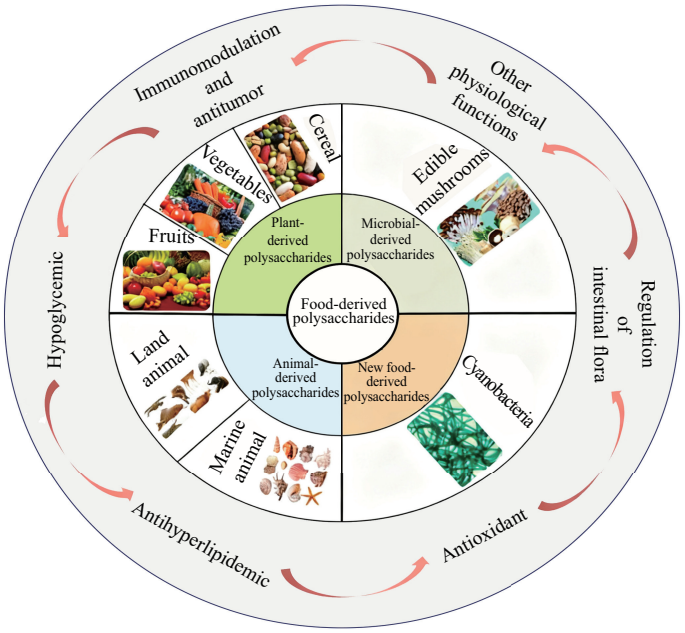

Fig. 1 Classification and physiological function of food-derived polysaccharides.

In this paper, we reviewed the structure-function relationship of food-derived polysaccharides. We elucidated their role in regulating glucose and lipid metabolism. The intervention mechanism of food-derived polysaccharides on the disorders of glucose and lipid metabolism in the body is described, mainly from the aspects of inter-organ crosstalk between the gut, liver, adipose tissue, and nervous system, in order to provide a reference for subsequent studies.

2. Structure-activity relationship of food-derived polysaccharides

The structural characterization of food-derived polysaccharides, including molecular weight, monosaccharide composition, linkage sequence, and mode of sugar residues, morphological characteristics of polysaccharide aggregates, etc. The molecular weight of natural polysaccharides varies from a few thousand to a few hundred thousand Daltons, and the way of biological activity is also very complex[8]. As shown in Fig. 2, the main structural types and characteristics of food-derived polysaccharides were also different. They are mostly composed of glucose, mannose, galactose, fructose, rhamnose, fucose, arabinose, xylose, and other monosaccharides and their different configurations are linked according to different connection modes[9]. Different polysaccharides have different monosaccharide composition and proportion. The morphological characteristics of polysaccharides aggregates can be observed by atomic force electron microscopy or scanning tunneling microscopy. There are the netted structure of branches, such as the polysaccharides from jujube[10], corn silk[11], Tibetan hull-less barley[12] and green tea[13]. They are sphere or sheet having holes, as in the polysaccharides from *Abelmoschus esculentus* L. flowers[14], watermelon rinds[15], glycyrrhiza uralensis[16] and senegrain seed[17].

Generally, monosaccharide components, molecular weight, functional groups, glycosyl linkage type, molecular chain conformation, and branch structure are detected and analyzed to reveal the structure-activity relationship of polysaccharides[18]. In the study of the polysaccharides from black bean[19], which was found to be composed of three components. Their antioxidant activity was positively correlated with xylose and galactose contents. *Salvia officinalis* L.[20] and marine polysaccharides[21] were consistent with this conclusion. Rhamnose content has also been confirmed to be closely related to the antioxidant activity of polysaccharides. Among the three components of the polysaccharides from *Pleurotus*[22], the components with high rhamnose-content showed higher antioxidant capacity. In addition, hydroxyl exposure is also closely related to antioxidant level. The more exposure of hydroxyl groups, the stronger the antioxidant activity. Modified polysaccharides tend to be more bioactive, mainly because the modification process exposes more hydroxyl groups[19]. The introduction of acetyl group, aldehyde group and sulfate can improve the OH exposure of polysaccharides and enhance their antioxidant activity[23]. On the other hand, the glycosidic bond is an important structural unit in polysaccharides and has an important influence on their activity. It has been shown that *Dendrobium* polysaccharide with *β*-configuration of pyranose has stronger activity than *α*-configuration[24]. The types of glycosidic linkage that constitute polysaccharide repeat units of *Dendrobium* polysaccharide mainly include (1→4), (1→6), (1→3), (1→3,6), and (1→4,6). (1→4)-*β*-*D*-Glcp and (1→4)-*β*-*D*-Manp are considered to be the core units of polysaccharide structure in *Dendrobium*, and may be the key fragments related to polysaccharide activity in *Dendrobium*. For example, the (1→4)-*β*-*D*-Manp and *o*-acetyl groups in *Dendrobium* polysaccharides are considered to be major structural features with antioxidant activity[24]. Molecular weight is also closely related to the antioxidant capacity of polysaccharides. Studies have pointed out that the smaller the molecular weight, the stronger the antioxidant capacity. However, most of the polysaccharides from food sources have a larger molecular weight, but their intervention on glucose and lipid metabolism is significant. The effect may be related to gut microbes.

Polysaccharide is one of the important energy substances of intestinal microorganisms. The metabolites of polysaccharides produced by microbial fermentation directly affect the intestinal flora structure. The polysaccharides from mulberry leaves have three components[25]. Component 3 (Sy01-23) has the function of improving intestinal flora, and its molecular weight is 7.5 kDa. This may be due to its rich rhamnose, galacturonic acid, arabinose. Sy01-23 can be degraded by *Bacteroides ovatus* (BO) and *Bacteroides cellulosilyticus* (BC) to

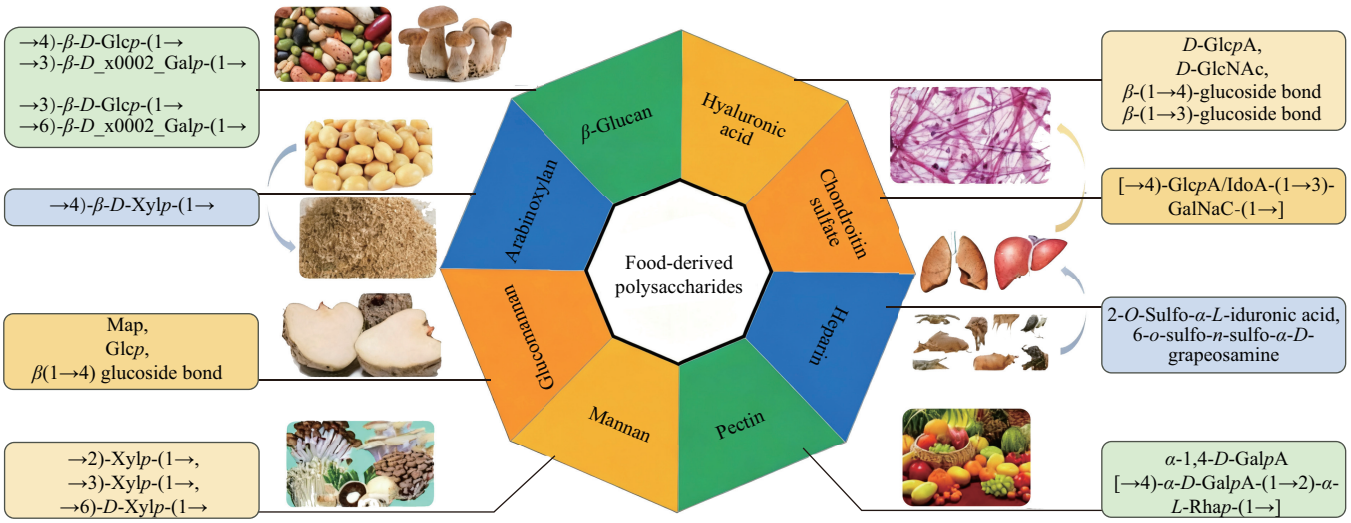

Fig. 2 Mainly structural types, characteristics, and sources of food-derived polysaccharides.

produce rhamnose, xylose, arabinose and other monosaccharides and oligosaccharides. These products provide nutrients for other strains such as *Bacteroides thetaiotaomicron* (BT) to grow. At the same time, BC can also produce acetic acid and propionic acid by glycolysis of Sy01-23. The polysaccharides from *Undaria* (HAW1-2) were rich in arabinose and galactose with a molecular weight of 8.94 kDa. Haw1-2 can promote the colonization of BT, BO, *Bifidobacterium longum* (BL) and other beneficial bacteria in the intestinal tract and regulate the structure of the bacterial community[26].

On the other hand, the study of intestinal microbiome-mediated catabolism of polysaccharides is also one of the hot topics in the future. The genome of gut microbiota could encode various and adequate carbohydrate-active enzymes, including glycoside hydrolases, carbohydrate esterases, polysaccharide lyases, and glycosyltransferases. Microbes in the gut can target polysaccharides and produce tools to degrade them into oligosaccharides or monosaccharides. In the symbiotic bacteroidetes culture experiment, it was found that *Bacteroides dorei* could degrade carob galactose, Konjac glucomannan promotes the growth of *Lactobacillus Helveticus*, *Bifidobacterium adolescentis*, and other probiotics, possibly by sharing mannose oligosaccharides and mannose with these intestinal probiotics[27]. Li et al.[28] found that all the 4 galactoglycans (porphyran, agarose, carrageenan, and arabinogalactan) could be used by gut *Bacteroides*. Porphyran could be used by *Lactobacillus* and *Bifidobacterium*. Arabinogalactan can be used by *Lactobacillus*, *Bifidobacterium* and *Roseburia*. The gut microbiota can also metabolize polysaccharides and transfer them to other active substances, primarily short-chain fatty acids (SCFAs). SCFAs are absorbed by gut tissues and offer multiple nutritional benefits[29]. It was proposed that a single microbiome in the human gut can break down the most complex carbohydrates in our diet[30]. Understanding these complex carbohydrates will provide us with new biological strategies and opportunities to improve human health. Due to the complex structure of polysaccharides and intestinal microbiota, our study on the structure-activity relationship between polysaccharides and intestinal microbiota is only the tip of the iceberg. Therefore, we need to continue to accumulate experimental data in this aspect, and prepare for the in-depth study of the structure activity relationship of polysaccharides.

3. Food-derived polysaccharides activate glucose and lipid metabolism signaling pathway

As shown as Fig. 3, food-derived polysaccharides on glucose and lipid homeostasis are mediated, at least in part, through the PI3K/AKT and AMPK signaling pathway. PI3K-AKT signaling pathway is the main signaling pathway that regulates glucose metabolism homeostasis in the body. Polysaccharides can activate the PI3K-AKT signaling pathway and induce the expression of downstream signals. In AKT/PKB signaling pathway, the dysfunction of PI3K will lead to the disorder of glucose metabolism. The direct downstream factor of PI3K is AKT, and the phosphorylation of AKT can promote the transport of glucose transporter 4 (GLUT4) to the plasma membrane and increase glucose uptake by cells[31]. On the other hand, it can effectively regulate glycogen synthesis by inhibiting phosphorylation of glycogen synthase kinase (GSK-3β) [32].

Konjac mannan oligosaccharides (KMOS) were a hydrolyzed product of Konjac mannan isolated from the konjac tuber. It was mainly composed of *β-D*-mannose and *β-D*-glucose by *β*-(1→4) glycoside bond[33]. KMOS can activate the GSK3β/CREB pathway in HepG2 cells induced by high glucose and improve insulin resistance. It also regulates liver triglyceride and glycogen metabolism by activating phosphorylation of liver Janus kinase 2 (JAK2) and transcriptional activator 3 (STAT3). Red bean polysaccharides (RBP) are mainly composed of 3 components with molecular weight of 131, 83 and 5 kDa. The ratio of *L*-arabinose, *D*-galactose, *D*-glucose, *D*-xylose, *D*-mannose and galacturonic acid in RBP was 2.27:0.83:10.78:1.99:11.23:2.78. RT-PCR and Western blotting results showed that RBP up-regulated the expression of INSR, IRS-1, PI3K, P-AKT and GLU-2, indicating that both upstream and downstream genes of the PI3K/AKT pathway were activated. The activated upstream gene PI3K promotes insulin sensitivity through IRS-1 feedback, and the activated downstream gene GLUT-2 regulates glucose metabolism by affecting glucose transport and glycogen production[34]. A brief introduction of related polysaccharides is shown in Table 1.

In the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway, AMPK can directly regulate the expressions of acetyl-CoA carboxylase (ACC)[35], HMG-CoA reductase (HMGR),

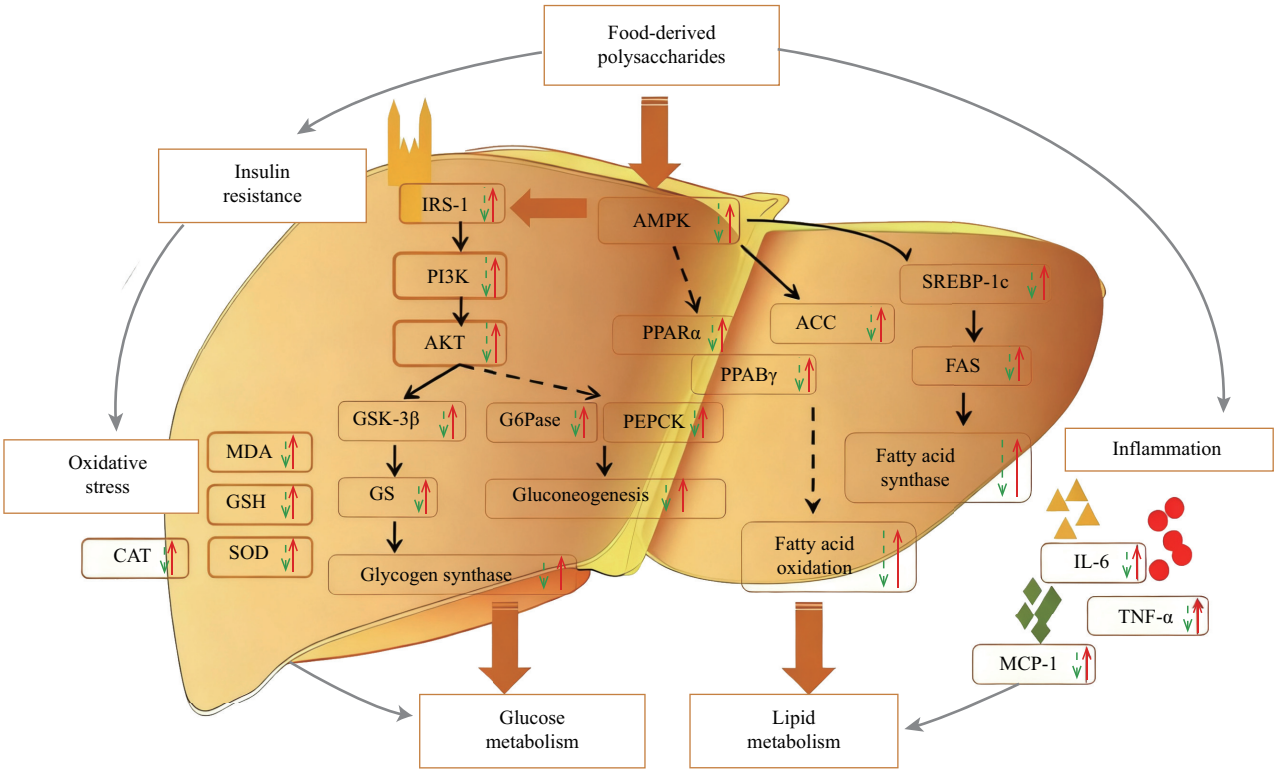

Fig. 3 Regulation of glucose and lipid homeostasis by food-derived polysaccharides is mediated by PI3K/AKT and AMPK signaling pathways.

sterol regulatory original binding protein (SREBP), glycogen synthase (GS), and TORC2 proteins. ACC, a key enzyme necessary for fatty acid biosynthesis, is negatively regulated by phosphorylated AMPK. HMGR is a rate-limiting enzyme in the process of cholesterol synthesis in hepatocytes, catalyzing the generation of mevalonic acid, inhibiting HMGR by phosphorylation of AMPK, and impeding cholesterol synthesis[36]. SREBP is a fat transcription factor regulated by glucose and insulin nutrition. Phosphorylation of AMPK can inhibit the expression of SREBP, thereby reducing the expression of fatty acid synthase (FAS), regulating the synthesis of long-chain fatty acids and fat storage, and reducing the TC and TG levels in body cells[37]. Phosphorylated AMPK also regulates glucose metabolism by inhibiting the activity of glycogen synthase (GS). In addition, it can inhibit the expression of TORC2 protein, thereby inhibiting the activity of phosphoenolpyruvate carboxykinase (PEPCK), which is a key enzyme in the gluconeogenesis process and a potential target for controlling blood glucose homeostasis.

Radish is one of the most common foods in our daily life. The polysaccharides of radish (PRG) play a role in regulating lipid metabolism. PRG is mainly composed of neutral sugars (70.8%) and uronic acids (22.3%), and its monosaccharide components include rhamnose, fucose, arabinose, xylose, mannose, galactose, glucose, glucuronic acid and galacturonic acid, with a molar ratio of 5.4:5.0:22.9:0.4:2.0:40.7:2.1:1.9:12.7. For obese mice induced by high fat diet, PRG can reduce the expression of SREBP-1, ACC and Fas proteins through AMPK signaling pathway, inhibit the expansion and size of adipocytes, and restore the lipid metabolism homeostasis of the body[38]. *Cichorium glandulosum* Boiss (CGP) is a kind of characteristic plant that can be used for both medicine and food, with the effect of lowering blood lipid in animal model. Ding et al.[39] conducted a relevant study on water-extracted polysaccharides of CGP. It was found that compared with the high-fat diet group, the expressions of fatty acid biosynthesis related gene (*FAS*) and fat generation related gene (*SREBP-1*) were significantly decreased in the CGP treatment group, and the lipid-oxidation related genes *PPAR-α* and *PPAR-β* was increased, thus inhibiting the formation of adipocytes, accelerating the catabolism of fat and regulating the homeostasis of fat metabolism. There are also many polysaccharides from food that interfere with glycolipid metabolism by affecting lipid signaling pathways. A brief introduction of related polysaccharides is shown in Table 1.

Table 1
Anti-fatigue response of amino acids and other compounds.

Materials	Molecular (kDa)	Monosaccharide composition	Surface characteristics	Signaling pathway	Reference
Ganoderma atrum	–	Glc, Man, Gal, GalA	–	PI3K/AKT	[40-41]
Abrus precatorius	131, 83, 5	Ara, Gal, Glc, Xyl, Man, GalA	–	PI3K/AKT	[34]
Coprinus comatus	495.8	Fuc, Rib, Ara, Xyl, Man, Gal, Glc	–	PI3K/AKT	[42]
Citrus maxima	110, 68, 31, 12	–	–	PI3K/AKT	[43]

Table 1 (*Continued*)

Materials	Molecular (kDa)	Monosaccharide composition	Surface characteristics	Signaling pathway	Reference
A. esculentus	26.9	Gal, GalA, Rha, Ara	–	PI3K/AKT	[44-45]
Green tea	–	Man, Rib, Rha, GlcA, GalA, Glc, Xyl, Gal, Ara, Fuc	Netted structure	PI3K/AKT	[46-47]
Corn silk	62.16	Ara, Man, Glc, GalA, Gal	Sponge-like	PI3K/AKT	[11-31]
Konjac mannan	910	Glc, Man	–	PI3K/AKT	[33-48]
Konjac mannan	910	Glc, Man	–	AMPK	[33-48]
Raphanus sativus	61.1	Rha, Fuc, Ara, Xyl, Man, Gal, Glc, GlcA, GalA	–	AMPK	[38]
C. glandulosum	8.5	Sor, Glc, Fru, Glc	–	AMPK	[39]
Agaricus blazei	10	Glc	–	AMPK	[49-50]
Cyclocarya paliurus	135, 9.3	Rha, Ara, Xyl, Man, Glc, Gal	Small sheet particles	AMPK	[51-52]
Grifola frondosa	155	Rha, Xyl, Man, Glc	–	AMPK	[53]

Note: Ara, arabinose; Fru, fructose; Fuc, fucose; Gal, galactose; GalA, galacturonic acid; Glc, glucose; GlcA, glucuronic; Man, mannose; Rha, rhamnose; Rib, ribose; Xyl, xylose. – indicates that no additional details are provided for that item.

4. Anti-fatigue effects of animal products

The complex composition of gut microbiota affects the health of the host. The disorder of microflora is closely related to the disorders of glucose and lipid metabolism, including obesity and diabetes. The intestinal flora is involved in the absorption of nutrients such as carbohydrates and fats in the body, and affects the metabolism of glucose and lipid, which is closely related to the health status of animals[54-55]. A large proportion of polysaccharides are macromolecular polymers that are not easily absorbed in the digestive tract, but enter the colon to participate in the process of intestinal microorganism fermentation[56]. Changes in intestinal microenvironment can increase or decrease the production of some metabolites (signal molecules), such as SCFAs, secondary bile acids and lipopolysaccharides (LPS). As shown in Fig. 4, these signal molecules activate or inhibit relevant signaling pathways and regulate glucose and lipid metabolism in the body.

SCFAs are signaling molecules that exist in the epithelial cells of ileum and colon and activate G-protein coupled receptors 41 and 43 (GPR41 and GPR43) related to glucose and lipid metabolism, and they play an important role in glucose and lipid metabolism[57]. They can induce the release of gastrointestinal peptide hormone PYY and glucagon-like peptide-1 (GLP-1), respectively. The decrease of PYY content will cause hunger, resulting in excessive food intake and the destruction of the balance of glucose and lipid metabolism. Decrease of GLP-1 leads to islet cell apoptosis, reduced insulin production, and disruption of glucose and lipid balance[58]. SCFAs also activate AMPK, promote the expression and transcription of GLUT4 in the body, stimulate the increase of glucose intake in the body, and maintain the glucose balance in the body[59]. AMPK also inhibits the activities of FAS and acetyl-CoA carboxylase, accelerates fatty acid catabolism, inhibits fat generation, and maintains lipid metabolism homeostasis.

Polygonatum kingianum is an edible and medicinal plant that is rich in sugar, fat, protein, carotene, vitamins and a variety of other nutrients. It is a kind of traditional Chinese medicine commonly used to treat diabetes and hyperlipidemia. Its polysaccharide also has the effect of lowering blood sugar and blood fat. In order to explore the mechanism of action, Gu et al.[60] isolated and purified total polysaccharides (PS) and high molecular weight

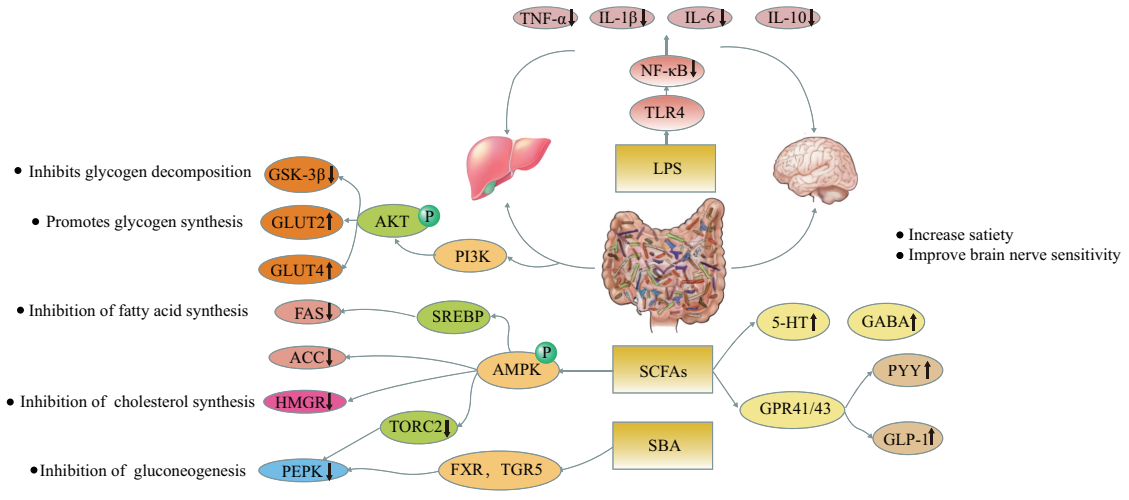

Fig. 4 Mechanism of food-derived polysaccharides in the intervention of glucose and lipid metabolism disorders by influencing intestinal flora.

polysaccharides (PSF) of *P. kingianum*, which were 134.7 and 178.6 kDa, respectively. The monosaccharide composition of the 2 polysaccharides was basically the same, consisting of mannose, galacturonic acid, galactose, and coenzyme, and the content difference was not significant[61]. By detecting the intestinal flora, it was found that the abundance of SCFAs in the intestinal flora of mice in the high-fat diet model group was significantly decreased, and the production of SCFAs was significantly lower than that in the normal group. Under the intervention of PS and PSF, the abundance of SCFAs producing bacteria and the production of SCFAs were significantly increased. Polysaccharides from *P. kingianum* may alleviate intestinal inflammation and improve energy metabolism by increasing the abundance of SCFAs producing bacteria in intestinal flora and increasing the production of SCFAs. Liu et al.[62] explored the hypoglycemic mechanism of pumpkin polysaccharide. The main component of pumpkin polysaccharide is 8.72 kDa. The polysaccharide is composed of 1,6-*α*-glucosyl, 1,2,6-*α*-mannosyl, 1,3,6-mannosyl, 1,2,6-*α*-galactosyl, terminal fucosyl and terminal glucose. Pumpkin polysaccharide can change the structure and relative abundance of intestinal flora. Correction of the corresponding SCFAs and intestinal microbiota suggests a mechanism by which pumpkin polysaccharide improves dyslipidemia or type 2 diabetes. Studies have shown that there are many other polysaccharides from food sources, including polysaccharides from okra[63], *Momordica charantia* L.[64], *Plantago asiatica* L.[65], *G. atrum*[40] and *Ophiopogon japonicas*[66], can improve intestinal flora and increase the content of SCFAs producing bacteria, thereby regulating glucose and lipid metabolism. Polysaccharides derived from okra and *M. charantia* L. can increase the content of total SCFAs in intestinal flora. Acetic acid, butyric acid and propionic acid play a major role in total SCFAs. Acetic acid is mainly involved in the balance of glucose metabolism in the liver[67]. Propionic acid plays a crucial role in fat metabolism and reduces obesity-related inflammation. Butyric acid is the main energy source for colon epithelial cells, which is closely associated with diabetes and insulin resistance[68]. The types of SCFAs produced by glycolysis are closely related to the monosaccharide composition of polysaccharides. Polysaccharides rich in glucuronic acid and xylose can produce more acetic acid and *n*-butyric acid through fermentation. Polysaccharides rich in arabinose and xylose produce more propionic acid through fermentation. Polysaccharides derived from *P. asiatica* L. and *Ophiopogon japonicus* can increase the levels of acetic acid, propionic acid, and butyric acid in intestinal flora.

Secondary bile acids are primary bile acids produced by the liver that enter the intestinal tract. They are processed and modified by intestinal flora enzymes catalyzed by a debinding reaction and hydroxyl removal. Secondary bile acids activate farnesoid X receptor (FXR) and G-protein coupled receptor (TGR5) and regulate energy balance and insulin sensitivity. On the one hand, intestinal flora can catalyze the production of secondary bile acids to regulate glucose and lipid metabolism. On the other hand, secondary bile acids can regulate the growth of intestinal flora, reduce the occurrence of bacterial migration, and maintain bacterial homeostasis. Secondary bile acids activate FXR mediated pathways to maintain glucose and lipid metabolism homeostasis, including the induction of fibroblast growth factor (FGF19) expression, regulating glucose homeostasis. In the liver, the expression of PEPK, G-6-P-enzyme, F-6-P-enzyme and other enzymes related to gluconeogenesis was down-regulated to promote the generation of liver glycogen and maintain blood glucose homeostasis. Activation of PPAR-γ signaling pathway and Wnt/*β*-actenin signaling pathway regulate adipocyte differentiation and body fat cell deposition; it also regulates the reverse transport of cholesterol and the balance of lipid metabolism[69]. Activation of TGR5 mediated signaling by secondary bile acids is usually mediated by activation of protein kinase A to achieve its role in maintaining glucose and lipid homeostasis. The monosaccharide composition of sulphated polysaccharides from *Gracilaria lemaneiformis* was galactose, glucose, caramel and mannose with molar ratio of 9.16:6.57:1.00:0.61. *G. racilaria lemaneiformis* can significantly reduce serum TC, TG, FFA levels and liver TC, TG levels in mice fed high fat diet, and prevent weight gain and fat accumulation induced by high fat diet. *G. racilaria lemaneiformis* can promote liver cholesterol metabolism, significantly increase the relative expression levels of liver X receptor α (*LXRα*) and *CYP7A1* genes, promote the transformation of primary bile acids to secondary bile acids, thereby reducing the secretion of very low density lipoprotein and regulating glucose and lipid metabolism[70]. The polysaccharides from *Radix Puerariae*[71], *Laminaria digitate*[72], *P. asiatica* L.[73], *C. paliurus*[74], *Sargassum fusiforme*[75] can also regulate intestinal flora, maintain bacterial homeostasis, increase the level of secondary bile acids, and regulate glucose and lipid metabolism.

LPS is a component of the cell wall of Gram-negative bacteria. When the intestinal flora is disturbed, the number of beneficial bacteria decreases and the number of G-bacteria increases greatly, resulting in impaired intestinal barrier function and increased intestinal wall permeability[76]. The passage of LPS into the blood through the intestinal wall is the way that LPS causes chronic low-grade inflammation throughout the body. LPS is an inducer of Toll-like receptor (TLR4) and mitogen-activated protein kinase (MAPK) signaling pathways, that can regulate inflammation, insulin resistance and glucose and lipid metabolism balance in the body[77]. TLR4 is the core of innate immunity, which can recognize the invasion of LPS, bind with its specific ligand, activate the NF-κB signaling pathway, release pro-inflammatory cytokines (such as TNF-α, IL-6, etc.), accelerate inflammation in the state of insulin resistance, and cause glucose and lipid metabolism disorders[78-79]. LPS is also an inducer of MAPK signaling pathway, involved in a variety of physiological processes such as cell proliferation, differentiation and glucose metabolism. This pathway is complex, and its involvement in the regulation of glucose and lipid metabolism remains to be further analyzed and verified.

Sea cucumber is a traditional food and medicine in China and other Asian countries, which has received widespread attention in recent years. It is rich in a variety of bioactive substances, including a variety of lipids, polysaccharides, saponins, and so on. Among these bioactive substances, only polysaccharides have been shown to regulate the gut microbiome. Sea cucumber sulfate polysaccharide and its depolymerized derivatives (SC-LCBs) can prevent obesity by altering the intestinal microbiota of mice fed high fat diet[80]. It was found that *Desulfovibrio, Enterorhabdus*, and *Blautia*, belonging to Gram-negative endotoxin-producing bacteria, were reduced in abundance at the genus level after treatment with SC-LCBS in mice. LPS levels in serum and feces also gradually decreased. Therefore, it is concluded that SC-LCBS can inhibit the growth of pathogenic LPS-producing bacteria and reduce the load of LPS entering the systemic circulation, which may be the reason why SC-LCBS regulates the

Table 2
Brief introduction of polysaccharides that activate inflammatory signaling pathway.

Materials	Molecular (kDa)	Monosaccharide composition	Surface characteristics	Signaling pathway	Reference
Arctium lappa	50, 30	GalA, Gal, Ara, Rha, Glc, Man	−	PKC/NF-κB	[85-86]
Cordyceps taii	−	Glc, Man, Gal	−	NF-κB	[87-88]
Chinese yam	16.6	Glc, Gal	Spherical shape	MyD88/NF-κB	[89-90]
Mytiloida	−	Glc	−	TLR4/NF-κB	[91]
P. kingianum	134.7, 178.6	Man, GalA, Gal, Fuc	−	TLR4/NF-κB	[60]
G. Lemaneiformis	18.5	Xyl, Man, Glc, Gal	−	NF-κB	[70,92]
Sea cucumber	180.8	Man, GlcN, GlcA, GalN, Glc, Gal, Fuc	−	TLR4/NF-κB	[80,93]
A. sphaerocephala Krasch	550, 39	−	−	NF-κB	[84]

Note: Ara, arabinose; Gal, galactose; GalA, galacturonic acid; GalN, galactosamine; Glc, glucose; GlcA, glucuronic; GlcN, glucosamine; Man, mannose; Xyl, xylose. − indicates that no additional details are provided for that item.

metabolic homeostasis of the body. SCL-CBS inhibits TLR4 and CD14 protein expression, regulates intestinal hilum, reduces LPS, and reduces body weight and fat weight. It has been reported that polysaccharides from *Lycium barbarum*[81], *Armillariella tabescens*[82], *Cordyceps cicadae*[83] and *Artemisia sphaerocephala* Krasch[84] can improve the intestinal flora, reduce the level of Gram-negative bacteria and LPS production, thereby reducing inflammatory responses. A brief introduction of related polysaccharides is shown in Table 2.

5. An inter-organ crosstalk between gut, liver, adipose tissue, and nervous system

Gut microbiota is now considered as a crucial partner implicated in the inter-organ dialogue, implying the control of physiological processes[94]. As shown in Fig. 5, the gut-liver, gut-brain, and gut-adipose tissue axis refer to the interactions between gut microbes and liver, brain, and adipose tissues.

Intestinal flora can affect the function of liver tissue through the immune system and endocrine system. When the organism is in a state of the disorder of glucose and lipid metabolism for a long time, it will lead to enhance the intestinal barrier permeability and bacterial translocation. Large amounts of LPS enter the bloodstream and stimulate the release of systemic inflammatory factors. These inflammatory factors act on liver tissue, exacerbating oxidative stress and causing liver inflammation[95]. Intestinal flora can regulate the production of SCFAs. SCFAs can reduce the synthesis of liver cholesterol and fatty acids through AMPK signaling pathway, and also affect the expressions of GLP-1 and PYY[96-97]. Therefore, the increase of SCFAs can reduce the accumulation of liver fat and reduce its oxidative damage. The production of PYY increases satiety and controls appetite. Bile acids are produced by the liver and enter the intestine, activating innate immune genes in the small intestine and directly or indirectly regulating the composition of gut microbes. It plays a crucial role in maintaining the integrity of the gut barrier.

The effect on brain tissue is mainly through the immune system, endocrine system and nervous system. A large number of inflammatory factors induced by LPS act on brain tissue increase the permeability of the blood-brain barrier, and cause nerve inflammation, nerve damage and cognitive impairment. SCFAs can stimulate the synthesis and secretion of 5-hydroxytryptamine (5-HT) in the intestine. 5-HT is a monoamine neurotransmitter that plays an important role in physiological processes such as cognition, learning and memory. The imbalance of intestinal flora can lead to decreased expression of γ-aminobutyric acid (GABA) and brain-derived neurotrophic factor (BDNA). GABA plays an important role in neuronal transmission, and abnormal secretion of GABA can lead to cognitive impairment[98]. BDNF plays an important role in the development, differentiation and cognition of the nervous system. The imbalance of intestinal flora can reduce BDNF levels in the hippocampus and cerebral cortex, leading to neurodegenerative diseases[99]. SCFAs may also promote the expression of GLP-1 and PYY, enhance sleep and inhibit the activity of appetite-generating neurons by stimulating GPR41 and GPR43. In addition, it has been shown that the increase of Firm-5 species *Lactobacillus apis* in intestinal flora can improve the contents of various glycerophospholipids in hemolymph and enhance the cognitive and memory ability of bees[100].

In the process of high-fat diet-induced glucolipid metabolism disorder, white adipose tissue (WAT) was the organ most affected in terms of gene expression, compared with the liver a nd intestine. Additionally, more than 75% of diet-altering genes were microbiome dependent, highlighting the significant influence of gut microbiota on WAT[101]. Indeed, fat storage and expansion are significantly modulated by gut commensals[102]. Research indicates that the disruption of gut microbiota is associated with metabolic disorders such as obesity and insulin resistance, suggesting a bidirectional relationship between the gut and fat[103]. There are 2 types of fat in mammals, WAT stores excess energy in the form of fat, while brown adipose tissue (BAT) converts energy from food into heat through uncoupling protein 1 (UCP1) in mitochondria. The quantity and composition of gut microbiota play a crucial role in energy

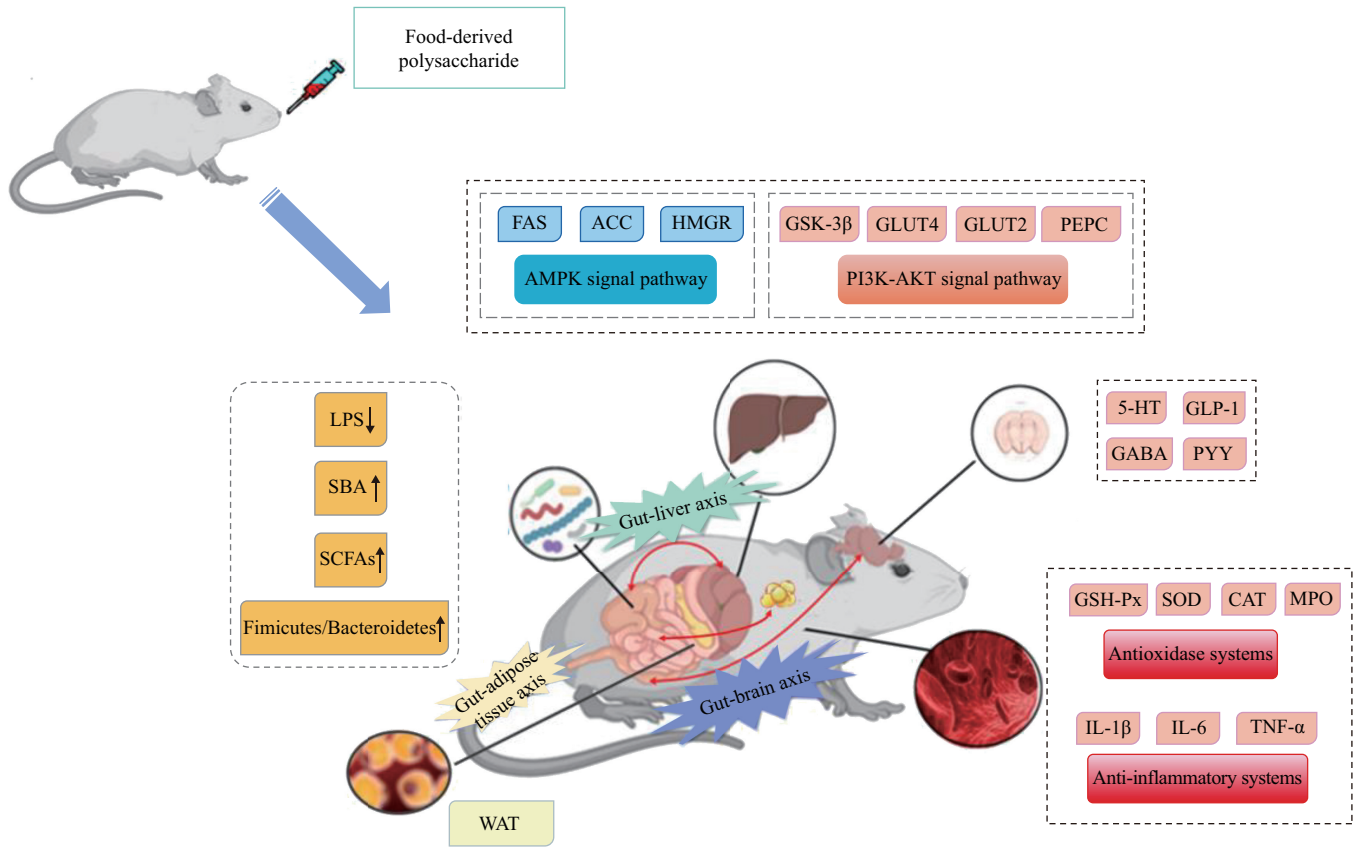

Fig. 5 The pathway through which food-derived polysaccharides interfere with glucose and lipid metabolism.

expenditure and fat thermogenesis in the body, with intermittent fasting, calorie restriction, and cold exposure leading to changes in gut microbiota composition, promoting browning of WAT and enhancing BAT activity[104]. Moreover, microbial-driven inflammation in WAT interacts with oxidative stress to disrupt mitochondrial function and insulin signaling. In obesity, a range of immune cells, primarily macrophages, gather within the WAT. Gut commensals control WAT inflammation through their metabolites, and metabolically activated macrophages play a more prominent role in insulin resistance[101,105]. Studies have shown that the expression of the miR-181 family (a type of microRNAs) in WAT of high-fat diet-induced obese mice is upregulated, inhibiting energy expenditure and promoting fat accumulation, insulin resistance, and WAT inflammation. However, tryptophan-derived metabolite indole from gut microbiota can inhibit miR-181, thereby improving diet-induced obesity and insulin resistance in mice[106]. Furthermore, exploring the interactions between innate and adaptive immune cells in WAT and gut microbes to reveal the role of WAT immunity in the progression of systemic insulin resistance. Therefore, targeting the gut-adipose tissue axis is emerging as a new therapeutic strategy for metabolic disorders.

The polysaccharide from *Rosa rugosa*[107] can increase the proportion of Firmicute and Lachnospira in the intestine through the gut-liver axis, relieve the systemic inflammatory response and oxidative stress, and thus alleviate the liver damage caused by alcohol. The polysaccharides from *Mussel*[91,108] can reshape the structure of intestinal flora, inhibit the activation of LPS-TLR4-NF-κB signal pathway, and regulate gut-liver axis abnormalities. It can relieve liver damage caused by alcohol. The polysaccharides from *Dendrobii officinalis*[109] can also reduce the permeability of the intestinal barrier and the secretion of inflammatory factors by affecting intestinal flora. In this way, liver damage caused by a high-fat diet can be alleviated[19]. The intervention of polysaccharides in food on brain injury caused by the disorder of glucose and lipid metabolism is relatively less studied. The polysaccharides from *Lentinula edodes*[110] can reduce neuroinflammation, improve the ultrastructure of synapses and increase the expression of BDNF in cerebral cortex of obese mice. The cognitive impairment caused by the disorder of glucose and lipid metabolism can be improved from these three aspects. The water-soluble polysaccharides from acorns and sago[111] increased SCFAs levels and decreased intestinal barrier permeability and inflammatory factors in obese mice. It can also enhance the expression of hypothalamus energy signal and improve glucose and lipid metabolism through positive regulation of gut-brain axis. The polysaccharides in *P. cymbium*[112] can also increase the production of SCFAs, stimulate GPR41 and 43 through the endocrine system, and promote the expression of GLP-1 and PYY. It regulates the disorder of glucose and lipid metabolism by suppressing appetite and increasing satiety. A brief introduction of related polysaccharides is shown in Table 3.

6. Conclusion and perspectives

The mechanism of food-derived polysaccharides to interfere with the metabolism of glucose and lipid in the body is often in multiple ways, which are interrelated and play roles together. However, most polysaccharides cannot be directly digested and absorbed by the small intestine due to their high molecular weight, but interfere with

Table 3
Brief introduction of polysaccharides that maintained the relative stability of gut microbiota.

Materials	Molecular (kDa)	Monosaccharide composition	Inter-organ crosstalk	Reference
P. kingianum	134.7, 178.6	Man, GalA, Gal, Fuc	Gut-liver axis	[60]
Pumpkin	–	Xyl, Ara, Glc, Rha, Gal	Gut-liver axis	[62-113]
M. charantia L.	20	GlcA, Xyl, Ara	Gut-liver axis	[64]
White hyacinth bean	230	Glc, Rha, GalA, Gal, Xyl, Ara	Gut-brain axis	[114]
O. japonicas	2.48	Fru, Glc	Gut-liver axis	[66]
G. Lemaneiformis	18.5	Xyl, Man, Glc, Gal	Gut-liver axis	[70-92]
Pseudostellaria heterophylla	8.771	Glc, Gal, Ara	Gut-brain axis	[115]
Radix *Puerariae lobatae*	18.7	Glc	Gut-liver axis	[71]
Sea cucumber	180.8	Man, GlcN, GlcA, GalN, Glc, Gal, Fuc	Gut-liver axis/gut-adipose tissue axis	[80-93]

Note: Ara, arabinose; Fru, fructose; Fuc, fucose; Gal, galactose; GalA, galacturonic acid; GalN, galactosamine; Glc, glucose; GlcA, glucuronic; GlcN, glucosamine; Man, mannose; Rha, rhamnose; Xyl, xylose. – indicates that no additional details are provided.

glucose and lipid metabolism by affecting intestinal flora during the process of fermentation by affecting the abundance of intestinal flora and regulating the secretion of secondary metabolites. Food-derived polysaccharides regulated glucose and lipid metabolism by affecting intestinal flora. These secondary metabolites (SCFAs, secondary bile acids, and LPS) enter the blood as signal molecules, activate various signaling pathways related to the regulation of glucose and lipid metabolism, relieve oxidative stress and suppress inflammation in the body, and regulate glucose and lipid metabolism homeostasis. The complex composition of gut microbiota is closely related to the health of the host. When the intestinal flora is disturbed, it will affect the health of the host through the gut-liver axis, gut-brain axis, and gut-adipose tissue axis. It is speculated that the inter-organ crosstalk between gut, liver, adipose tissue, and nervous system are the main pathways through which polysaccharides, as a kind of macromolecular polymers, interfere with glucose and lipid metabolism. As a macromolecular nutrient, it holds significant potential for the development and utilization of food-derived polysaccharides in the intervention of disorders related to glucose and lipid metabolism.

In future research, key challenges include elucidating the mechanisms by which polysaccharides modulate gut microbiota and clarifying the relationship between polysaccharide structural features (such as functional groups, glycosidic bond types, and monosaccharide composition) and their effects on microbial communities. In addition, multi-omics combined analysis method can be used to explore the relationship between intestinal microbes and biological metabolites. For example, proteomics, metabolomics and other sequencing methods combined with bioinformatics knowledge were used to analyze the relationship between target genes or target metabolites and intestinal flora. The direct effect of polysaccharides on intestinal flora and the mechanism of improving glucose and lipid metabolism disorder were investigated by bacterial community transplantation after fermentation with healthy feces. This study proposes a novel research direction for the intervention of glucose and lipid metabolic disorders using various biological macromolecules.

Conflict of interest

The authors have declared no conflicts of interest.

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