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Advancements in Natural Polysaccharides for Regulating Intestinal Flora to Improve Type 2 Diabetes Mellitus

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Abstract: Natural polysaccharides can promote the proliferation of beneficial bacteria in the intestinal tract, inhibit pathogenic bacteria growth, and maintain intestinal flora diversity. They can also improve diseases caused by microbiota dysbiosis by regulating intestinal flora composition. Type 2 diabetes mellitus (T2DM) is a typical chronic metabolic disease, and its onset and progression are closely associated with dysbiosis of the intestinal flora. Natural polysaccharides can treat and alleviate diabetes by affecting the intestinal flora's species, quantity, abundance, and metabolic pathway. Treatment and intervention of T2DM by regulating intestinal flora have become directions in diabetes treatment. This study reviewed the natural polysaccharides that improve T2DM by regulating intestinal flora in recent years, including the relationship between intestinal flora and T2DM and the regulation and mechanism of natural polysaccharides on the intestinal tract of T2DM. This work guides the future utilization of natural polysaccharide resources and the management of T2DM.

Keywords: Polysaccharide; Biological activity; T2DM; Intestinal flora; Mechanisms

Introduction

Type 2 diabetes mellitus (T2DM) constitutes the most significant proportion of diabetes cases, representing over 90% of the global diabetic population (1). The age-standardized prevalence of T2DM is expected to rise from 5.9% in 2021 to 9.5% in 2050 (2). T2DM is primarily caused by insulin resistance, and then there is a decrease in the function of the pancreas, which gradually leads to hyperglycemia and, finally, diabetes. The development of T2DM is related to a variety of factors. Obesity leading to a high body mass index (BMI) (3), a diet high in calories and sugar, lack of exercise, work stress, smoking, and drinking may all lead to the development of T2DM (4). The most significant harm of T2DM is a series of chronic complications (5), mainly including these types: macrovascular lesions, such as coronary heart disease and stroke (6, 7); microvascular lesions (8), such as retinopathy and diabetic nephropathy (9); peripheral neuropathy, such as neuralgia and diabetic foot (10). The complications of diabetes have a significant impact on both the patient's quality of life and the economic burden on the family. A substantial proportion of the world's diabetic population remains untreated due to inadequate and unevenly distributed healthcare resources. Therefore, improving rates of diabetes treatment and managing diabetes complications is a huge challenge today.

Natural polysaccharides are biological macromolecules with multiple bioactive functions, like nucleic acids and proteins. They are commonly found in the cells of plants, animals, and microorganisms and significantly impact the life process. Since the concept of glycobiology came into being in the 1980s, sugar science has entered a stage of rapid development (11). Studies have shown that many natural polysaccharide compounds have specific preventive and therapeutic effects on diseases such as tumors (12), hypertension (13), hyperlipidemia (14), and diabetes (15).

In the treatment of diabetes, natural polysaccharides such as *Astragalus* (16), *Cyclocarya paliurus* (17), *Ganoderma lucidum* (18), and mulberry leaves polysaccharides exert hypoglycemic effects through various mechanisms. Additionally, these compounds help regulate the overall physiological balance of the body, contributing to improvements in diabetes-related complications (19). The hypoglycemic effect of natural polysaccharides is primarily achieved through various mechanisms. Natural polysaccharides modulate the activity of digestive enzymes, such as α-amylase and α-glucosidase, decelerating carbs' degradation and absorption in the intestines, which subsequently lowers postprandial blood glucose levels (20). Natural polysaccharides protect pancreatic β-cells and promote insulin secretion to control blood glucose levels (21). Natural polysaccharides promote insulin signaling pathways, boosting the response of target tissues (including the liver, muscles, and adipose tissue) to insulin, thus raising insulin sensitivity (22). They also modulate intestinal flora metabolism and composition, enhancing gut functionality and rectifying glucose metabolic abnormalities (23). Moreover, natural polysaccharides regulate glucose metabolism in the liver and skeletal muscles by enhancing glycogen synthesis and suppressing gluconeogenesis (24). This enhances glucose utilization and reduces blood glucose levels.

The intestinal tract is an essential digestive and nutrient-absorbing organ of an animal body. Microbes in the gut can affect the host's health by producing harmful or beneficial metabolites (25). The host provides energy and environment for the bacteria, while the microorganism supplies essential amino acids, vitamins, and short-chain fatty acids to the host. Recent research suggests that the

structure of the intestinal flora of T2DM patients differs significantly from that of non-diabetic patients (26). Natural polysaccharides enhance the growth of beneficial bacteria and contribute to the variety of microorganisms in the human gut, thus acting as a blood sugar regulator. This research aims to analyze the effects of natural polysaccharides with hypoglycemic effects in the past five years and then review the regulatory effects and mechanisms of natural polysaccharides on intestinal flora in T2DM.

Intestinal flora and type 2 diabetes

The intestinal flora is a vast and intricate community, mainly consisting of many bacteria and a smaller proportion of fungi, viruses, archaea, and protozoa (27). More than 1000 species of bacteria live in the intestinal tract, with a total of about 100 trillion (28), which is regarded as a novel and intricate autonomous organ. The gut carries more than a hundred times more genes than the human genome (29), also referred to as the human second genome. These large groups of bacteria are involved in more than 50 different species, mainly in *Firmicutes* (60% to 65%), *Bacteroidetes* (20% to 25%), *Proteobacteria* (5% to 10%), and *Actinobacteria* (about 3%) (30). Dominating the composition of the intestinal flora are the *Firmicutes* and *Bacteroidetes*. *Firmicutes* are the largest bacterial group in the intestine, and most are gram-positive, spherical, or rod-shaped. *Firmicutes*, including *Lactobacillus*, generate acetate, lactate, and antibiotic compounds that hinder the growth of harmful microorganisms and promote optimal health. In addition, other probiotics of *Firmicutes*, such as *Coprobacterium prevotelli*, are essential producers of butyric acid (31). Butyrate serves as an energy source for intestinal cells, facilitates the restoration and expansion of intestinal epithelial cells, and restrains the proliferation of detrimental bacteria to uphold intestinal health. *Bacteroidetes* are mainly composed of many different gram-negative bacteria, and the *Bacteroidetes* in the intestinal cavity have an intricate and typically advantageous symbiotic interaction with their hosts. *Bacteroides* play a crucial role in various essential processes within the human colon, such as the breakdown of carbohydrates through fermentation, using nitrogen-containing compounds, and converting bile acids (32).

The structure of intestinal flora determines the level and proportion of metabolites in various flora. It plays an important pathophysiological function intricately linked to multiple diseases' occurrence and progression. The intestinal flora can break down polysaccharides and generate short-chain fatty acids, stimulating the growth and specialization of epithelial cells and enhancing the intestinal mucosa's barrier function (33). Through adhesion and reproduction on the surface of the intestinal mucosa, it produces a variety of antibacterial substances to resist pathogen invasion of the body, which plays a vital function in promoting gut immunity and coordinating the immune system across the body. In addition, intestinal flora can synthesize compounds advantageous to the body, including vitamin B, vitamin K, conjugated linoleic acid, and some non-essential amino acids, which have critical nutritional effects on human hair, skin, and immunity (34). In its physiological state, the intestinal flora regulates the physiological and pathological processes of the body, such as metabolism, immunity, and inflammation, through the above ways. An imbalance in the intestinal flora disrupts its composition and function, resulting in reduced beneficial bacteria, increased harmful bacteria, and the onset of various disorders.

Several studies have demonstrated that individuals with T2DM have notable irregularities in the composition and quantity

of their intestinal flora compared to healthy individuals. Zhang et al. found that *Firmicutes* increased in insulin-resistant patients, *Bacteroidetes* decreased, and the ratio between the two increased (35). Qin et al. performed metagenomic sequencing of microbiota DNA in fecal samples from T2DM and non-diabetic patients (36). The primary bacteria genera in T2DM patients' stool samples were opportunistic pathogens, such as fecal *Bacteroides*. The main bacterial genera in the healthy control group were butyrate bacteria, including *Clostridium*. Additionally, researchers found that T2DM patients were rich in sulfate-producing *desulphurvibrio*. Larsen et al. applied the 16S rRNA sequencing method to investigate normal and diabetic populations (37). They found that the abundance of *Bacteroides* and *Proteobacteria* was high in the T2DM group, while the *Firmicutes* were low. Patients with T2DM have a decreased proportion of *Firmicutes* and an increased proportion of *Proteobacteria* in the gut. The content of *Probiotics*, such as *Bifidobacterium*, was significantly reduced. Karlsson et al. discovered a higher abundance of four types of *Lactobacillus* in T2DM patients, which showed a positive correlation with fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) levels. The abundance of five *Clostridium* species decreased, and their abundance was negatively correlated with FBG, HbA1c, and plasma triglycerides (38), indicating that these bacteria could potentially contribute to the development of T2DM. Gou et al. found 21 variables that could effectively predict the risk of T2DM in their study on gut microbes (39). Among them, the abundance of *g_Roseburia* was substantially less than that of healthy people. It can produce butyrate, improving the body's tolerance to glucose. *Pedersen* et al. found that the proportion of *Prehoella* and *Bacteroides* common in the gut of T2DM patients increased, resulting in an increased content of branched-chain amino acids (BCAA) in serum and insulin resistance (IR) (40). In a clinical study, gastric bypass surgery was performed on patients with T2DM. Three months after the surgery, it was found that the abundance of *Firmicutes* and *Bacteroidetes* in the gut decreased while the abundance of *Proteobacteria* increased. The abundance of 11 bacterial genera and 22 species changed, with the most significant differences observed in the increased abundance of *Enterobacter cancerogenus* and the decreased abundance of *Faecalibacterium prausnitii* and *Coprococcus comes* (41). In conclusion, the onset and development of T2DM are intricately linked to the imbalance of intestinal flora. Still, the relevant studies also show specific differences, which may be caused by insufficient sample size, individual differences, research methods, and databases.

Natural polysaccharides to improve T2DM based on intestinal flora regulation

Natural polysaccharides are derived from several sources and are primarily located in plants' roots, stems, leaves, and fruits. The most studied natural polysaccharides are edible plants, medicinal and edible homologous plants, and botanical drugs. A variety of natural polysaccharides were discovered to possess hypoglycemic effects. However, due to their significant structural differences, the mechanism of hypoglycemic effects of different natural polysaccharides is also different. The molecular weight, monosaccharide composition, glucoside linkage, and advanced structure greatly influence the hypoglycemic mechanism of polysaccharides. From the perspective of intestinal flora regulation, natural polysaccharides that can improve T2DM are summarized below. The sources, experimental model, polysaccharides dose and duration, and critical microbiota species associated with diabetes are listed in Table 1.

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References
Glycyrrhiza uralensis	Male C57BL/6j mice	0.1, 0.2, and 0.4 g/kg, 4 weeks	Relieved (hyperglycemia; IR; OS) Reduced (liver lipid; pro-inflammatory cytokines; serum LPS; serum creatinine; urea nitrogen)	Promoted (*Akkermansia*; *Lactobacillu*; *Romboutsia*; *Faecalibaculum*) Decreased (*Bacteroides*; *Escherichia-Shigella*; *Clostridium*)	(42)
Phellinus linteus	Male Wistar rats	0.3 g/kg, 8 weeks	Decreased (OGTT-AUC; GSP; TC; TG; LDL-C; AST; ALT; HOMA-IR) Increased (HDL-C; FINS; HOMA-β; SCFAs)	Increased abundance (*g_Bacteroides*; *g_Alistioes; g_Parabacteroides*)	(43)
Red quinoa	Male C57BL/6J mice	0.2 g/kg, 6 weeks	Decreased (FBG; AUC; INS; TC; TG; LDL-C; MDA; NO; ALT; TNF-α; IL-1β) Increased (HDL-C; GSH; GSH-PX; CAT; SCFAs)	Increased (*norank_f_Lachnospiraceae*; *unclassified_f_Lachnospiraceae; Akkermansia*; *unclassified_f_Atopobiaceae*) Decreased (*norank_f_Muribaculaceae*; *Lachnospiraceae_NK4A136_group*)	(44)

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References
Laminaria japonica	Male ICR mice	0.8 g/kg, 4 weeks	Decreased (FBG; OGTT; GSP; ALT; HOMA-IRI) Increased (HOMA-β; HOMA-ISI; GLP-1; SCFAs)	Increased (*Candidatus_Saccharimonas; Enterorhabdus*; *Bifidobacterium*) Decreased (*Lachnospira*; *Limnohabitans*; *Campylobacter*)	(45)
Phyllostachys nigra	*Db*/*db* mice	0.05 g/kg, 10 weeks	Decreased (blood glucose; T-CHO; OGTT; ISN; LDL-C) Controlled lipid and glucose metabolism	Decreased (*Escherichia-shigella*; *Clostridia_UCG-014*) Increased (*Lactococcus*)	(46)
Fructus mori	Male C57BL/6j mice	0.6 g/kg, 6 weeks	Decreased (FBG; GSP; OGTT; blood glucose; TC; TG; LDL-C; INS; HOMA-IR) Increased (HDL-C; HOMA-β; pancreatic index)	Increased (*Bifidobacterium*; *Allobaculum*) Decreased (*Shigella*)	(47)
Angelica	Male KKAy mice	0.4 g/kg, 4 weeks	Decreased (FBG; INS)	Increased (*Akkermansia*; *Lach-nospiraceae*) Decreased (*Desulfovibrio*)	(48)

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References
Fucus vesiculosus	Male Sprague-Dawley rats	0.2, 0.4 g/kg, 8 weeks	Decreased (FBG; HbAlc; AUC; TC; TG; LDL-C; INS; HOMA-IRI; Cr; BUN; ALT; AST) Increased (muscle glycogen; HDL-C; HOMA-βI; SOD; GSH-Px)	Decreased (*Escherichia-Shigella*) Increased (*Muribaculaceae_norank*; *Bacteroides*; *Blautia*; *Romaboutsia*; *Eubacterium_coprostanoligenes_group*; *Prevotellaceae_NK3B31_group*; *Desulfovibrio*; *Rose-buria*; *UBA1819*; *Ruminococcus_1*)	(49)
Onchidium struma	Kungming SPF mice	0.2 and 0.4 g/kg, 4 weeks	Decreased (FBG; OGTT; Proinflammatory cytokines) Alleviated insulin resistance	Increased (*Lachnoclostridium; Bilophila; Parabacteroides*) Decreased (*Enterococcus*; *Lactobacillus; Candidatus-Sacchairmonas*)	(50)
Dendrobium officinale	Male C57BL/6j mice	0.4 g/kg, 6 weeks	Relieved glucolipid metabolism, lipopolysaccharide leakage, and metabolic inflammation level	Decreased (*Helicobacter*) Increased (*Allobaculum*; *Bifidobacterium*; *Lactobacillus*)	(24)

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References
Cordyceps militaris	Male C57BL/6 mice	0.4 g/kg, 6 weeks	Improved glucose metabolism, lipid metabolism, hormone secretion, and diabetes complications.	Decreased (*Ruminococcus_torques_group*; *Enterococcus*) Increased (*Allobaculum*; *norank_f_Muribaculaceae*; *Alistipes*; *Lachnospiraceae_NK4A136_group*)	(51)
Corn silk	Male SD rats	0.1, 0.2, and 0.4 g/kg, 8 weeks	Relieved diabetes and diabetic kidney disease	Increased (*Dubosiella ;* *Lachnospiraceae_NK4A136_group*) Decreased (*Romboutsia*; *Prevotella-9*; *Megamonas*; *Acinetobacter*; *Ligilactobacillus*; *Anaerovibrio*)	(52)
Highland barley	Male C57BL/6j mice	0.4 and 0.8 g/kg, 4 weeks	Decreased (FBG; HOMA-IR; OGTT-AUC; MAD; INS; GHb; ALT; TNF-α; IL-1β) Increased (CAT; GSH)	Decreased (*Parasutterella*) Increased (*Lachnospiraceae_UCG-006; Eggerthellaceae; Streptococcaceae*)	(53)

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References
Ulva lactuca	ICR male mice	0.1 and 0.2g/kg, 4 weeks	Decreased (FBG; OGTT; INS) Increased (CAT; SOD) Improved INS tolerance	Decreased (*Alloprevotella; Faecalibaculum*; *Streptococcus*; *Family_XIII_AD3011_group*) Increased (Parasutterella, Dubosiella, Prevotellaceae_UCG-001)	(54)
Red kidney bean	Male Wistar rats	0.1, 0.2 and 0.4 g/kg, 4 weeks	Decreased (FBG; TC; TG; LDL-C; INS) Increased (HDL-C)	Increased (*Bacteroides*, *Succinivibrio*, *Phascolarctobacterium*, *Blautia*) Decreased (*Oscillospira*; *Mucispirillum*)	(55)
Mussel	Male C57BL/6 mice	0.3 and 0.6g/kg, 4 weeks	Decreased (FBG; INS; LDL-C; TC; TG) Increased (SOD; GSH-Px; HDL-C)	Increased (*Akkermansia*; *Siraeum*; *Eubacterium*; *Allobaculum*) Decreased (*Vibrio*)	(56)
Polygonatum sibiricum	Male db/db mice	1 g/kg, 6 weeks	Decreased (FBG; GSP; LDL-C; AUC; TC; TG; NEFA) Increased (SOD; GSH-Px; HDL-C; Leptin level)	Increased (*Turicibacter*; *Ruminococcus*) Decreased (*Romboutsia*; *Lachnospiraceae*)	(57)

| Source | Experimental model | Polysaccharides dose and duration | Impact on T2DM | Alterations in critical intestinal flora associated with T2DM | References |

Ginseng	Male SD rats	0.1 and 0.3 g/kg, 4 weeks	Alleviated polyphagia, irritable thirst, weight loss, hyperglycemia, hyperlipidemia, and hepatic lipid accumulation.	Decreased (*Escherichia_Shigella*; *Desulfovibrio*; *Ruminococcus,* *Romboutsia*) Increased (*Akkermansia*; *Lactobacillus*; *Saccharibacteria_genera_incertae_sedis*)	(58)
Lycium barbarum	Male C57BL/6j mice	0.05, 0.1, and 0.2 g/kg, 6 weeks	Relieved hyperglycemia, hyperlipidemia, and insulin resistance. Increased (CAT; SOD; GSH-Px)	Decreased (*Allobaculum*; *Dubosiella*; *Romboutsia*) Increased (*Bacteroides*; *Mucispirillum*; *Rumin* *Intestinimonas*)	(59)
Auricularia auricula	Male C57BL/6j mice	0.1, 0.2, and 0.4 g/kg, 10 weeks	Decreasing (FBG; OTGG) Increasing (SOD; CAT; GSH-Px)	Increased (*Faecalibaculum*; *Dubosiella*; *Alloprevotella*) Decreased (*Desulfovibrio*; *Enterorhabdus*; *Helicobacter*)	(60)

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References

Astragalus membranaceus	Male C57BL/6j mice	0.4 g/kg, 6 weeks	Improved glycolipids metabolism disorders, oxidative stress, inflammation, and organ injury	Decreased (*Shigella*) Increased (*Allobaculum*; *Lactobacillus*)	(61)
Cyclocarya paliurus	Male Wistar rats	0.2, 0.3 and 0.4 g/kg, 3 weeks	Reduced diabetes symptoms Promoted nutrition and energy metabolism	Increased (*Ruminococcaceae UCG-005*)	(62)
Coix seed	Male C57BL/6J mice	0.175, 0.35 g/kg, 4 weeks	Increased (INS; HDL-C) Decreased (TG; TC; LDL-C)	Decreased (*Helicobacter*; *Ruminococcus*; *Clostridia*; *Eubacterium*) Increased (*Bacteroides; Bifidobacterium*; *Lachnospiraceae*; *Akkermansia*)	(63)
Ganoderma lucidum	Male SD rats	0.4 g/kg, 4 weeks	Decreased (FBG; TG; TC; LDL-C; IL-1β; IL-6; MDA) Increased (SOD; CAT; GSH-Px; HDL-C)	Increased (*Blautia*; *Dehalobacterium*; *Bacteroides*; *Parabacteroides*) Decreased (*Aerococcus*; *Ruminococcus*; *Proteus*)	(64)

Source	Experimental model	Polysaccharides dose and duration	Impact on T2DM	Alterations in critical intestinal flora associated with T2DM	References

Rosa roxburghii Tratt	Male db/db mice	0.3, 0.6 and 0.9 g/kg, 8 weeks	Decrease (body weight; FBG; liver hypertrophy; INS; lipids)	Increased (*Bacteroidaceae*; *Bacteroidaceae S24-7 group*; *Lactobacillaceae*)	(65)
Grifola frondosa	Male Kunming mice	0.3 and 0.9g/kg, 4 weeks	Reduced (FBG; OGT; TC; TG; LDL-C) Increased (BAs; HDL-C)	Decreased (*Staphylococcus*; *Aerococcus*; *Alistipes*; *Enterococcus*)	(66)

Anti-diabetes mechanism of natural polysaccharides through intestinal flora

Regulates bile acid metabolism

Bile acids (BAs), synthesized by host metabolism, play a vital role in lipid digestion and are essential for assimilating dietary fats, cholesterol, and fat-soluble vitamins. Furthermore, BAs can act as a crucial signaling regulator, regulating glucose and lipid metabolism and energy homeostasis. BAs can activate two signaling molecules: farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor 5 (TGR5) (67). These molecules play a crucial role in regulating the liver's glucose metabolism. Numerous studies have demonstrated that total bile acid concentrations tend to rise in diabetic environments (68, 69), indicating a tight relationship between BAs content and the onset and progression of T2DM. Intestinal flora influences BAs metabolism, and changes in its content may also affect intestinal flora and their metabolites. Bile acids can directly produce equivalent antibiotic effects by altering the water solubility of bacterial cell membranes (70, 71). They can also indirectly produce antimicrobial effects through receptors. Zheng et al. used Fucus vesiculosus polysaccharide (FVP) to interfere with T2DM rats. The total bile acid level in the cecum was measured with a bile acid kit, and the composition of intestinal flora was conducted by 16S rRNA gene sequencing (49). The study revealed that the concentration of TBA in the cecum of diabetic rats treated with FVP polysaccharide was significantly elevated. Additionally, there was a negative correlation between the TBA concentration and the content of *Alistipes*. Liu et al. intervened with *Phellinus linteus* polysaccharides (PLP) in T2DM rats to significantly increase the abundance of *g_Bacteroides*, *g_Parabacteroides,* and *g_Alistioes*, which are closely related to bile acid biosynthesis (72). By analyzing the expression of the enzyme metabolizing BAs in the liver, BAs promote the secretion of glucagon-like peptide-1 (GLP-1). PLP treats diabetes by regulating intestinal flora and BA metabolism, promoting GLP-1 secretion, and increasing insulin release.

Effects on the synthesis of short-chain fatty acids (SCFAs)

Natural polysaccharides have the characteristics of high molecular mass, difficult digestion, and poor bioavailability. Once taken orally into the gastrointestinal tract, intestinal flora can ferment them to synthesize SCFAs. Organic acids of 1-6 carbons, primarily acetic, propionic, and butyric acids, compose SCFAs. The types and quantities of SCFAs closely correlate with the types of polysaccharides, their duration in the intestine, and the types of intestinal flora. Different polysaccharides selectively enhance the abundance of bacteria that produce SCFAs. Many SCFA-producing bacteria exist in the intestinal flora, such as *Bacteroides*, *Faecalibacterium*, *Clostridium*, *Eubacterium*, *Roseburiam*, and *Alloprevotella* (73). SCFAs may ameliorate T2DM by facilitating energy metabolism, controlling gluconeogenesis, and enhancing insulin sensitivity. SCFAs activate signaling pathways managed by G protein-coupled receptors. These pathways improve lipid metabolism, fatty acid oxidation, and glycogen synthesis, ultimately affecting blood glucose levels. In DM patients, SCFAs can improve glycated hemoglobin and increase glucagon-like peptide-1 (GLP-1) synthesis. GLP-1 enhances satiety to reduce eating, stimulates insulin secretion, and inhibits glucagon release to control blood sugar (74). Liu et al. discovered that *Dendrobium officinale* polysaccharide (DOP) increased the abundance of SCFA-producing bacteria in the intestines of pre-diabetic mice and promote the expression of SCFA receptors FFAR2/FFAR3 (75), which can aid in the restoration of

damaged pancreatic islets, reduce appetite, and enhance insulin resistance (76). DOP significantly reduced the relative risk of T2DM in prediabetes.

Regulate the body's inflammatory response

Lipopolysaccharide (LPS) is an endotoxin in the outer membrane of gram-negative bacteria, constituting a component of their outer wall. Following the demise of bacteria, LPS is discharged into the blood and transported from the intestinal epithelial cells to other tissues through newly synthesized chylomicrons to act on different cells. LPS is an activator of the inflammatory response. It binds to the Toll-like receptor four on the surface of immune cells to form a complex, prompting macrophages to release significant quantities of inflammatory cytokines such as TNF-α and IL-6. These inflammatory factors lead to systemic diabetic inflammation that causes insulin resistance and promotes pancreatic β-cell apoptosis. Pussinen et al. found that the activity of LPS in diabetic patients was higher than in normal individuals, which was notably positively associated with the risk of diabetes (77). Therefore, chronic low-grade inflammatory response is the essential feature of T2DM. In contrast, some probiotics can also control inflammatory cytokines and reduce inflammation and insulin resistance levels. *Bacteroides fragilis* can improve glucose metabolism through TLR2/IL-10 signaling pathways (78). *Roseburia intestinalis* can promote the synthesis of IL-22 and activate the STAT3 signaling pathway to reduce IR (79). Therefore, natural polysaccharides can regulate inflammation in the body and reduce the symptoms of T2DM by regulating the flora associated with the inflammatory response. Chen et al. discovered that *Fructus mori* polysaccharide (FMP) improved the proliferation of *Allobaculum* and *Bifidobacterium* and significantly inhibited endotoxin-producing *Shigella*. FMP reduced intestinal inflammation and oxidative stress levels and alleviated hyperglycemia and insulin resistance in T2DM mice by inhibiting TLR4/NF-κB pathway activation (47). A kind of heteropolysaccharide isolated from *Ganoderma lucidum* can increase the abundance of *Lactobacillus*, *Bacteroides*, and *Ruminococcus* in diabetic mice, reduce the release of intestinal endotoxins, decrease the level of inflammatory factors, and alleviate insulin resistance (33).

Discussions

As a natural product of anti-diabetes, natural polysaccharides have a broad space for development. In recent years, people have been trying to screen anti-diabetes drugs with good activity from natural polysaccharides, and many natural polysaccharides were found to possess hypoglycemic activity. Nevertheless, owing to the intricate composition of polysaccharides, there is no clear structure-activity relationship between the hypoglycemic effects. The structure of polysaccharides is the foundation for the investigation of the activity. Current studies on the structure-activity relationship mainly focus on the primary structure relationship, such as molecular weight (80), monosaccharide composition (81), type of glycoside bond (82), chemical structure modification, and other effects on hypoglycemic activity (83). There are relatively few structure-activity studies involving deficiency and higher structure, but higher structure is a crucial factor affecting activity. In the future, traditional structure research methods should be innovated to clarify the structure of polysaccharides and further study the activity.

The intestinal flora is the largest micro-ecosystem in the human body. Exploring the mechanisms by which natural polysaccharides treat diabetes from the perspective of gut microecology may serve as the key to unlocking novel approaches for preventing and

treating diabetes. With advances in research techniques that have greatly improved the understanding of intestinal flora, it is possible to link the pathophysiology of T2DM to alterations in the composition of the intestinal flora. However, the role of intestinal flora and the mechanism by which it influences human metabolic function are still poorly understood. Research into the intestinal flora of T2DM also faces some problems. There are objective differences in intestinal flora among different populations, such as genes, climate, diet culture, gender, and region (84, 85). Presently, the studies on altering the structure of intestinal flora by drugs do not consider the differences in the structure of bacterial flora in different populations, resulting in significant differences in drug efficacy or no effect on some populations. Most research on the hypoglycemic activity of polysaccharides by regulating intestinal flora is still in the animal experimental stage. However, the intestinal flora of animals is very different from that of human beings, and the strain and feeding environment of animals will have a significant impact on the intestinal flora, resulting in low repeatability of animal experimental data and little reference value for clinical research (86). Due to the limitations of research methods and techniques, the study of the mechanism of polysaccharide regulation of intestinal flora to reduce blood glucose has not been in-depth. In the future, the exact activity mechanism of polysaccharides can be further studied at the molecular level through multiple omics techniques, such as glycomics, metagenomics, transcriptomics, metabolomics, and proteomics.

The lack of an exact action target makes the natural polysaccharide a significant challenge in clinical hypoglycemia research (87). The absence of clearly defined molecular targets presents a considerable challenge in the clinical study of natural polysaccharides for blood glucose regulation. The complexity of polysaccharide structures and mechanisms of action, combined with numerous uncontrollable factors in clinical trials, makes such studies difficult to conduct. Different polysaccharides target distinct intestinal flora, suggesting that selecting polysaccharides based on the intestinal flora characteristics of diabetic patients could offer a novel, personalized strategy to restore microbiota abundance and diversity for T2DM treatment. Clinical applications should account for the differences in how various polysaccharides improve intestinal flora and related biomarkers. Designing controlled trials comparing the effects of different polysaccharides on diabetes treatment is crucial (88). Additionally, comparative studies on the therapeutic efficacy of polysaccharides at various stages of diabetes, as well as investigations into their mechanisms for treating diabetic complications, are worthy of further exploration.

Conclusions

T2DM is a persistent metabolic disorder with a high incidence characterized by hyperglycemia and insulin resistance. With advances in microbiome technology, intestinal flora, and metabolites are strongly associated with diabetes. Natural polysaccharides have been widely studied in preventing and treating diabetes. Hundreds of natural polysaccharides with hypoglycemic effects have been reported so far. Parts can be directly digested and utilized after the natural polysaccharide enters the digestive tract. In contrast, the undigested part enters the intestinal fermentation, which can improve T2DM by regulating or producing metabolites to stimulate the intestinal flora structure. Natural polysaccharides have the potential to lower blood glucose levels by controlling insulin and islet beta cells, regulating essential enzyme activity, improving glucose metabolism, regulating critical protein expression, and improving

oxidative stress levels in the liver (89, 90). The anti-diabetic mechanism of natural polysaccharides through intestinal flora regulates bile acid metabolism, produces SCFAs, and regulates the body's inflammation. The regulation mechanism of intestinal flora on T2DM is complex, which may result from the interaction between various pathways.

Credit authorship contribution statement

Conceptualization, Rong Li and Venkata Sathya Saiappala RajuVelaga; literature search, Rong Li; writing original draft preparation, Rong Li; writing-review & editing, Weiyun Chew and Muhammad Fattah Fazel. All authors have read and agreed to the published version of the manuscript.

Declaration of interest statement

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

Data availability

Not Applicable.

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