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Research Progress in the Mechanism of Polysaccharide in Relieving Type 2 Diabetes

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Abstract. Type 2 diabetes is one of the most common metabolic and endocrine disorder syndrome in the world. According to the statistics of the international diabetes federation, its incidence has risen sharply in recent years, which has seriously affected the human life and health. At present, most of the clinical therapeutic drugs have serious adverse reactions, which bring a variety of worries and difficulties for patients taking drugs for a long time. In view of the recent discovery of a large number of natural products with anti-diabetes activity, this paper reviews related literature in recent years, and compares and discusses their different activities and target spots, in order to provide new reference and ideas for the development of high-efficiency and low-toxicity diabetes drugs.

Key words: polysaccharide; type 2 diabetes; hypoglycemic; mechanism of action; antidiuretic activity.

INTRODUCTION

Diabetes is a chronic metabolic disease characterized by persistent hyperglycemia due to the inability of the pancreas to properly produce insulin or the relative insufficiency of insulin biological effects (i.e., insulin resistance). In 2017, the international diabetes federation (IDF) released the world's eighth edition of diabetes map, and the data showed that the number of diabetes patients worldwide reached 425 million in 2017, and it is estimated that the number of diabetes patients will reach 629 million in 2045, with a significant upward trend. It has nearly quadrupled from 125 million in 2000. The number of patients with diabetes in China is 141 million, and about 90% to 95% of them belong to type 2 diabetes [1].

Before, diabetes is divided into two broad categories: type 1 diabetes and type 2 diabetes. Type 1 diabetes, also known as insulin dependent diabetes mellitus, is mainly characterized by insufficient insulin secretion or inability of the pancreas in insulin secretion, resulting in insulin deficiency and increased blood sugar, and the mechanism of action is not yet clear. People with type 1 diabetes generally need long-term insulin injection. Type 2 diabetes, also known as non-insulin dependent diabetes mellitus, is mainly caused by insulin resistance and dysfunction of insulin beta cells, resulting in decreased tissue sensitivity to insulin and insufficient biological effects, leading to hyperglycemia [2]. With the aggravation of diabetes, there are many complications, such as diabetic nephropathy, diabetic foot, cardiovascular disease, lactic acidosis, and hypertonic syndrome of diabetes. Type 2 diabetes drugs currently used mainly include: sulfonylurea, glucagon-like peptide-1 receptor agonist, DDPV – IV inhibitor, biguanides, TZDs drugs, insulin and its analogs, alpha-glycosidase inhibitor and so on, long-term use are showing more severe adverse reactions [3]. As there is no effective drug to cure type 2 diabetes and diabetes patients need to take drugs for a long time, it is particularly important to find effective drugs with high efficiency and low toxicity, which is also the focus of front-line researchers.

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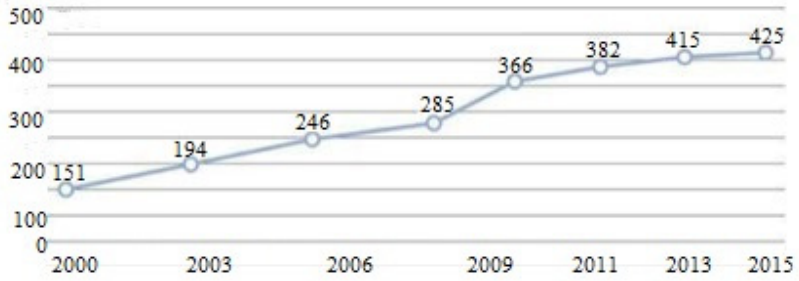

FIGURE 1. Global diabetes growth trend

Polysaccharides, also known as polyshvacchdyre, are polymers formed by the condensation and water loss of many different or identical single sugar molecules. In general, polysaccharides are composed of 9 or more monosaccharides connected by the glycosidic bond, which is a kind of carbohydrate with complex molecular structure and large size. Its molecular weight is generally tens of thousands to several million, which is usually represented by CX(H2O)y, so it is also called carbohydrate. Polysaccharides are widely distributed in nature and are important macromolecular substances in organisms, closely related to the various life activities of organisms. With the study of polysaccharides in recent years, polysaccharides have become more and more important in medicine. Polysaccharides can be used as components of plant cell walls, such as peptidoglycan and cellulose; It also acts as a store of nutrients for plants and animals, such as glycogen and starch. Some polysaccharides have special biological activity, for example, heparin in human body has anticoagulant effect, and polysaccharides in pneumococcal cell wall have antigenic action. Polysaccharides are the most abundant biological polymers in nature. They exist in almost all organisms, and have many biological functions such as energy storage, structural support, defense function and antigen determination. Therefore, polysaccharide and nucleotide, protein and lipid are called the four most important biological macromolecules in the life science. However, due to the complex structure of polysaccharides and the diversity of monosaccharides, the technology and methods of polysaccharides are still not perfect at present, which limits the research on polysaccharides and significantly lags behind the development of protein and nucleotide. A large number of studies have shown that polysaccharides and their derivatives have a variety of pharmacological activities, such as anti-oxidation, immune regulation, anti-tumor, anti-diabetes, liver protection, antibiosis and anti-fatigue [4-10].

In view of the serious adverse reactions of current drugs for relieving or treating diabetes after long-term use, polysaccharides are abundant in nature and have low toxic and side effects. Therefore, it is of great significance to search for polysaccharide drugs that can potentially relieve diabetes. Numerous studies have shown that polysaccharides can exert their anti-diabetes activity through various mechanisms. This paper summarizes the natural anti-diabetes polysaccharides and their derivatives in the last 8 years, discusses their potential therapeutic targets, and provides ideas for the subsequent development and utilization.

POLYSACCHARIDES THAT ENHANCE THE INSULIN SIGNALING PATHWAY

Activator of PI3K/Akt Pathway

PI3K (phosphatidyl inositol 3-kinase) is a complex that exists in the cytoplasm. It is a lipid kinase that catalyzes the phosphorylation of phosphatidyl inositol D3. It is related to the product of oncogene, and PI3K itself has the activity of serine/threonine kinase, as well as the activity of phosphatidylinositol kinase. It is a heterodimer composed of regulatory subunit p85 and catalytic subunit p110 [11]. Akt, also known as protein kinase B (PKB), is an important target protein downstream of PI3K signaling pathway. Activation of PI3K/Akt signaling pathway is mainly activated by two ways, one is activated by interaction with the receptor or protein with tyrosine residue, the other is that Ras directly binds p110 and leads to PI3K activation. Insulin binding activates insulin receptor substrate (IRS) phosphorylation through insulin receptor, and PI3K activation leads to the production of phosphatidylinositol-3,4, 5-triphosphate, resulting in three known Akt isomers being pyruvate dehydrogenase kinases. Akt is a key multi-effective kinase, which can activate phosphofructokinase and promote GLUT4 translocation by inactivating glycogen synthase kinase (GSK) [12,13](figure 2). Studies have shown that the PI3K/Akt signaling pathway is one of the key pathways for insulin to regulate blood sugar balance. Moreover, it is found that the functional defects of genes of PI3K regulatory subunit p85 and catalytic subunit p110 could all lead to the dazzling of glucose and lipid metabolism by using gene

knockout techniques, indicating that PI3K plays an important role in regulating glucose and lipid metabolism [14].

Dendrobium officinale polysaccharide DOS extracted from dendrobium officinale significantly relieved the symptoms of type 2 diabetic mice induced by streptozotocin. Pharmacological experiments show that DOP can regulate the synthesis of glycogen and lower the blood glucose level by regulating the gene expression of glycogen synthase kinase 3β (GSK-3β), glycogen synthase (GS) and glucose transporter 4 (GLUT4) in liver and muscle [15]. GSK-3 is a serine/threonine protein kinase with two highly homologous isomers: GSK-3α and GSK-3β. Insulin stimulates the rate-limiting enzyme GS in glycogen synthesis by promoting its dephosphorylation, while GSK-3 phosphorylation further inhibits GS. Inactivation of GSK-3β is the main mechanism of insulin - induced muscle GS activation. Therefore, GSK-3β could be identified as an insulin-mediated GS regulated negative regulator [16]. Lycium barbarum polysaccharide MDG-1 extracted from lycium barbarum can play an anti-diabetic role by activating the InsR/IRS/PI3K/Akt/GSK-3 / GLUT-4 signaling pathway. It is found that MDG-1 can promote the protein expression of InsR, IRS-2, PI3K, Akt and Glut4, and promote the transport and utilization of glucose, so as to achieve the purpose of hypoglycemia [17]. In addition, other studies have found that lycium barbarum polysaccharide can alleviate insulin resistance in C57BL/6L mice induced by HepG2 cells co-cultured with brown tree acid and by high-fat diet. It can up-regulate the expression levels of p-IRS-1, p-PI3K and p-AKt protein, and up-regulate the expression and phosphorylation level of nuclear factor E2 [18]. Zhou yunfeng et al. found in their study that astragalus polysaccharide can reduce the blood glucose level of rats with type 2 diabetes, and can effectively increase the levels of InsR, IRS-1 and PI3K to increase the tissue sensitivity to insulin and improve the insulin receptor and post-receptor link signal transduction [19]. It can be seen that polysaccharides have been shown to act on the PI3K/Akt pathway and activate other protein kinases to improve glucose and lipid metabolism.

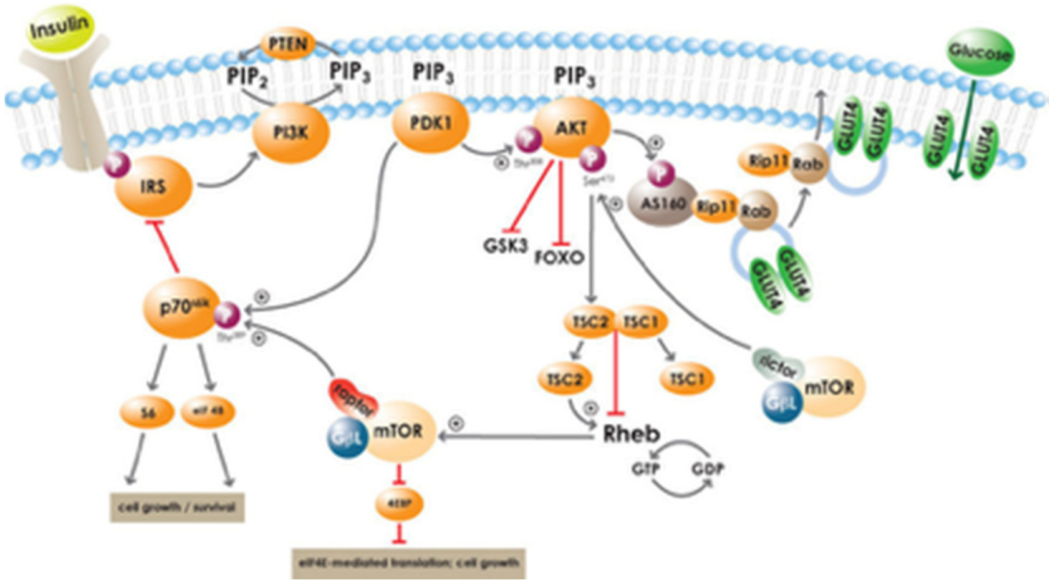

FIGURE 2. InsR / IRS/ PI3K / Akt / GSK-3 / GLUT-4 insulin signaling pathway

MAPK Pathway Activator

MAPK is a relatively common protein kinase, which is responsible for the intracellular transmission of extracellular signal. When stimulated by the external signal, it is activated by fluidization acidification and further transfers the signal to the cell. It is involved in various biological processes such as proliferation, differentiation, growth and apoptosis of cells, and also coordinates the synchronization of physiological and biochemical reactions among cells. In general, different extracellular signals can activate different signal transduction pathways. Each MAPK is activated by a specific MAPK kinase (MAPPK, MEK), which in turn is activated by MAPKKK kinase (MAPKKK, MEKK). MAPK signaling pathway is activated by the successive transmission of three signals of MAPKKK-MAPKK-MAPK, and then regulates the activity of downstream transcription factors, skeleton protein/actin and various proteases after fluidization. Therefore, the growth and division of cells can be regulated, which is closely related to the release of diabetes and inflammatory factors [20]. Relevant signal transduction pathways

are shown in figure 3[21].

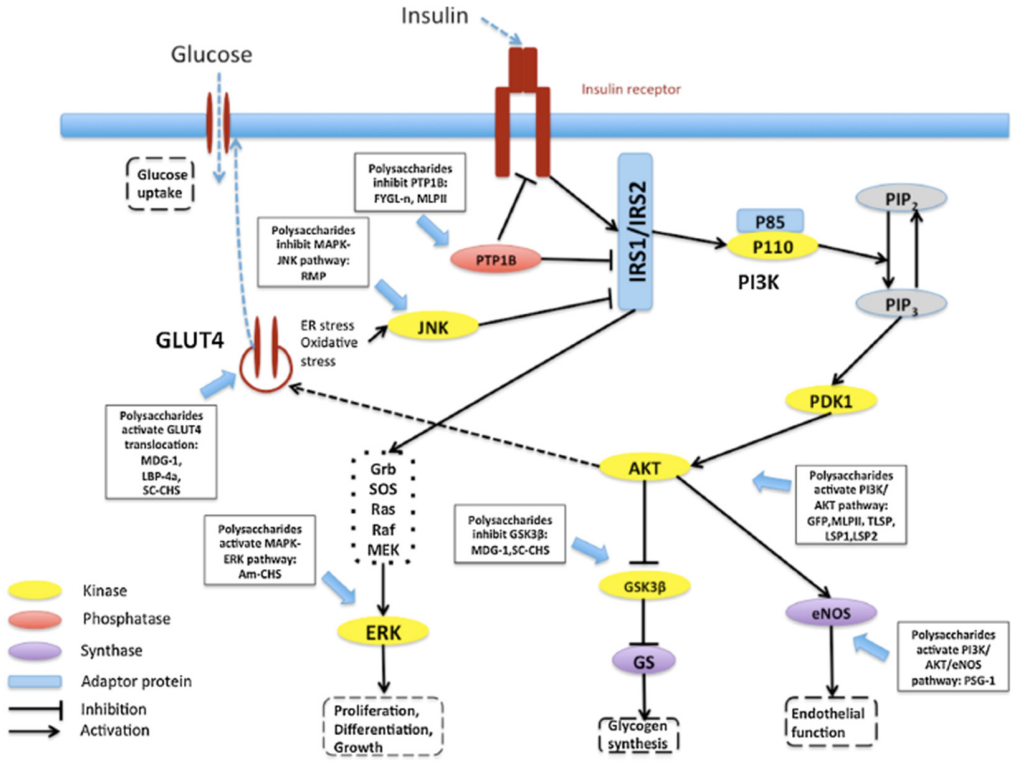

FIGURE 3. Regulation of MAPK islet signaling pathway by polysaccharide

Studies have shown that fucosylation chondroitin sulfate extracted from sea cucumber can reduce blood sugar, and that it is not regulated through the PI3K/Akt pathway. Further results indicated that the fucosylation chondroitin sulfate could promote the translocation of Glut4, enhance the uptake of glucose and enhance the phosphorylation of PKB and ERK, and promote the expression of m-GLUT4, p-PKB (Ser473), p-ERK1 / 2, p-PI3K p85 and p-IRS-1 (Tyr612) This indicates that the main pathway of action is MAPK pathway rather than PI3K, which further indicates that MAPK is another feasible development path for diabetes drugs [22].

POLYSACCHARIDE RELIEVING OXIDATIVE STRESS IN THE TREATMENT OF TYPE 2 DIABETES

PPARγ Pathway Activator

AMP- activated protein kinase (AMPK) signaling pathway plays an important role in oxidative stress on islet cells and can affect the occurrence and development of diabetes. The mechanism of metformin is to activate AMPK signaling pathway to increase insulin sensitivity and thereby reduce blood glucose. Peroxisome proliferator-activated receptor-γ, (PPAR-γ), is a type of nuclear transcription factors activated by ligands, which are distributed in tissues with active energy metabolism, and are the downstream factors of AMPK. AMPK activation can activate . PPARγ to enhance the oxidation of fatty acids and reduce lipid precipitation, which is also the molecular mechanism of thiazolidinedione , an insulin sensitizer. At the same time, PPARγ can not only regulate the metabolism of fatty acids, but also regulate the metabolism of glucose and participate in the expression of genes related to glucose and lipid metabolism. Therefore, PPARγ signaling pathway plays an important role in the control of diabetes and the development of diabetes drugs [23]. In human body, there are four isomers of PPAR-γ mRNA, namely PPAR-γ1, PPAR-γ2, PPAR-γ3 and PPAR-γ4. PPAR-γ1, PPAR-γ2, and PPAR-γ4 Mrna generate the same gene product PPAR-γ. PPAE-γ2 Mrna produces a protein with 28 amino acids on the NH2 side. Four PPAR-γ mRNA isomers are not

identical in different tissues.PPAR-γ1 is expressed at different levels in all tissues, PPAR-γ2 is expressed in adipose tissue, PPARγ3 is expressed in adipose tissue, colon, macrophages and T lymphocytes, while the expression of PPAR-γ4 is not clear. PPAR-γ related signal transduction pathways include PPAR-γ activation and regulation of target gene transcription expression pathways. This includes ligand activation of PPAR-γ, activation of PPAR-γ interaction with PPRE, participation in lipid metabolism, cell proliferation, differentiation and apoptosis by regulating biological effects such as gene transcription and translation. PPAR-γ in the PI3K signaling pathway can promote the expression of PI3K gene, enhance insulin sensitivity, and also promote the expression of GLUT4 gene and promote the uptake of glucose [24]. Multiple studies have shown that polysaccharides can increase the expression of PPAR-γ signaling pathway. For example, in the experiment on the effect of astragalus polysaccharides on the expression of PPAR-γmRNA in rats with insulin resistance to type 2 diabetes, the results showed that astragalus polysaccharides can enhance the expression of PPAR-γmRNA [25]. In the experiment on the therapeutic effect of rehmannia polysaccharides on the rat model of diabetic nephropathy and its effect on PPAR-γ signaling pathway, the results showed that the expression levels of PPAR, aP2 and GLUT4 protein in the rats injected with rehmannia polysaccharides were all increased relative to the model group, and the higher the dose of rehmannia polysaccharides was, the higher the protein expression was [26]. In addition, experiments have proved that Pumpkin polusaccharide (PP) [27] and Momordica charantin Linn polysaccharides [28] can enhance the expression of PPAR-γmRNA. To sum up, partial polysaccharides can enhance the expression of insulin to signaling pathway, thereby reducing insulin resistance and alleviating type 2 diabetes.

Polysaccharides That Ameliorate Islet Cell State with Antioxidant Effect

Studies have shown that the increase of free radicals in the pathogenesis of diabetes is closely related to blood sugar and lipid peroxidation (LPO) [29]. Diabetic patients usually show oxidative stress (ROS) due to persistent and chronic hyperglycemia, which promotes the generation of free radicals [30]. And oxygen free radicals can react with polyunsaturated fatty acids to cause LPO[31]. LPO elevation can change the function of membrane-bound enzymes and receptors, resulting in functional damage [32]. MDA, as a by-product of LPO, can reflect the degree of oxidation in the body. At the same time, excess NO can inhibit mitochondrial metabolism and promote further increase of LPO [33]. SOD and GSH, as free radical scavengers and major endogenous antioxidants, are severely reduced in diabetic patients, exacerbating oxidative stress damage and leading to further damage to islet and liver cells.

After 5 weeks of Wistar rats induced by high-fat and high-sugar diet and guava polysaccharide GP administration STZ , the antioxidant enzyme levels of CAT, SOD, GSH, etc. can be significantly improved, oxidative stress damage can be reduced, lipid peroxidation caused by various free radicals can be reduced, thus affecting the distribution of lipids. This suggests that guava polysaccharides may achieve the effects of lowering blood glucose, lowering blood lipids and relieving insulin resistance through the oxidative stress pathway [2]. It is reported that mulberry polysaccharides extracted from mulberry can reduce blood sugar and protect islet cells by reducing oxidative stress [34].

POLYSACCHARIDES REDUCING THE DECOMPOSITION OF STARCH AND THE ABSORPTION OF BLOOD SUGAR

Elevated blood sugar after meals has always been a major threat to diabetics, and failure to control it in time could endanger lives. After the patient has a meal, the food is first degraded preliminarily through amylase, and then reaches the small intestine to stimulate α-glucosidase for intestinal absorption into blood. This is also the target of acarbose, a commonly used diabetes drug. Acarbose can inhibit the activity of α-glucosidase and reduce the absorption of glucose by the intestinal tract. In the search for natural anti-diabetes drugs, α-glucosidase inhibitors have been a key exploration area. With the intensified exploration of natural products, a large number of low-toxicity and efficient inhibitors have emerged.

Lycium barbarum polysaccharides extracted from lycium barbarum can significantly inhibit the activity of α-glucosidase and reduce the digestion and absorption of blood sugar. The mechanism is found to be non-competitive inhibition [35]. At the same time, tea with a variety of biological activities such as anti-oxidation, anti-cancer, hypoglycemia, anti-mutation, has the effect of inhibiting α-glucosidase. Black tea polysaccharides extracted from all fermented black tea have a significant inhibitory effect on α-glucosidase, and the inhibitory effect increases with the increase of black tea polysaccharides, showing a good concentration dependence [36]. See table 1 for detailed data.

TABLE 1. α-glucosidase or α-amylase inhibits active polysaccharides

Name	Source	Drug action	Reference
Lycium barbarum polysaccharide	Lycium barbarum	α-glucosidase inhibits activity	[35]
Black tea polysaccharide	Black tea	α-glucosidase inhibits activity, and antioxidant activity, α-amylase inhibits activity	[36]
Helicteres angustifolia polysaccharide	Helicteres angustifolia	α-glucosidase inhibits activity	[37]
Kunlunchrysanthemum polysaccharide	Kunlunchrysanthemum	α-glucosidase inhibits activity, and antioxidant activity, α-amylase inhibits activity	[38]
Polygahatous polysaccharide	Polygonatum kingianu,	α-glucosidase inhibits activity	[39]
Camellia sinensis L. polysaccharide	Camellia sinensis L.	α-glucosidase inhibits activity, and antioxidant activity	[40]
Annona squamosal polysaccharide	Annona squamosa	α-glucosidase inhibits activity	[41]
Guava polysaccharide	Guava	α-glucosidase inhibits activity	[42]
Black currant polysaccharide	blackcurrant	α-glucosidase inhibits activity, α-amylase inhibits activity	[43]
Inonotus obliquus polysaccharide	Inonotus obliquus	α-glucosidase inhibits activity, α-amylase inhibits activity	[44]
Green tea polysaccharide	Green tea	α-glucosidase inhibits activity, α-amylase inhibits activity	[45]
Camellia oleifera polysaccharide	Camellia oleifera	α-glucosidase inhibits activity	[46]

PROSPECT

Type 2 diabetes is currently a global health problem that leads to a number of serious diseases and death rates, but there is currently no complete cure for type 2 diabetes. Currently, a variety of synthetic anti-diabetes drugs including thiazolidinedione, meglitinide, biguanide, sulfonylurea, α-glucosidase inhibitor, GLP-1 analogue and DPP-4 inhibitor can be used to treat T2DM. However, many of these medications have serious side effects, with an average of 10-20 percent of diabetics stopping taking their medications due to side effects. Common side effects of oral diabetes drugs include hypoglycemia, weight gain, gastrointestinal side effects (abdominal pain, nausea, vomiting, diarrhea, temperament and abdominal distension), edema and increased low density lipoprotein [72]. With the development of polysaccharide research, people have more and more knowledge about the structure, physical and chemical properties and biological activities of polysaccharides. Polysaccharides, the most abundant substance in nature, are mostly non-toxic and are believed to cause fewer side effects than other drugs. As a result, screening active anti-diabetes ingredients from natural sources, including polysaccharides, is increasingly attractive. According to the above summary, many polysaccharides have been found and have the effects of anti-oxidation, lowering blood glucose, lowering blood lipid and inhibiting α-glucosidase. Along with the in-depth study of these polysaccharides, these polysaccharides are expected to become a breakthrough in the treatment of diabetes.

In summary, this review analyses and illustrates the potential mechanism of action of different types of anti-diabetes polysaccharides, which provides an effective basis for further research and more rational use of polysaccharides.

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