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Research Progress on the Mechanism of Action of Danggui-Shaoyao-San Polysaccharide on Some Complications of Type II Diabetes Mellitus: A Review

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ABSTRACT

Type II diabetes mellitus (T2DM) is a group of metabolic diseases characterized by hyperglycemia, and it will cause a variety of complications. Through the research on Danggui-Shaoyao-San (DSS), scholars found that it has an active role in the treatment of diabetes and some complications. Danggui-Shaoyao-San polysaccharide (P-DSS) is the main component of Danggui-Shaoyao-San. P-DSS can participate in the physiological regulation of oxidative stress, anti-inflammatory, glucose and lipid metabolism, endoplasmic reticulum stress, bile acid metabolism and iron metabolism, especially bile acid can effectively regulate the disorder of glucose and lipid metabolism in the body, which provides a new idea for the treatment of diabetes. In addition, the therapeutic effect of P-DSS on diabetic complications may also be related to cell autophagy and intestinal flora, but there is little systematic analysis on the mechanism of P-DSS in treating diabetes and its complications. Therefore, this article reviews the potential mechanism of P-DSS in treating diabetes and its complications in detail, providing a reasonable theoretical basis for further research on P-DSS in treating T2DM.

Keywords: P-Dss; T2dm; Bile Acid; Iron Metabolism; Autophagy; Signal Pathway

Abbreviations: ASP: Angelica Polysaccharide; AMP: Atractylodes Polysaccharide; ALP: Alisma Polysaccharide; RPAP: Paeonia Lactiflora Polysaccharide; WRP: Poria Polysaccharide; LCP: Chuanxiong Polysaccharide; RPAP: Paeonia Lactiflora Polysaccharide; PCP: Poria Polysaccharide; ALP: Alisma Polysaccharide; AMP: Atractylodes Polysaccharide; ASP: Angelica Polysaccharide; LCP: Chuanxiong Polysaccharide

Introduce

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia, including type I diabetes mellitus (T1DM) and type II diabetes mellitus (T2DM). In severe cases, typical «more than three but less» symptoms will appear. According to the report of the World Health Organization, more than 95% of the patients with diabetes are type II diabetes. The patients usually show the characteristics of hyperglycemia, relative lack of insulin, insulin resistance, etc. This makes T2DM patients more likely to suffer from a variety of diabetes related complications (including retinopathy, neuropathy and kidney disease) and complications (including hypertension and arterial stiffness). At present, these complications are the main cause of death of diabetic patients, It is also found that compared with T1DM patients, T2DM patients are more likely to suffer from complications and complications among young people diagnosed with diabetes in childhood or adolescence. [1] The International Diabetes Alliance data report shows that in

2021, the number of deaths of adult diabetes patients worldwide will be 6.7 million, accounting for 12.2% of all deaths worldwide. Therefore, there is still a strong demand to find effective drugs to treat diabetes (Figure 1).

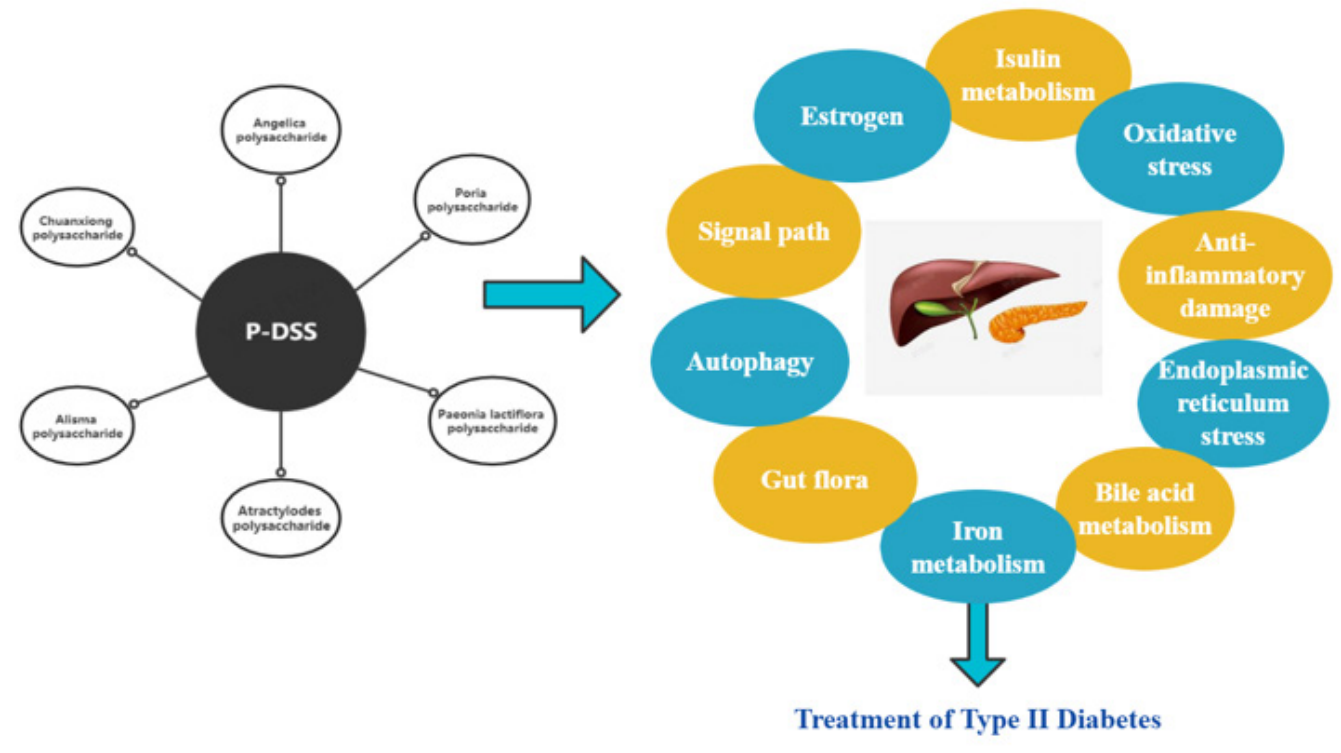

Figure 1.

Bile acid is the main component of bile, which originates from the catabolism of cholesterol in the liver. The synthesis of bile acid can be divided into classical and alternative pathways. In the classical pathway of bile acid synthesis, cholesterol is expressed by CYP7A1 enzyme at 7 α In the alternative route of positional hydroxylation, cholesterol is first converted into hydroxysterol, and then hydroxylated by the enzyme CYP7B1 or CYP39A1. After the above steps, primary bile acids including chenodeoxycholic acid (CDCA) and cholic acid (CS) are produced Dehydroxy, redox and other multi-step metabolic reactions generate deoxycholic acid (DCA), lithocholic acid (LCA) and other secondary bile acids. [2] On the other hand, some hydrophobic bile acids, such as DCA, also directly inhibit the growth of bacteria, play an important role in regulating the structural composition of intestinal flora and maintain the integrity of intestinal barrier. Most bile acids are reused after being actively reabsorbed at the end of ileum, while a small part of bile acids that are not reabsorbed will be passively reabsorbed in the colon after being modified by intestinal microorganisms to generate secondary bile acids. [3] In addition to cholesterol elimination and lipid absorption, bile acid also plays an important role in a series of signaling factors and metabolic regulators, participating in energy metabolism and inflammatory reaction, and interacting with intestinal bacteria to affect the occurrence and development of digestive tract diseases. Experimental studies have proved that bile acid can participate in glucose metabolism and energy regulation by activating FXR receptor and TGR5 receptor, and BAs that can activate TGR5 can improve glucose homeostasis and reduce liver steatosis by increasing energy consumption and GLP-1 secretion, while promoting macrophage driven inflammatory response. [4] Some experimental studies have shown that hepatic insulin resistance and hyperglycemia will increase the synthesis of bile acids, leading to changes in the composition of bile acids [5].

Danggui-Shaoyao-San (DSS) was first recorded in the ancient Chinese medicine book «Golden Chamber Synopsis». The original prescription is mainly composed of six traditional Chinese medicines, namely, Angelica sinensis, Radix paeoniae alba, Poria cocos, Rhizoma alismatis, Rhizoma atractylodis macrocephalae and Rhizoma chuanxiong, and is commonly used to treat gynecological diseases. In recent years, studies have found that Danggui-Shaoyao-San can also be used for the treatment of diabetes, and its main component, Danggui-Shaoyao-San Polysaccharide (P-DSS), has a positive effect on the treatment of diabetes and some complications. [6] Danggui-Shaoyao-San mainly improves

T2DM from insulin metabolism, oxidative stress, anti-inflammatory damage, endoplasmic reticulum stress, bile acid metabolism, iron metabolism and cell autophagy. However, there are few in-depth studies on P-DSS in the treatment of T2DM. Therefore, this paper mainly studies the mechanism of P-DSS in the treatment of T2DM and its complications from the above aspects, such as insulin metabolism (Table 1).

Table 1: Hypoglycemic mechanisms of P-DSS.

Main components	Mechanism	Reference
ASP	Reduce serum insulin and IR related inflammatory factors IL-6 and TNF- α	[11]
	Improve the activities of GSH Px, SOD and CAT in model mice, and have a strong ability to scavenge free radicals	[18,20]
	PPAR can be upgraded γ And the expression of IRS-2, PI3K, Akt, p-Akt and GLUT2, which increase the expression of anti apoptotic protein Bcl-2 and reduce the expression of pro apoptotic protein Bax	[101]
	Weakened the Nrf2 pathway barrier induced by 5-FU	[21]
	Reduce the expression of miR-223 and NF in PC-12 cells mediated by lipopolysaccharide- κ The activity of B pathway activates PI3K/Akt and mTOR signal pathways and improves RAGE-JNK/p38-IRS signal transduction in the liver of diabetic rats	[30,100-107]
	Inhibit the expression of ferrimodulin in vivo, up regulate the expression of Nrf2, increase the serum iron content, and reduce the iron load in the tissues of iron overload model mice	[56,58-60]
	Selectively activate ATF6 branch in UPR, induce activation of ATF6 and increase of ATF6 target protein	[97,35]
	Inhibit MAPK pathway and reduce the abundance of bifidobacteria in intestine	[48]
	Reduce the number of autophagic vesicles, regulate mitochondrial autophagic homeostasis, activate mTOR and Notch signaling pathways, and down regulate BNIP3 to block apoptosis and autophagy.	[79,80]
AMP	Reduce the plasma insulin level, increase the sensitivity of tissue cells to insulin, and improve the glucose tolerance of the body	[13]
	Suppress NF- κ B expression, interference with oxygen free radicals, reduction of IL-1, enhancement of B-lymphocyte tumor 2 protein expression, reduction of Bcl-2 related X protein expression, and down-regulation of miR-320c expression	[32,87]
	Regulate the composition and activity of intestinal flora, promote the growth of bifidobacteria and lactic acid bacteria, and promote the ability of intestinal bacteria to digest reducing sugar	[27,71]
	Regulate SCFA production by intestinal microbiota and host metabolism	[74]
	Activate LKB1-AMPK-ACC and AMPK-ACCase Malonyl CoA to improve the abnormality of glucose and lipid metabolic axis	[94,93]
	Activate TLR4-MyD88-NF κ B signal path	[104]
ALP	Reduce the plasma insulin level, increase the sensitivity of tissue cells to insulin, improve the glucose tolerance of the body, and significantly increase the activities of GSH Px, SOD and CAT in model mice	[15]
	Regulate oxidative stress and autophagy in liver cells of methionine choline deficient mice, and promote the development of immune organs	[81,85]
	Reconstruction of intestinal microbiota increases its diversity, increases the abundance of actinomycetes and bifidobacteria, and decreases the abundance of lactobacillus.	[56]
	Inhibition of ERK and JNK phosphorylation and NF- κ B signal pathway, reducing the relative expression of p38MAPK mRNA	[82,47,91]
RPAP	Reduce the plasma insulin level, increase the sensitivity of tissue cells to insulin, and improve the glucose tolerance of the body	[14]
	Significantly increase the activities of GSH Px, SOD and CAT in model mice	
	Dose dependent DPPH scavenging activity can also significantly protect PC12 cells from H2O2 damage	[22]
	Reduce IL-18 and IL-1 in liver β` TNF- α` Overexpression of NLRP3, ASC and Caspase-1	
	Increase the level of IL-4, down regulate the expression of CD4, CD8, IL-2, IL-6, IL-10, and up regulate TGF- β expression	[27-29]
	By suppressing IRE1 α/ NF- κ B signal path	[36]
WRP	Reduce the levels of serum insulin, glucagon, TC, TG, LDL-C, increase the level of HDL-C, improve insulin resistance, and regulate lipid metabolism	[8,9]
	Suppress serum TNF- α ` IL-6 and NO, inhibit TLR4/NF in aorta- κ Activation of B pathway blocks the expression of matrix metalloproteinase-2 and intercellular adhesion molecule 1 protein	[31]
	Increase the abundance of clostridium cecum XIVa and clostridium IV, and increase the abundance of bifidobacteria	[67,68]

WRP	Inhibit the excessive expression of Bax gene in renal tissue of NIDDM mice, and inhibit the tendency of renal cell apoptosis	[24]
	Respectively activate JNK, ERK1/2 signal pathway and NLRP3 inflammatory body, and up regulate PI3K/Akt/FoxO1 pathway	[64,102]
	Inhibiting p38 MAPK phosphorylation and activating PPAR- γ access	[90]
LCP	Eliminate free radicals, reverse oxidative damage and block NF- κ Route B	[49]

Note:

(1) ASP: Angelica polysaccharide;

(2) AMP: Atractylodes polysaccharide;

(3) ALP: Alisma polysaccharide;

(4) RPAP: Paeonia lactiflora polysaccharide;

(5) WRP: Poria polysaccharide ;

(6) LCP: Chuanxiong Polysaccharide

Insulin Metabolism

T2DM patients often show insulin resistance (IR), chronic hyperglycemia and hyperinsulinemia, and hyperglycemia will lead to pancreatic islets β Cell dysfunction, [7] these are caused by abnormal insulin metabolism. The pancreas secretes too much insulin to produce hyperinsulinemia, which leads to the reduction of the body's tissue cells to excessive insulin sensitivity and insulin resistance. The experimental study showed that after the mice fed with high glucose and high fat diet and injected with streptozotocin (STZ) intraperitoneally with different doses of poria polysaccharide (WRP), the levels of glucagon and insulin resistance index in serum decreased, and the levels of TC, TG and LDL-C in serum also decreased significantly, while the levels of insulin and high-density lipoprotein increased significantly, [8] This shows that WRP can improve the abnormal glucose tolerance and lipid metabolism in diabetic mice. According to the research, the main components of Poria cocos polysaccharide β- Glucan has a significant protective effect on insulin resistance in different populations. [9] The crude polysaccharide from Poria cocos showed good glucose stimulated insulin secretion (GSIS) effect. [10] Wang Kaiping et al. found that the abnormal fasting serum insulin in STC induced diabetic mice was improved after treatment with Angelica polysaccharide (ASP). In addition, ASP can reduce the inflammatory factors related to insulin resistance (IL-6, TNF-α` Alleviate insulin resistance, [11] increase the content of adiponectin (ADPN) in serum and reduce the content of leptin (LEP) and resistin (RSTN), which can repair and protect adipose tissue to a certain extent. [12] It has been proved that the polysaccharide compound from Atractylodes macrocephala (AMP-B) and the polysaccharide from paeony root can also reduce fasting blood glucose, increase fasting insulin level, increase the sensitivity of tissue cells to insulin, and improve the glucose tolerance of the body to alleviate diabetes. [13,14]. Alisma orientalis polysaccharide has the same effect [15].

Oxidative Stress

Recent studies have shown that oxidative stress caused by the increase of reactive oxygen species (ROS) is responsible for pancreatic islets β One of the causes of cell damage, it can also mediate insulin resistance related signal pathways, leading to the occurrence and development of diabetes and its related complications. The main mechanism is the imbalance of prooxidants and antioxidant enzymes, which leads to ROS production exceeding the defense capacity of the antioxidant defense system [16] In addition, ROS can also directly participate in the oxidative modification of T2DM related proteins. [17] Therefore, antioxidant therapy is essential for the treatment of T2DM. The oxidative stress experiment analysis of various traditional Chinese medicine polysaccharides in DSS showed that P-DSS can significantly improve the activities of GSH Px, SOD and CAT in model mice, [14,15-18] and ASP and PCP of different doses can increase the content of IgA, IgG and IgM in the serum of DM rats to varying degrees, while WRP has no significant effect on GSH Px. [19] In addition, ASP has a strong ability to scavenge free radicals and resist oxidation [20]. It can also reduce ROS content by alleviating the decrease of Bcl-2 protein and increase of Bax protein induced by 5-FU, as well as the increase of alanine aminotransferase (ALT), triglyceride (TG) and aspartate aminotransferase (AST) content. ASP can also increase the activities of glutathionease, sodium stimulated insulin and CAT to reduce ROS content and weaken the Nrf2 pathway barrier induced by 5-FU, Thus, it can alleviate oxidative stress damage. [21] RPAPS, a new type of acidic polysaccharide from paeony root, showed a dose-dependent DPPH scavenging activity and could significantly protect PC12 cells from H2O2 damage. [22] A polysaccharide LCP containing protein was extracted from the rhizome of Scutellaria baicalensis Georgi. LCP has strong antioxidant activity and good free radical scavenging capacity. In addition, LCP can partially reduce the mortality of zebrafish embryos exposed to hydrogen peroxide

and the incidence of pericardial edema. and prevent the production of ROS and cell death induced by H2O2 in zebrafish embryos. It suggested that LCP might reverse oxidative stress injury. [23] Experiments have proved that WRP can enhance the antioxidant capacity of the kidney, reduce lipid peroxidation, protect free radical mediated oxidative damage, reduce the concentration of malondialdehyde, increase the activities of superoxide dismutase and glutathione peroxidase, inhibit the overexpression of Bax gene in the kidney tissue of NIDDM mice, inhibit the apoptosis trend of renal tissue cells, and can prevent diabetic nephropathy to a certain extent. [24] WRP can also play a protective role in oxidative stress and inflammation by activating ERK/Nrf2/HO-1 signaling pathway.

Anti-Inflammatory Damage

T2DM is considered to be an inflammatory disease. [25] Research shows that inflammatory factors can pass IKK/NF- κ B pathway, JNK pathway and SOCS pathway inhibit insulin signal transduction and reduce the synthesis and expression of insulin receptor substrate. [26] Paeoniflorin is a polysaccharide of paeony. It has been found that paeoniflorin can significantly reduce IL-18 and IL-1 in liver β` TNF- α` The overexpression of NLRP3, ASC and Caspase-1, [27] can also increase the level of IL-4. In addition, the expression of CD4, CD8, IL-2, IL-6 and IL-10 in model mice was down regulated after the administration of paeony polysaccharide, while TGF- β the expression is up-regulated, indicating that paeony polysaccharide has immunosuppressive effect on the immune inflammatory reaction of autoimmune hepatitis, thereby reducing inflammatory damage. [28,29] ASP can significantly down regulate the serum inflammatory factors IL-6 and TNF in ACD rats- α It can also reduce the over expression of inflammatory factors and apoptosis of PC-12 cells mediated by lipopolysaccharide. ASP can block NF by down regulating the expression of miRNA-223- κ B pathway protects PC-12 cells from lipopolysaccharide mediated injury. [30] Poria cocos polysaccharide can inhibit serum TNF- α` the increase of IL-6 and NO can also inhibit TLR4/NF in aorta- κ the activation of B pathway blocks the expression of matrix metalloproteinase 2 and intercellular adhesion molecule 1. [31] Studies have found that polysaccharide from Atractylodes macrocephala can inhibit NF- κ the expression of B can interfere with the damage of oxygen free radicals to the liver, reduce the production of inflammatory factor IL-1, increase the expression of Bcl-2 protein, reduce the expression of Bcl-2 related X protein [32], and then alleviate the inflammatory response of the body.

Endoplasmic Reticulum Stress

Plasmoplasmic reticulum stress can not only induce the expression of endoplasmic reticulum molecular chaperones such as glucose regulated proteins GRP78 and GRP94 to produce a protective effect on tissue cells, but also independently induce endogenous cell apoptosis, ultimately affecting the fate of stress cells, such as adaptation, injury or apoptosis. Endoplasmic reticulum stress will damage insulin signal transduction, inhibit Akt phosphorylation [33] and insulin stimulated sugar absorption, [34] reduce insulin sensitivity, thus leading to insulin dysfunction. Angelica polysaccharide can induce H9c2 cell damage by activating ATF6 pathway, thereby improving endoplasmic reticulum stress. [35] Paeoniflorin, a polysaccharide from paeony root, can alleviate the excessive production of ER stress markers (78 kDa glucose regulatory protein (GRP78) and CCAAT/enhancer binding protein homologous protein (CHOP)), and we also found that the ultrastructural abnormalities in ER stress can be reversed by paeoniflorin, so paeoniflorin can inhibit IRE1 by α/ NF- κ B signal pathway improves endoplasmic reticulum stress related inflammation induced by lipopolysaccharide[36].

Bile Acid Metabolism

Bile acid is closely related to glucose and lipid metabolism, plays the role of metabolic regulator, and participates in energy metabolism and inflammatory reaction. Bile acid can promote fat metabolism, reduce gluconeogenesis, improve insulin resistance of body cells, thus reduce hyperglycemia and hyperlipidemia, and alleviate some related symptoms of diabetes and its complications. In addition to the role of lipid digestion, bile acid can also play a role as a signal molecule, which can regulate body metabolism through the combination of FXR receptor and TGR5 receptor. Bile acids processed by microorganisms may regulate lipid metabolism through interaction with FXR receptors, especially the transport, synthesis and utilization of triglycerides [37] In addition, FXR can also change the composition of microbiota [38] and participate in glucose tolerance, which mainly plays a role through the intestinal microbiota FXR signal transduction axis, and BSH increases T- β- After MCA, intestinal FXR signal transduction is inhibited and ceramide synthesis in the body is reduced, leading to the decrease of liver mitochondrial acetyl CoA level and pyruvate carboxylase activity, inhibition of liver glycolytic gene expression, and [39] reduction of liver gluconeogenesis [40].

TGR5 receptor mainly affects skeletal muscle and brown adipose tissue to promote energy digestion. [41] TGR5 signal transduction can also promote intestinal cells to release GLP-1 to improve obesity. [42] In addition, TGR5 combined with bile acid can promote the production of cyclic adenosine monophosphate (cAMP), thereby activating the protein kinase A (PKA) pathway, mainly by inhibiting the activation of NLRP3 inflammatory bodies through TGR5-cAMP-PKA axis. [43] Therefore, the combination of blocking intestinal FXR and activating TGR5 signal may be an effective method to control blood glucose in T2DM patients. According to the research, the combination of tea brownin (TB) and poria cocos polysaccharide (PCP) shows the overall lipid lowering function, which can regulate the metabolism of bile acid and fatty

acid, so as to improve the role of fatty liver. [44] Alisma orientalis polysaccharide can significantly increase AdipoR2 and PPAR in the liver α MRNA expression effectively regulates AdiopR2/PPAR in liver α Signal transduction pathway, [45] promotes fat degradation by lipase to glycerol, fatty acid and other products included in bile acid particles, increasing bile acid secretion. Paeoniflorin can inhibit NF by activating SIRT1/FXR signaling pathway- κ B/NLRP3 inflammatory corpuscle regulates bile acid metabolism, alleviates cholestatic liver injury, and regulates body glucose and lipid metabolism. [27] Atractylodes macrocephala polysaccharide can regulate the composition and activity of intestinal flora, promote the growth of bifidobacteria and lactic acid bacteria, and the promotion of intestinal flora is related to the amount of polysaccharide added. [46] The conjugated bile acid hydrolase of Bifidobacterium can hydrolyze various conjugated bile acids into free bile acids, and CA and CDCA can combine with 7 α- Dehydroxylation forms secondary bile acids (DCA & LCA).

3-oxoLCA, a metabolite of bile acids, can inhibit Th17 development, while isoalloLCA can enhance Treg cells in the body to affect related inflammatory responses in the body, [47] thereby indirectly relieving diabetes related symptoms. T α- MCA and T β- MCA is formed by BSH α- MCA. β- MCA. However, lactic acid bacteria mainly participate in the esterification of bile acid and increase the synthesis of bile acid through the above ways. Angelica polysaccharide can combine with deoxycholic acid in free bile acid. Studies have proved that bile acid can combine with endotoxin to reduce bile acid reabsorption back to portal vein. Angelica polysaccharide can inhibit NF by regulating miR-10a and miR-223 in HT22 cells- κ B and JAK2/STAT3 pathways can reduce lipopolysaccharide and other endotoxin. Angelica polysaccharide can also reduce the production of inflammatory mediators, down regulate the mRNA expression of TLR4, MyD88 and some proinflammatory chemical factors (CCL2, CCL20, CXCL2, CXCL8, CXCL10), and inhibit NF- κ B and MAPK signal pathways reduce the abundance of bifidobacteria in the intestine by inhibiting MAPK pathway, thereby affecting bile acid metabolism. [48] Ligusticum chuanxiong pectin polysaccharide (LCP-II-I) can block NF- κ B pathway and upstream signal activate Nrf2 pathway. Through the study on caspase-3, Bax family and MAPK family and their upstream signals in different cell types, it was found that [49] LCP-II-I could increase the number of intestinal stem cells in the intestinal tract of mice under the effect of bile acid, and promote intestinal regeneration through the mechanism involving TGR5, [50] regulate intestinal cell apoptosis, thereby protecting mice from the invasion of acute colitis. In addition, LCP-II-I can also promote antioxidant enzymes and their main regulator PGC-1 α and promote the expression of antioxidant enzymes, thereby promoting the alleviation of oxidative stress by bile acids [49].

In addition, the effective component of Poria cocos polysaccharide that changes its chemical structure through hydroxymethylation β- (1-3) - D-glucan and its carboxymethyl derivatives can improve the ability to bind bile acid, [51] inhibit the reabsorption of bile acid and increase its excretion. We also found that the sub oligosaccharide (PCO) from Poria cocos can significantly reduce the expression of lipid related metabolic genes and gluconeogenesis related genes, increase the expression of bile acid synthase, and increase the content of cholic acid and ursodeoxycholic acid [52] (Table 2).

Table 2: Effects of P-DSS on bile acids.

Main ingredient	Effects on bile acids	References
RPAP	Upregulation of SIRT1/FXR expression and inhibition of NF-κB /NLRP3 inflammasome to regulate bile acid metabolism	[27]
PCP	Enhances the ability to bind bile acids in vitro and inhibits bile acid reabsorption	[32]
	Increased expression of bile acid synthase	[55]
ALP	Significantly up-regulated the expression of Adipo R2 and PPARα mRNA in the liver	[45]
AMP	Regulates the composition and activity of intestinal flora and promotes the growth of bifidobacteria and lactobacilli	[46]
ASP	And miR-223 in HT22 cells to inhibit NF-κB and JAK2/STAT3 pathways and reduce endotoxins such as lipopolysaccharide	[48]
	Reduced production of inflammatory mediators, down-regulated mRNA expression of TLR4, MyD88 and pro-inflammatory chemokines (CCL2, CCL20, CXCL2, CXCL8, CXCL10)	
	Inhibit NF-κB and MAPK signaling pathways	
	Reduced abundance of bifidobacteria in the gut by inhibiting the MAPK pathway	
LCP	Block NF-κB pathway and upstream signaling, activate Nrf2 pathway Promotes antioxidant enzymes and its main regulator PGC-1 α Expression of	[49]
	Stem cell regeneration through a mechanism involving TGR5	[50]

Note:

(1) RPAP: Paeonia lactiflora polysaccharide;

(2) PCP: Poria polysaccharide ;

(3) ALP: Alisma polysaccharide;

(4) AMP : Atractylodes polysaccharide;

(5) ASP : Angelica polysaccharide;

(6) LCP: Chuanxiong Polysaccharide

Iron Death

Iron death is an iron dependent cell death driven by lipid peroxidation. The mechanism is related to the imbalance of iron homeostasis, lipid peroxidation and SLC7A11 GSH GPX4 antioxidant system. [53] As we are familiar with, iron is a key regulator of glucose and lipid metabolism. Excessive serum ferritin is related to the increase of free radicals and will affect insulin resistance. [54] Ferrimodulin is a gluconeogenic sensor in mice during starvation. During starvation, tissue iron is retained for important activities, but it can lead to excessive iron retention and hypoferremia in the diseases of gluconeogenesis and insulin resistance that are continuously activated. The increase of ferrimodulin can reduce the content of iron transporter (FPN, a kind of receptor for ferrimodulin) in intestinal cells and macrophages, leading to the enhancement of insulin resistance in the liver. [55] Research in recent years shows that iron storage in the body is related to insulin signal. Iron overload may aggravate the body's insulin resistance, destroy insulin sensitivity and cause a variety of metabolic disorders related diseases. Therefore, iron removal treatment has become a new idea for treating diabetes. The treatment of iron deprivation can improve insulin resistance, promote insulin secretion, and improve the abnormal level of liver enzymes. [54] Angelica polysaccharide in DSS can inhibit the expression of iron modulin in vivo and promote the iron utilization of tissues and cells [56], and different concentrations of Angelica polysaccharide have different inhibitory effects on iron modulin, [57] At the same time, Angelica polysaccharide can also increase the iron content in serum, significantly reduce the iron content in tissues [58] and reduce the iron load in tissues of iron overload model mice. [59] In addition, Angelica polysaccharide can up regulate the expression of Nrf2 in hypoxic damaged H9C2 myocardial cells and inhibit iron death induced by iron overload [60].

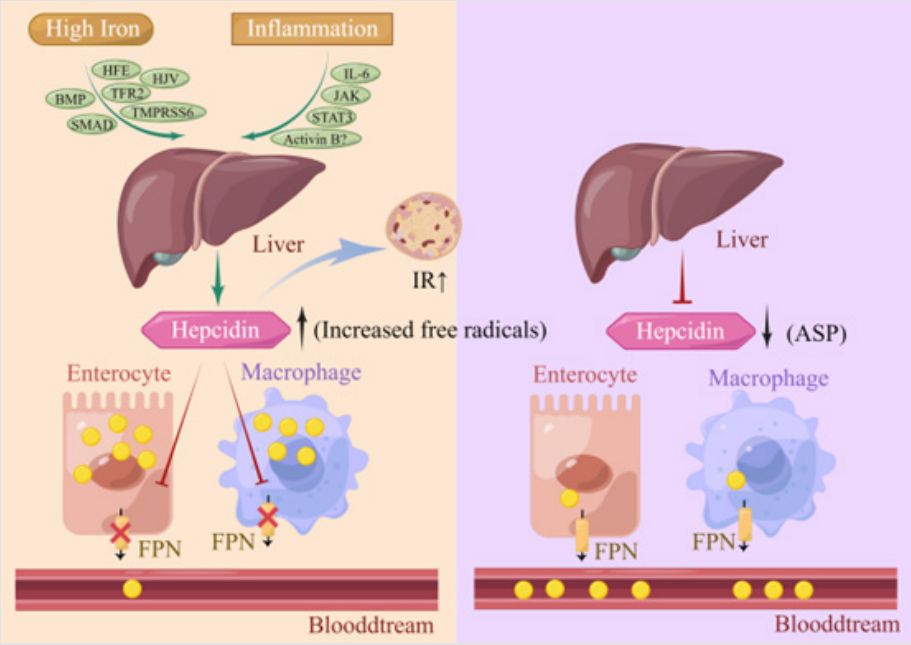

Figure 2: Effect of iron metabolism on the body.

Atractylodes macrocephala polysaccharide can alleviate the changes of iron death pathway gene and cytokine expression caused by lipopolysaccharide, thus up regulating iron death and inflammation levels, and relieving inflammation and iron death. At the same time, Atractylodes macrocephala polysaccharide can restore the expression and distribution of GPX4, reduce the oxidative stress caused by lipopolysaccharide, and reduce the iron content in the spleen. Atractylodes macrocephala polysaccharide can also significantly reduce the relative expression of p38MAPK mRNA [47], which indicates that the effective polysaccharide in DSS can regulate the above factors closely related to iron death, thereby inhibiting the occurrence of iron death. (Figure 2)

Gut Flora

Intestinal flora is the largest microecosystem in the human body, and the changes of its structure and metabolites are closely related to the occurrence and development of type II diabetes. It has been proved that diabetic mice have obvious intestinal flora homeostasis imbalance, and the diversity and abundance of the flora are reduced to a certain extent. It may increase insulin sensitivity by referring to the metabolite of intestinal flora, short chain fatty acids [61] In rodents and humans, lipid entering the upper part of the intestine directly increases the level of upper intestinal long-chain fatty acyl coenzyme A (LCFA-CoA), and inhibits glucose production, The vagus nerve blocks the neural connections where lipid inhibits glucose production. This suggests that upper intestinal lipids activate the gut brain liver nerve axis to inhibit glucose production. [62] Changes in the composition and function of intestinal microbiota can also help improve insulin sensitivity, glucose tolerance, reduce fat increase, and promote fat browning, which can be explained by the microbiota immune system fat signal transduction axis. [63] Studies have shown that P-DSS can regulate the composition of intestinal flora and conjugated bile acids. Therefore, we speculate that P-DSS may increase the level of ceramide lipids by regulating intestinal flora and taking advantage of the inhibition and relief of intestinal microorganisms on FXR in the ileum, while secondary bile acids increase the absorption of lipids, thus activating the gut brain liver nerve axis to inhibit glucose production to reduce liver gluconeogenesis and regulate liver glucose homeostasis. Metabolites of intestinal microorganisms, such as short chain fatty acids (SCFA), lipopolysaccharides (LCP) and bile acids (BA), directly or indirectly participate in glucose metabolism.

In clinical trials, we found that increasing the intake of indigestible but fermentable carbohydrates, such as dietary fiber (a kind of polysaccharide), can promote the growth of intestinal microorganisms, while some of the bacteria that can produce acetate and butyrate can regulate the metabolism of short chain fatty acids to reduce inflammation, regulate satiety, and thus reduce the disease phenotype of T2DM, which is quite different from the treatment response. [64] In the diabetic model mice, the Firmicutes significantly increased, Bacteroides significantly decreased, and the short chain fatty acids as its metabolites also significantly decreased. [65] DSS can increase the abundance of Lactobacilliaceae, and reduce the relative abundance of Helicobacter pylori in Campylobacter proteus and myxobacteria in Deferribacter. [66] Poria cocos polysaccharide in DSS can increase the abundance of clostridium XIVa and clostridium IV in the cecum, thereby promoting the generation of secondary bile acids. [67] In addition, Poria cocos polysaccharide can also increase the level of intestinal bifidobacteria, increase the flora producing butyrate, thereby increasing the intestinal butyrate production, [68] increase the species richness and diversity. In the model mice treated with PCO, the ruminal coccidae and anaerobic plasma bacteria were down regulated, but the abundance of lactobacilli and Riemannia bacteria were up regulated. [55] The water-soluble polysaccharide from Poria cocos can also regulate the imbalance of intestinal flora. [69] Atractylodes macrocephala polysaccharide (PAMK) can regulate the composition and activity of intestinal flora, promote the growth of bifidobacteria and lactic acid bacteria, promote the generation of bile acid in the body, and regulate energy metabolism. [27] An active polysaccharide extracted from the rhizome of Atractylodes macrocephala (PAM) was identified to improve and regulate the intestinal flora in disorder.

PAM consists of rhamnose, glucose, mannose, xylose and galactose. The intestinal microflora Bacteroides thetaiotaomicron can use the rhamnose and galactose components to degrade the macromolecular carbohydrate in food into glucose and small molecule substances that are easy to be absorbed and can also adjust its own genome to maintain the health of the entire intestinal microflora. [70] The anaerobic culture of intestinal flora by PAM confirmed that PAM promoted the ability of intestinal bacteria to digest reducing sugar. [71] PAMK can also improve intestinal flora disorder and alleviate goose cortical enteritis induced by lipopolysaccharide by maintaining small intestine morphology, cytokines, tight junctions and relative stability of immunoglobulins. [72] Water soluble atractylodes macrocephala polysaccharide (AMP) regulates intestinal microbiota by enhancing overall abundance and diversity, greatly reducing the abundance of harmful bacteria such as Stricto1 and Escherichia Shigella and increasing the proportion of potentially beneficial bacteria such as Faecalibalum and Bifidobacterium. [73] AMP also partially restored the composition of disturbed intestinal microbiota induced by DSS. Non targeted fecal and plasma metabonomics showed that AMP could regulate SCFA production by intestinal microbiota and host metabolism. [74] Angelica polysaccharide can inhibit the MAPK pathway, reduce the abundance of bifidobacteria in the intestine, affect the metabolism of bile acid, and then affect the metabolism of glucose and lipid in the body. [48] Alisma orientalis polysaccharide can rebuild intestinal microbiota, increase the diversity of intestinal microbiota, increase the abundance of actinomycetes

and bifidobacteria, and reduce the abundance of lactobacillus. [56] The paeoniflorin and paeoniflorin from the aqueous extract of paeony can increase the diversity of intestinal flora and the relative abundance of beneficial bacteria. [75] (Figure 3)

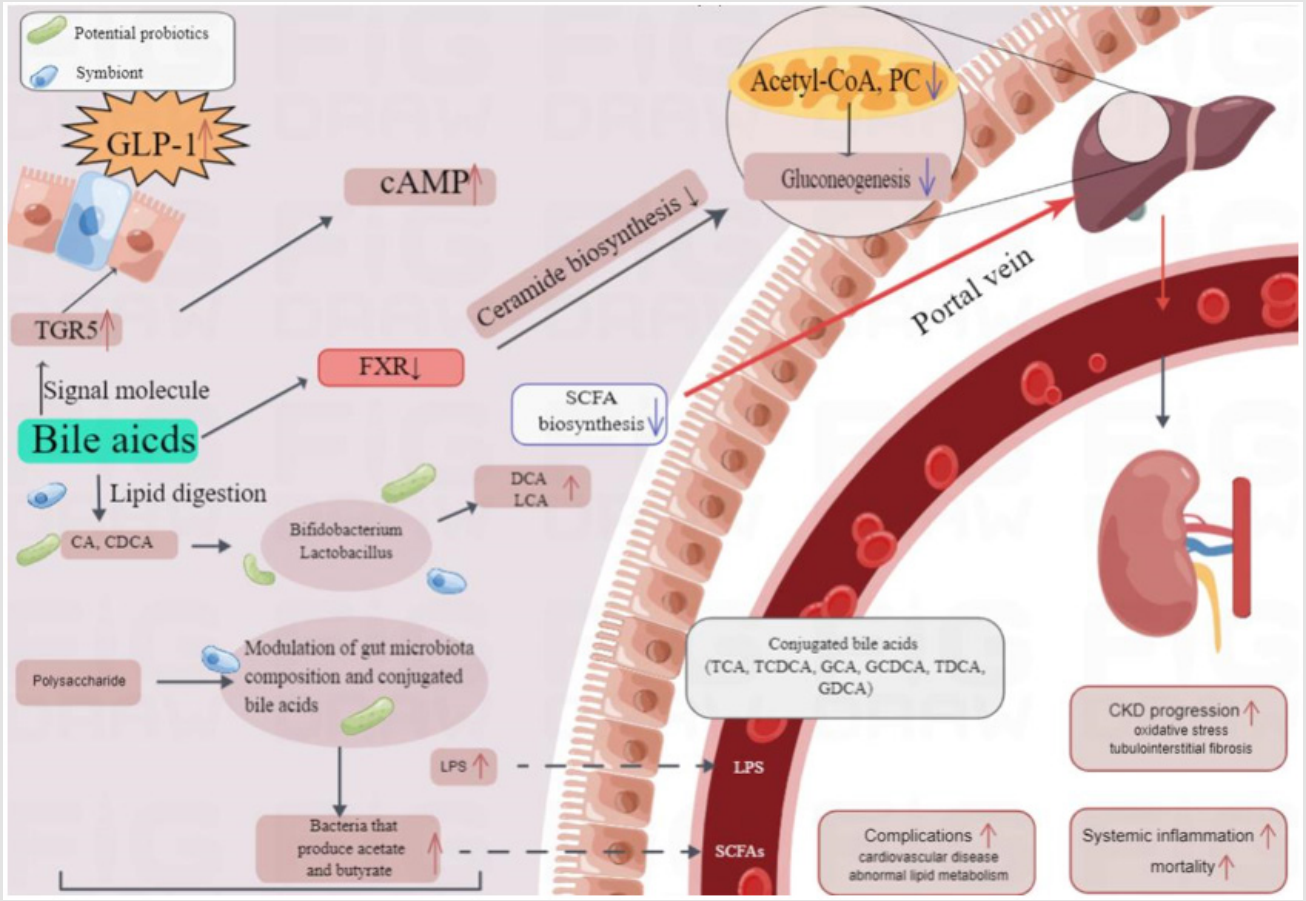

Figure 3: Mechanism of action of bile acid gut microbiota.

Autophagy

Autophagy plays a key role in cell homeostasis through the degradation and recycling of mitochondria or endoplasmic reticulum (ER) and other organelles. [76] More and more studies show that autophagy deficiency is involved in the development of diabetic nephropathy and plays an important role. [77] Diabetic foot is one of the complications of diabetes. Some studies have shown that autophagy damage may be involved in the pathogenesis of podocyte loss. If podocyte function is not complete, it can lead to massive proteinuria and kidney damage. [78] Angelica polysaccharide in DSS can reduce the number of autophagic vesicles, regulate mitochondrial autophagic homeostasis, and reduce mitochondrial damage and apoptosis. [79] In addition, Angelica polysaccharide can also block cell apoptosis and autophagy by maintaining cell viability, activating mTOR and Notch signaling pathways and down regulating BNIP3. [80] Rhizome decoction of Alisma orientalis can regulate oxidative stress and autophagy in liver cells of methionine choline deficient mice, and reduce liver injury related to NASH (nonalcoholic steatohepatitis) [81]. The experimental study shows that Aurantii Fructus Immaturus and Atractylodis Macrocephalae Rhizoma may protect glutamate stimulated ICC (Cajal interstitial cells) and reduce autophagy by inhibiting PI3K/Akt/mTOR pathway. [82] DSS can also protect the kidney by improving renal fibrosis, which may be related to reducing tissue hypoxia and regulating autophagy. [83] The neutral heteropolysaccharide component of Smilax glabra (SGRP1) is a new polysaccharide with complex structure composed of mannose, fucose and glucose. SGRP1 can increase iNOS, 1L-6 and TNF of macrophages- α And up regulate the expression of JNK and ERK1/2 proteins. It can promote RAW264.7 cells to secrete inflammatory factors by activating NLRP3 inflammatory bodies in macrophages. In addition, SGRP1 can also interact with a variety of membrane surface receptors mainly TLR2 on RAW264.7 cells non-specific, respectively activating JNK, ERK1/2 signal pathways

and NLRP3 inflammatory bodies. On the other hand, SGRP1 may promote the formation of lysosomes through mannose receptors (MR), and enhance the phagocytosis of macrophages, [84] In addition, a certain amount of polysaccharide from Ligusticum chuanxiong Hort can promote the development of immune organs in mice, enhance the function of defense organs, and thus enhance the effect on pancreatic islets β Cell repair function. Atractylodes macrocephala polysaccharides can alleviate the cyclophosphamide induced apoptosis of chicken liver cells by promoting the secretion of cytokines and regulating the expression of genes and proteins related to autophagy and apoptosis. [85] Atractylodes macrocephala polysaccharide can down regulate the expression of miR-320c in cells and negatively regulate the expression of adiponectin receptor 1 (ADIPOR1), thereby reducing apoptosis of glomerular podocytes (HPC) in a dose-dependent manner and protecting HPC injury induced by high glucose [86].

Effect of Signaling Pathways on DM

Effect of MAPK Signaling Pathway on DM: A large number of studies have shown that AMPK plays an important role in regulating glucose and lipid metabolism, promoting browning of white fat, anti-inflammation, anti-oxidative stress and other aspects, which is conducive to improving the body's insulin resistance and islets β Cell damage is considered as an important target for diabetes treatment. [87,88] It has been shown that pachyman in P-DSS can activate PPAR by inhibiting p38 MAPK phosphorylation- γ the pathway protects the kidney damage of model mice, and Western blot results show that with the increase of pachyman concentration, the level of p-p38 MAPK in kidney tissue gradually decreases, PPAR-γ The level rises gradually. [89] In addition, Angelica polysaccharide blocks NF in MIN6 cells- κ B and p38 MAPK to promote miR-143 and release TNF- α Induced damage, TNF- α Induction can inhibit pancreatic insulin secretion and reduce insulin activity. [90] The drug «Poria cocos Alisma» can activate the expression of AMPK signal pathway and inhibit its downstream targets ACC, SREBP-1C, PCSK9, PPAR γ ` HMGCR expression affects cholesterol and fatty acid metabolism. [91] Atractylodes macrocephala polysaccharide can prevent and treat nonalcoholic fatty liver disease by activating LKB1-AMPK-ACC signal transduction pathway, [92] It can also improve the abnormal situation of AMPK-ACCase Malonyl CoA lipid metabolism axis in rats with fatty liver [93].

Effect of ATF6 Signaling Pathway on DM: ATF6 signaling pathway mainly affects endoplasmic reticulum stress, and activation of ATF6 will increase the expression of Er resident protein to avoid the toxic effect of misfolded protein. [94] In addition, it also induces antioxidant stress genes encoding ER external proteins. Angelica polysaccharide (ASP) can selectively activate the ATF6 branch in UPR, leading to an increase in the expression of ER protein induced by ATF6, thus improving the folding ability of ER protein, [95] such as GRP78, GRP94 and pdia6. Overexpression of GRP94 can reduce stress induced cell death. [96] ASP can also play a beneficial role by inducing and activating ATF6 and increasing the level of ATF6 target protein, thereby reducing ER stress and increasing antioxidant activity. [35] Atractylodes macrocephala polysaccharide can antagonize the up regulation of ATF-6 expression induced by Cr (VI), thus protecting the excessive apoptosis of cells caused by Cr (VI). [97]

Effect of PI3K/AKT and mTOR Signaling Pathway on DM: PI3K/Akt regulates glucose metabolism through FoxO1 and GSK-3 and regulates lipid metabolism through mTORC1 and SREBP. [98] Angelica polysaccharide in DSS can reduce cell oxidative damage in HaCaT cells by up regulating miR-126 to activate PI3K/Akt and mTOR signaling pathways. [99] ASP can increase PPAR γ the expression of IRS-2, PI3K, Akt, p-Akt, GLUT2 and other insulin signaling proteins in the liver increases the expression of anti apoptotic protein Bcl-2, decreases the expression of pro apoptotic protein Bax, and protects the mice from liver damage. [100] Aurantii Fructus Immaturus and Atractylodis Macrocephalae Rhizoma can reduce autophagy by inhibiting PI3K/Akt/mTOR pathway. [82] Poria cocos polysaccharide can up regulate PI3K/Akt/FoxO1 pathway, reduce the protein expression of PEPCK and G6Pase, key enzymes of gluconeogenesis, and inhibit liver gluconeogenesis. [101]

TLR4-MyD88-NF κ Effect of B Signal Path on DM: NF- κ B (nuclear factor activated B cell κ- Light chain augmentation) is a protein complex that controls transcribed DNA, cytokine production, and cell survival. NF- κ B exists in almost all animal cell types and participates in cell responses to stimuli. Atractylodes macrocephala polysaccharides from DSS can promote NF in transfected and untransfected lymphocytes- κ B enters the nucleus to make nucleoprotein- κ. The content of NF in B increased significantly, promoting the expression of related genes. [102] And atractylodes macrocephala polysaccharide can activate TLR4-MyD88-NF κ B signal path, reducing IL-1 β, IL-6 and TNF-α It can increase the level of IL-4, inhibit the level of GSH-PX and MDA, and reduce the inflammatory damage and oxidative stress in mice. [103] Poria cocos polysaccharide can inhibit TLR4/NF in aorta-κ the activation of B pathway blocks the expression of matrix metalloproteinase-2 and intercellular adhesion molecule 1 protein. [31] Inhibitory effect of paeoniflorin on NF- κ the inhibition of B/NLRP3 inflammatory corpuscles can regulate bile acid metabolism, thereby relieving diabetes. [27] Angelica polysaccharide can inhibit NF by regulating miR-10a and miR-223 in HT22 cells to reduce inflammatory mediators, down regulate the mRNA expression of TLR4, MyD88 and some proinflammatory chemical factors- κ B and JAK2/STAT3 to reduce lipopolysaccharide and other endotoxin. [48] It can also reduce TLR4, MyD88, NF in kidney tissue- κ B mRNA and protein expression, indicating that TLR4/NF- κ B signal pathway alleviates diabetic nephropathy. [104] Ligusticum chuanxiong

pectin polysaccharide (LCP-II-I) can also block NF- κ B way. [49] It has been found that ERK and JNK phosphorylation and NF in liver tissue of model mice treated with Alisma orientalis extract- κ The B signal pathway was inhibited. [105] In vivo, APS-1I can also significantly improve RAGE-JNK/p38-IRS signal transduction in the liver of diabetic rats, which indicates that APS-1I may be a potential drug to improve IR in type II diabetes [106,107] (Figure 4).

Figure 4: Potential therapeutic effects of P-DSS on T2DM via insulin metabolism, stress, bile acid.

Conclusion

More and more studies have shown that traditional Chinese medicine plays an important role in the treatment of diseases and is used to treat and prevent various diseases. We believe that traditional Chinese medicine is still a valuable medical resource, and its mysteries need to be developed. In recent years, studies have found that Danggui-Shaoyao-San is an excellent choice of traditional Chinese medicine to treat diabetes and its complications, which can effectively solve the toxic effects of diabetes drugs on the body. Moreover, the therapeutic effect of Danggui-Shaoyao-San on diabetes and its complications may be closely related to its polysaccharide and other macromolecular substances. P-DSS has good antioxidant and anti-inflammatory effects, which can effectively alleviate oxidative stress and anti-inflammatory damage. In addition, P-DSS can improve T2DM by regulating insulin metabolism, glucose and lipid metabolism, bile acid metabolism and iron death. In addition, P-DSS also plays an important role in intestinal flora, autophagy and various signal pathways in T2DM patients. This article explains the potential role of T2DM in detail through P-DSS, which provides a new idea for the follow-up treatment of T2DM, and also provides a theoretical basis for the treatment of diabetes with biological macromolecules such as traditional Chinese medicine polysaccharides. A more accurate and reliable treatment mechanism remains to be further explored.

Highlights

- P-DSS, the main component of DSS, has positive significance in the treatment of T2DM and its complications.
- P-DSS can improve T2DM and some complications through intestinal flora and autophagy.
- P-DSS can also play a role through bile acid and iron metabolism.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Author's Contribution

YCQ wrote and revised the manuscript. FX guides the revision of the manuscript. All authors participated in the revision of the manuscript and read and approved the submitted version.

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