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Research progress on the hypoglycemic effect of mulberry leaves

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Abstract: *Mulberry leaf, as a traditional Chinese medicine with medicinal and food values, is nowadays widely used in the clinical treatment of diabetes and hyperlipidemia. Its active ingredients are mainly flavonoids, polysaccharides, alkaloids and other substances, which have good efficacy in regulating insulin secretion, hypoglycemia and lipid lowering. In recent years, a large number of experimental studies and some clinical studies have proved that mulberry leaf does have hypoglycemic effect, and it is widely available, easy to obtain and low in price. In this paper, we review the research progress on the mechanisms of mulberry leaf inhibition of α-glucosidase activity, promotion of insulin secretion, improvement of pancreatic islet function, promotion of glucose utilization by peripheral tissues, and enhancement of hepatic glycogen. It is expected to provide guidelines for in-depth research on the mechanism of action of mulberry leaves in regulating blood glucose and preventing diabetic complications, and to provide a basis and reference for the development and utilization of mulberry leaf resources.*

Keywords: *Mulberry leaf; Diabetes mellitus; Hypoglycemia; Review; Mechanism of action*

1. Introduction

Diabetes mellitus is a chronic, systemic, metabolic disease caused by a combination of genetic and environmental factors over a long period of time, characterized by increased plasma glucose levels. It can affect normal physiological activities and manifest itself in a variety of acute and chronic complications. Diabetes can be classified into type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and other special types of diabetes (such as gestational diabetes), and more than 90% of people with diabetes are T2DM. DM has been the most prevalent metabolic disease in the world, posing a serious threat to human health. According to the data of the 7th National Census of China National Bureau of Statistics, the elderly population (≥60 years old) in China accounted for 18. 7% (260.4 million) of the total population in 2020, and about 30% of them have diabetes and more than 9-5% of them have T2DM. The prevention and treatment of diabetes has been included in the "Health China 2030" planning outline [1]. Although metformin and sulfonylureas are clinically effective in the treatment of diabetes, they have low efficacy, low durability, and large toxic side effects, and cannot fundamentally eliminate the cause of the disease and prevent the occurrence of complications. Therefore, the research and development of drugs with low toxic side effects that can both regulate blood glucose and prevent the occurrence of complications has become an important direction and hot spot in the development of diabetes drugs. More and more herbal medicines have been elucidated to have therapeutic effects on diabetes, and many efforts have been made to elucidate the possible mechanisms. Therefore, the discovery of natural herbs is of great importance for the prevention and treatment of diabetes.

Mulberry leaf is the dried leaf of Morus alba, family Moraceae, genus Morus. It is cold in nature, sweet and bitter in taste, and has the effect of dispersing wind-heat, clearing lung and moistening dryness, and clearing liver and brightening eyes. It is mainly used clinically for treating wind-heat colds, lung-heat and dry cough, dizziness and headache, and red and faint eyes. The root bark, branches, leaves and fruits of mulberry can be used as medicine, among which the mulberry leaves were first published in Shennong Ben Cao Jing and listed as the middle grade. Modern pharmacological studies have shown that the hypoglycemic active ingredients of mulberry leaves include alkaloids, flavonoids, polysaccharides, etc. [2], and the active ingredients, total extracts and compound preparations of mulberry leaves have

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hypoglycemic effects, and both single and compound preparations of mulberry leaves have therapeutic effects on diabetic patients [3]. This paper only describes the study of the hypoglycemic effect of mulberry leaves and its mechanism, aiming to have a more comprehensive analysis of the existing studies on mulberry leaves for the treatment of diabetes and to provide reference for future scholars to further explore the hypoglycemic effect of mulberry leaves.

2. Mulberry leaves in ancient Chinese medical texts

Mulberry leaf was first used as medicine in Shennong Ben Cao Jing [4], and was given its proper name, which has been used since then. It is bitter and sweet in taste and cold in nature, and is used for dispersing wind-heat, clearing the lung and moistening dryness, and clearing the liver and brightening the eyes. The Compendium of Materia Medica also records that mulberry leaves are used for treating coughs caused by strain and fever, brightening the eyes and growing hair, and relieving thirst [5]. For a long time, mulberry leaves have been one of the commonly used medicines in many prescriptions for thirst. In the Materia Medica [6], under mulberry leaves, it is recorded that "the leaves of the branch are called chicken mulberry and are most useful." The word "fork" means splitting, and it is probably because the leaves are split like chicken claws that they are called chicken mulberry, which is the best for medicine. Through the herbal examination can be seen, ancient records of mulberry leaves to the head of the leaves, the snow or after the frost harvest for the best; its shape to the leaf is good; modern to the leaf is large and thick, yellow-green, hold the hands of the sting, no impurities for the best. In summary, the mulberry leaf herb is preferred to those with large, thick, yellowish-green leaves that are prickly to hold and frosted. Regarding the harvesting season of mulberry leaves, the Eastern Jin Dynasty's "Divine Service and Food Formula" [7] recorded two harvesting periods: "the leaves are harvested in April when the mulberry is in full bloom" and "after the frost in October", while the rest of the herbs are recorded as harvesting after the frost of mulberry leaves. Most of the processing methods are sun-drying with impurities removed, but there are also shade-drying and roasting.

3. The active ingredients of mulberry leaf to reduce sugar

3.1 Alkaloids

Modern research shows that eight alkaloid monomers can be isolated from mulberry leaves, among which 1-deoxynojirimycin (1-DNJ) is known to have efficient glycosidase inhibitory effect, fagomine can promote insulin secretion and reduce insulin resistance, meanwhile, the total alkaloids of mulberry leaves also have the activity of inhibiting glycogenolysis [8]. Mulberry leaf alkaloids are mainly pyrrolizidine alkaloids, norscopolamine alkaloids and imino alkaloids, all of which have 2 to 5 hydroxyl groups in the molecule. At present, most of the methods for the determination of alkaloids in mulberry leaves are based on 1-deoxynojirimycin, and relatively little research has been done on the determination of total alkaloids.

3.2 Flavonoids

Morus alba flavonoids is a collective name for a variety of flavonoids, flavonoid glycosides and flavonoid derivatives isolated from Morus alba [9]. Due to the differences in parent structures, they can be classified into 10 groups, including flavones, flavonols, dihydroflavones, dihydroflavonols, isoflavones, dihydroisoflavones, chalcones, orange ketones, anthocyanins, and flavanones [10].Sun [11] et al. isolated nine flavonoid monomers from mulberry leaves, such as purpureol and quercetin.Doi [12] et al. found a high content of brassinin in butanol extract of mulberry leaves, containing 470-2670 mg of brassinin per 100 g of dried product. Jun [13] et al. selected 12 mulberry leaf varieties from Korea and found that their flavonoid content remained in the range of 7.485-12.979 mg/g; among the 17 flavonoids isolated, isoquercitrin and rutin dominated the content.

3.3 Polysaccharides

The polysaccharides in Morus alba are rich in content and complex components, which is another active ingredient with hypoglycemic effect discovered in recent years. After the separation and extraction of mulberry leaf polysaccharides by diethylaminoethyl cellulose column chromatography and gel column chromatography, Lv Qing [14] et al. obtained three homogeneous polysaccharides named SD2- 3, SD3-3, and SD3-4, respectively.The analysis of infrared spectrograms showed that all three fractions contained

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the basic information of sugar compounds, and all of them might contain glyoxylate, while none of them had mannose residues. Hu Runfeng et al [15] prepared mulberry leaf polysaccharide (MLP) by aqueous extraction and alcoholic precipitation, and further purified it by ion exchange column chromatography to obtain four mulberry leaf polysaccharide fractions (MLP-1, MLP-2, MLP-3 and MLP-4) with molecular masses of 6.14, 8.08, 10.25 and 2017.55 ku, respectively; all four polysaccharide fractions were composed of six monosaccharides including rhamnose The four polysaccharide fractions were composed of six monosaccharides, including rhamnose, arabinose, xylose, mannose, glucose and galactose, but with different monosaccharide ratios; the four polysaccharide fractions had typical polysaccharide absorption peaks and contained pyranose ring structures.

4. Mechanism of action of mulberry leaves in preventing and treating diabetes

4.1. Inhibition of α-glucosidase activity

Alpha-glucosidase inhibitors are a class of mainstay drugs for the treatment of type II diabetes, which can competitively inhibit various alpha-glucosidases in the small intestine, block 1, 4-glycosidic bond hydrolysis, delay the process of hydrolysis of carbohydrates in food to glucose, and effectively lower postprandial blood glucose levels [16]. α-glucosidase inhibitors as oral hypoglycemic agents are safe and easy to use, fast-acting and have few side effects. Studies have shown that the alkaloids, flavonoids and polysaccharides in mulberry leaf extract have certain glucosidase inhibitory activities, among which the alkaloids are 1-deoxynojirimycin (DNJ), which has the highest content and the most significant efficacy [17].

1-DNJ, a polyhydroxy alkaloid isolated from mulberry leaves, branches and roots, is a polar sugar analogue, a potent α-glucosidase inhibitor, which can reversibly and non-competitively bind α-glucosidase, inhibit the conversion of disaccharides in vivo, lower fasting blood glucose, and significantly inhibit the sharp rise in postprandial blood glucose [18]. Wei Xiaoyan [19] studied the inhibition of glucosidase by purified substances under in vitro conditions and in isolated organs , and the results showed that under in vitro conditions and in isolated organs , there was a certain inhibition effect on glucosidase on the small intestinal mucosa , and the higher the purity , the stronger the inhibition effect; the in vivo hypoglycemic effect of enriched mulberry leaf extract on diabetic mice was studied , and the test results showed that diabetic mice "The higher the dose of the extract, the better the hypoglycemic effect, and the best hypoglycemic effect of the high dose, showing a dose-effect relationship. Yao Jia et al [20] gave DNJ extract from mulberry leaves to diabetic nephropathy rats after 6 weeks of feeding and found that compared with the model group, the fasting blood glucose level of rats decreased significantly and could effectively restore the glucose tolerance level of rats.

4.2. Promotion of insulin release

The active components of Morus alba may affect the signaling pathways involved in glucose metabolism and improve the insulin resistance status of HepG2 cells, thus increasing the body's sensitivity to insulin and lowering blood glucose [21]. Mulberry leaf polysaccharide can promote insulin secretion from pancreatic β-cells, improve insulin resistance and promote hepatic glycogen synthesis, thus achieving the purpose of regulating glucose metabolism and lowering blood glucose. Chunjiu Ren [22] used immunofluorescence histochemistry, western blots and RT-PCR to detect the effects of Morus alba polysaccharide MLP on insulin secretion-related factors in high glucose cultured INS-1 cells, and the results showed that Morus alba polysaccharide MLP could significantly increase the expression of PDX-1 in the nucleus and promote Ca2+ inward flow, which in turn improved insulin synthesis and secretion. Wang Deping [23] et al. found through experiments that Morus alba MLP attenuated insulin resistance in diabetic mice, enhanced pancreatic islet sensitivity, enhanced glucose utilization by effector cells, and significantly lowered blood glucose, with effects comparable to those of the positive drug metformin; Morus alba MLP significantly enhanced antioxidant enzyme activity in diabetic mice, and improved oxidative damage to pancreatic islets and liver tissues by scavenging free radicals and inhibiting lipid peroxidation. Ren et al [24] found that Morus alba polysaccharide could promote the expression of key genes of insulin signaling pathway and improve the insulin secretion capacity of pancreatic β cells. Chen et al [25] found through experiments that mulberry leaf polysaccharide increased insulin secretion by improving the antioxidant capacity of tetraoxonin diabetic mice, and at the same time increased the combined effects of liver HK and PK activity, which prompted blood glucose to enter hepatocytes, increased hepatic glycogen synthesis and accelerated glucose oxidative decomposition, thus achieving the effects of regulating glucose metabolism, lowering blood glucose and improving diabetic

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symptoms.

4.3. Promotes islet beta-cell repair

The proliferation and apoptosis of β-cells determine the number of β-cells, therefore, promoting the repair of pancreatic β-cells is essential to maintain the number and function of β-cells. Current studies have shown that mulberry leaf flavonoids and mulberry leaf polysaccharides have antioxidant and free radical scavenging effects, which can maintain or repair the physiological function of pancreatic β-cells and increase insulin secretion, thereby reducing blood glucose levels. Zhang Y et al [26] treated STZ-induced diabetic model mice with high purity Morus alba polysaccharide extract and found that Morus alba polysaccharide could promote pancreatic cell regeneration and insulin secretion; meanwhile, Morus alba polysaccharide had an effect on lipid metabolism and could reduce blood lipids. Total flavonoids of Morus alba can alleviate apoptosis of pancreatic β-cells by up-regulating the level of anti-apoptotic gene Bcl-2 and down-regulating the expression of pro-apoptotic gene Bax, and improve the body's sensitivity to insulin and protect pancreatic β-cells. Chen Lingling [27] found that mulberry leaf flavonoids improve the antioxidant capacity of tetraoxopyrimidine diabetic mice by increasing liver SOD activity, reducing MDA content, promoting pancreatic islet β-cell repair, and increasing insulin secretion; at the same time, they increase the activity of hepatic hexokinase and other comprehensive effects to promote the entry of blood glucose into hepatocytes, increase the synthesis of liver glycogen, and accelerate the oxidative decomposition of glucose, so as to regulate glucose metabolism, lower blood glucose, and improve diabetic symptoms. The effect is to regulate glucose metabolism, lower blood sugar and improve the symptoms of diabetes.

4.4. Inhibition of non-enzymatic protein glycosylation

The chronic and persistent hyperglycemic state of diabetes can lead to non-enzymatic binding of glucuronide or ketone groups in the blood to ε-amino acids of lysine or hydroxylysine in protein molecules in the body, i.e., non-enzymatic glycosylation reactions. Glucose binds to proteins in the early stages of glycosylation to form reversible early glycosylation products, which then undergo rearrangement, cross-linking, and eventually irreversible glycosylation end products (AGEs). AGEs accumulate in various cells and tissues and organs in the body, which in turn induce oxidative stress and inflammatory responses and are the main mechanisms involved in the development and progression of diabetes and its complications [28]. Studies have demonstrated that AGEs have a more potent and prolonged toxic effect on pancreatic β-cells than high glucose and are an important factor in the persistent deterioration of diabetes and its complications [29]. Therefore, inhibition of protein non-enzymatic glycosylation is of great importance for the prevention and treatment of diabetes and its complications. The hypoglycemic mechanism of flavonoid compounds in Morus alba is related to the inhibition of protein glycosylation in vitro, which may act through scavenging free radicals, increasing the activity of antioxidant enzymes such as SOD, and blocking protein glycosylation [30]. Total flavonoids of Morus alba can inhibit glucose binding to proteins and reduce the synthesis of glycosylation end products, thereby controlling organ aging and diabetic complications [31].

4.5. Regulation of related signaling pathways

Alkaloids, flavonoids and mulberry leaf polysaccharides in mulberry leaves can also exert hypoglycemic activity by regulating related signaling pathways and so on. Cai Yu [32] showed that activated Akt in the activated PI3K pathway can cause a cascade response, prompting insulin to play a metabolic regulatory role, affecting the body's uptake and utilization of glucose and achieving hypoglycemic effects. Mulberry leaf flavonoids can enhance GLUT-4 protein expression and increase its translocation, reduce the abnormal glucolipid metabolism in 3T3-L1 adipocyte insulin resistance model, reduce the level of free fatty acids, and increase the oxidative consumption of glucose, thus effectively alleviating the symptoms associated with insulin resistance in type 2 diabetes [33]. High levels of soybean oil inhibit this signaling pathway, which in turn affects glycolysis, gluconeogenesis, glucose transport, gluconeogenesis, and lipogenesis through a number of pathways [34]. In addition, studies have also shown that the PI3K/Akt pathway in adipose tissue of rats with type 2 diabetes can be impaired to varying degrees and that limonene can promote lipid synthesis and storage through this pathway, which in turn affects lipid neogenesis and lipid deposition in liver cells, mitigating the negative effects of disorders of glucolipid metabolism [35].

Duan Yuhui [36] et al. observed the pharmacodynamic effects of total mulberry leaf flavonoids to

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improve hepatic lipid metabolism disorders in type 2 diabetes mellitus (T2DM) rats, and explored their mechanism of action based on hepatic peroxisome proliferator-activated receptor-α (PPAR-α) and carnitine palmitoyltransferase-1 (CPT-l) proteins. The results showed that the total flavonoids of Morus alba could effectively reduce blood glucose and improve hepatic lipid metabolism disorders in T2DM rats, and the mechanism of its hypoglycemic and lipid-regulating effects may be through activation and regulation of PPAR-α and CPT-1 proteins and promotion of fatty acid oxidative decomposition to play a regulatory role in lipid metabolism and thus hypoglycemic effects.

Liu Yinghui et al [37] found that both mulberry leaf polysaccharides and flavonoids have certain effects on promoting glucose absorption, effectively attenuating JNK, IRS-1 gene and protein expression, enhancing PDX-1 gene and protein expression, and having significant inhibitory effects on JNK signaling pathway. Luo Mingli [38] demonstrated that the amino-terminal kinase (JNK) signaling pathway is an important pathway involved in the pathogenesis of diabetes mellitus. In the diabetic state, oxidative stress in pancreatic β-cells can lead to JNK activation, which impairs the nuclear insulin signaling pathway, thereby decreasing insulin gene expression levels and disrupting insulin synthesis. In addition, activation of JNK can phosphorylate the insulin receptor substrate IRS-lser307 site, leading to insulin resistance. The regulation of JNK, IRS-1, Akt-1 and PDX-l mRNA expression in the JNK signaling pathway by polysaccharide and flavonoid components in mulberry leaves may be the molecular mechanism of mulberry leaves to lower blood glucose and protect and repair islet cell function, among which the regulation of IRS-1 can increase the body's sensitivity to insulin; the regulation of JNK, Akt-1 and PDX-1 can increase the body's sensitivity to insulin. The regulation of JNK, Akt-1 and PDX-1 can increase the synthesis of insulin in pancreatic islet cells and thus promote the function of pancreatic islets.

5. Conclusion

Traditional Chinese medicine has been used for the treatment of diabetes for thousands of years and has been gradually recognized and adopted worldwide in recent years. Most diabetic patients choose Chinese medicine for its multi-target, holistic treatment and low side effects, and a large number of studies have reported that Chinese medicine has the effects of enhancing insulin sensitivity, protecting pancreatic β-cells, correcting lipid metabolism disorders and regulating intestinal flora. As a natural plant, mulberry leaf has medicinal and food values, especially in hypoglycemic effect. In addition, the effective hypoglycemic components in mulberry leaf extract have the effects of improving vascular reactivity and lowering blood lipids. At present, the research on the hypoglycemic active ingredients in mulberry leaves, such as alkaloids, flavonoids and polysaccharides, has been more in-depth, and its hypoglycemic mechanism of action is also multi-faceted and multi-targeted, but it is mostly focused on animal research, and clinical trials need to be further explored and improved. Moreover, domestic and foreign research lacks research on the total extract of mulberry leaf and whether there is the same hypoglycemic effect or mutual pharmacological effect research between single active ingredient. The treatment of diabetes is not only focused on lowering blood sugar, but also on preventing and treating its complications. Mulberry leaf can lower sugar and prevent complications, and has a broad prospect in the prevention and treatment of diabetes.

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