International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 10, No. 3, 2025

Research Progress on Cinnamon in the Treatment of Diabetes

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Abstract: Cinnamon has a long history of medicinal use in traditional Chinese herbal medicine. With advancements in modern medical technology, it has been discovered to possess multiple pharmacological activities, including anti-inflammatory, antipyretic, analgesic, neuroprotective, antitumor, and antibacterial effects. Additionally, it demonstrates efficacy in improving metabolic syndrome (hypoglycemic, antihypertensive, antithrombotic activity, lipid-lowering, vascular endothelial function optimization, and myocardial remodeling). The molecular mechanisms by which cinnamon regulates blood sugar may involve four primary pathways: insulin-mimetic effects; enhanced insulin sensitivity and improved insulin resistance; inhibition of α-glucosidase activity; and scavenging free radicals to combat lipid peroxidation.

Keywords: Cinnamon; Treatment of Diabetes; Summary.

1. Research Progress on the Pharmacological Effects of Chinese Herbal Medicine Cinnamomi Cortex

Cinnamon is a general term for the barks of plants such as Cinnamomum japonicum, C. burmannii, C. subavenium, C. cassia, or C. wilsonii in the Lauraceae family. In Synopsis of Prescriptions of the Golden Chamber, there are nearly thirty prescriptions with cinnamon as the main ingredient, which have the effects of tonifying fire and supporting yang, guiding floating fire back to its origin, dispelling cold and relieving pain, and promoting blood circulation and dredging meridians. Cinnamon contains a relatively high amount of volatile oil, with a content ranging from 0.43% to 1.35%. The main component in the volatile oil is trans - cinnamaldehyde (TCA), with a content ranging from 62.29% to 78.75%. In addition to volatile oil, cinnamon also contains cinnamic acid, cinnamyl acetate, polyphenols (mainly flavonoids and their polymer compounds: catechins, glucosides, cinnamon polyphenols, epigallocatechin gallate (EGCG), proanthocyanidins, etc.). There are obvious differences in the chemical components of cinnamon essential oil contained in cinnamon barks of different varieties and from different origins, which also vary with different extraction methods and the polarity of the solvents used.

Cinnamon has a long - standing history in the use of traditional Chinese medicinal materials in China. In Treatise on Febrile Diseases, prescriptions such as "Guizhi Decoction", "Mahuang Decoction", and "Gegen Decoction" all use cassia twig. It is commonly used for treating wind - cold type common cold, cold pain in the stomach and abdomen, amenorrhea due to cold in the blood, arthralgia, phlegm - fluid retention, edema, palpitation, and rushing qi syndrome. As a traditional Chinese medicine, it is mainly used for its functions of dispelling cold and relieving pain, warming the spleen and stomach, and nourishing the liver and kidneys. As a spice, it is mainly used as a seasoning for meat cooking. With the advancement of modern medical technology, cinnamon has been found to have various pharmacological activities, including anti - inflammatory, antipyretic and analgesic, neuroprotective, anti - tumor, and antibacterial effects. It also has the efficacy of improving metabolic syndrome (such as hypoglycemic, antihypertensive, antithrombotic activities, lipid - lowering, improving vascular endothelial function and myocardial remodeling, etc.) [1-4]

In ancient times, diabetes and diabetic peripheral neuropathy belonged to the categories of "xiaoke" (consumptive thirst), "bi syndrome" (arthralgia syndrome), "xuebi" (blood bi syndrome), "weibi" (flaccidity and arthralgia syndrome), and "tuoju" (gangrene of the extremities) in traditional Chinese medicine. Zhang Zhongjing, the medical sage in the Eastern Han Dynasty, stated in Article 337 of "Treatise on Cold - Induced Febrile Diseases": "All cases of jue are due to the failure of the yin and yang qi to connect smoothly, and jue is manifested as coldness of the hands and feet." In "New Compilation of Materia Medica, Volume 7, Wood Section, Cinnamon Twig", it is recorded that "Li Gao said: Cinnamon twig acts on the arms transversely because it is a twig." Assisted by Aconite Root, Cinnamon Twig has a stronger effect in dispelling cold, expelling wind, and relieving pain. In the later stage of wind - dampness syndrome, when yang qi is even weaker, Modified Licorice and Aconite Decoction is used, and Cinnamon Twig is still used to dredge the meridians. If wind - dampness transforms into heat, later generations use formulas like White Tiger Decoction with Cinnamon Twig. It can be seen that Cinnamon Twig is suitable for both cold and heat types of bi syndrome. In modern times, compounds with potential anti - diabetic effects found in Cinnamon Twig include cinnamaldehyde, cinnamon polyphenols, water - soluble A - polyphenol polymers, cinnamic acid, and hydroxy - chalcone compounds with insulin - like effects, etc. Whether in animal experiments or clinical human experiments, a large amount of evidence shows that cinnamon has a hypoglycemic effect.

In the early 1990s, the beneficial effects of cinnamon in treating type II diabetes and insulin resistance began to be discovered. Khan et al. [5] extracted an unknown component

from cinnamon and named it insulin - enhancing factor. Since then, a series of animal and clinical experiments on the hypoglycemic effect of cinnamon have emerged at home and abroad. This chapter reviews the research on the effect of cinnamon in treating diabetes. **3.2**

2. Research Progress on the Treatment of Diabetes with Cinnamon

2.1. Animal Experimental Research

Xu Xinyuan et al. [6] administered cinnamon extracts from two different origins, Yulin in Guangxi and Zhaoqing in Guangdong, to alloxan - induced diabetic model mice. They found that the cinnamon extract from Yulin, Guangxi had no significant hypoglycemic effect on diabetic mice, while the blood glucose level of the group administered with the cinnamon extract from Zhaoqing, Guangdong decreased significantly. The results suggest that cinnamon extract has a hypoglycemic effect, but there are significant differences in the hypoglycemic effects of cinnamon from different origins. Couturier et al. [7-8] continuously fed cinnamon to Wistar rats for 12 weeks and found that cinnamon could increase the glucose uptake and utilization in insulin - resistant rats. It could also enhance liver glycogen synthesis by regulating insulin signaling and glycogen synthesis, and improve insulin sensitivity to achieve a hypoglycemic effect. Ping et al. [9] conducted an oral glucose tolerance test on KK - Ay mice and found that intragastric administration of cinnamon oil could significantly reduce post - meal blood glucose, especially at 120 minutes. Meanwhile, C - reactive protein, serum cholesterol, and triglycerides all decreased, while high - density lipoprotein increased. This study suggests that cinnamon extract has the effects of reducing post - meal blood glucose and regulating blood lipids. Cinnamon polyphenols in cinnamon components play a significant role in the hypoglycemic effect. Jia et al. [10] found that when STZ - induced diabetic rats were fed 100, 200, and 300 mg/kg of cinnamon polyphenols (mainly procyanidin - B) daily for 2 consecutive weeks, the blood glucose concentrations decreased by 11.1%, 22.5%, and 38.7% respectively, and the serum insulin level increased significantly. It could also dose - dependently reduce the blood glucose level of normal rats and improve insulin resistance. Verspohl et al. [11] used rat epididymal adipocyte experiments and found that cinnamon phenols could enhance insulin activity by more than 3 times. Both in vivo and in vitro experiments confirmed that cinnamon extract has a direct anti - diabetic effect, and its molecular mechanism may be related to the inhibition of the activity of nuclear transcription factor NF - kB, thereby inhibiting the gene expression of inducible nitric oxide synthase iNOS [12]. Kim et al. [13] found that after 2 weeks of administration of cinnamon extract (mainly procyanidin - A oligomers), while significantly reducing the blood glucose level of db/db mice, the triglyceride (TG), total cholesterol (TC), and intestinal α - glycosidase activity also decreased significantly, and the high - density lipoprotein cholesterol (HDL - C) level increased significantly compared with the control group ($P < 0.01$). Cinnamon polyphenols can also reduce the levels of triglyceride (TG), total cholesterol (TC), and low - density lipoprotein cholesterol (LDL - C) in patients with type 2 diabetes, rats fed with a high - sugar diet, and rats fed with a high - cholesterol diet [14] [15]. It can also dose - dependently reduce the body weight of rats [16].

2.2. Clinical Experimental Research

Clinically, positive hypoglycemic effects have also been observed when using cinnamon to intervene in patients with type 2 diabetes. Khan et al. [17] randomly divided 60 patients with type 2 diabetes into six groups. Three groups were given 1 g, 3 g, and 6 g of raw cinnamon respectively per day, while the other three groups were given placebos. The administration lasted for 40 consecutive days. The experimental results showed that cinnamon could significantly reduce the fasting blood glucose level (with an average decrease of 18% - 29%), while there was no significant change in the placebo group. Twenty days after discontinuing the medication, the fasting blood glucose in the cinnamon - intervention group was still lower than that before the treatment. This study suggests that daily intake of a small dose of cinnamon is beneficial for the prevention and treatment of type 2 diabetes.

Prasad et al. [18] It seems there is an error here, perhaps it should be a specific year like 200X]) enrolled 79 patients with type 2 diabetes. Each patient orally took the aqueous extract of cinnamon (equivalent to 3 g of cinnamon) daily for 4 consecutive months. The results showed that the average fasting blood glucose of the patients decreased by 10.3%, but there were no significant changes in glycated hemoglobin (HbA1c) and blood lipids.

Crawford [19] conducted a randomized controlled trial and recruited 109 patients with type 2 diabetes (HbA1c > 7.0%) from 3 basic clinical trial centers. The patients were randomly divided into two groups. One group orally took cinnamon equivalent to 1 g per person per day in addition to the original medications, while the other group was the placebo group. The trial lasted for 90 days. The results showed that the HbA1c level in the cinnamon group decreased by 0.83% (95% CI, 0.46 - 1.20), and that in the placebo group decreased by 0.37% (95% CI, 0.15 - 0.59), suggesting that cinnamon has a therapeutic effect on type 2 diabetes.

A randomized, double - blind clinical study conducted by Lu et al. [20] involved 66 patients with type 2 diabetes. These patients were given placebo, cinnamon extract (120 mg/360 mg), or sulfonylureas (oral diabetes medications) for 3 months. The results confirmed that cinnamon supplements could significantly improve blood glucose and HbA1c levels in patients with type 2 diabetes. It was recommended for cases where blood glucose could not be well - controlled after diet, exercise, and the original drug treatment. In the placebo group, there was no significant reduction in HbA1c and fasting blood glucose levels compared with the treatment groups.

Hlebowitz et al. [21] conducted a crossover experiment on 14 healthy subjects. Standardized real - time ultrasound imaging was used to detect whether cinnamon would affect the gastric content emptying rate. The results showed that the intake of 6 g of cinnamon could reduce post - meal blood glucose and delay gastric emptying time.

Akilen et al. [22] randomly divided 58 patients with type II diabetes into two groups. One group orally took 2 g of cinnamon per person per day, while the other group took a placebo for 12 weeks. The results showed that in the cinnamon group, HbA1c decreased from 8.22% to 7.86%, systolic blood pressure dropped from 132.6 mmHg to 129.2 mmHg, and diastolic blood pressure decreased from 85.2 mmHg to 80.2 mmHg, with no obvious changes in blood lipids. In the placebo group, there were no statistically significant differences in HbA1c, systolic blood pressure, diastolic blood pressure, and blood lipid levels before and

after the experiment. The results suggested that cinnamon helps reduce HbA1c and blood pressure in patients with type II diabetes. Subsequently, Akilen et al. [23] conducted a retrospective study on 6 clinical trials. Among 435 subjects who took 1 - 6 grams of cinnamon per day and were followed up for 40 days to 4 months, the average glycated hemoglobin level decreased significantly by 0.09%. Another review of a clinical trial showed that after 543 subjects took cinnamon or its extract for 4 - 18 weeks, the levels of fasting blood glucose, total cholesterol, low - density lipoprotein, and triglycerides decreased significantly, while there was no significant change in glycated hemoglobin [24].

In conclusion, cinnamon and its extracts have certain improving effects on the fasting blood glucose level, cholesterol, low - density lipoprotein, and triglyceride in patients with type II diabetes, while their improving effect on glycated hemoglobin is limited.

3. The Mechanism of Action of Cinnamon in Reducing Blood Sugar

Animal experiments and clinical trials have shown that both cinnamon and its extracts have certain hypoglycemic effects. However, the research on the hypoglycemic effect of cinnamon is still in its infancy, and the active ingredients responsible for its hypoglycemic effect remain unclear. The molecular mechanisms by which cinnamon regulates blood glucose may include the following four forms:

3.1. Insulin-like Action

Multiple studies have found that the methylhydroxy chalcone polymer (MHCP), a hydroxy chalcone compound in cinnamon, has similar effects to insulin. A study by Li Zongxiao et al. [25] showed that the methylhydroxy chalcone polymer extracted from cinnamon stimulates glucose absorption through cells and has insulin - like effects in promoting glycogen synthesis and glycogen synthase activity and inhibiting 3T3 - L1 adipose steroids. It can serve as an insulin analog and, like insulin signals, activate the exhausted insulin receptors. Carter et al. (2006) [26] found that MHCP can improve the insulin signaling cascade by stimulating the tyrosine phosphorylation of insulin receptor substrate (IRS1), thereby increasing the glucose uptake of mouse skeletal muscle cells. Cao et al. (2007) [27] discovered that the polyphenols of procyanidin type - A polymers in cinnamon also have insulin - like effects. They can increase the mRNA levels of insulin β - receptor (IR - β), glucose transporter 4 (GLUT4, whose main function is to rapidly increase glucose intake under the condition of elevated insulin and plays an important role in maintaining blood glucose homeostasis), and lipoprotein 36 (TTP/ZFP36) in 3T3 - L1 adipocytes. They also stimulate the autophosphorylation of insulin receptors, promote glucose absorption and glycogen biosynthesis, activate glycogen synthase, and inhibit glycogen synthase kinase - 3β.

3.2. Increase Insulin Sensitivity and Improve Insulin Resistance.

Khan et al. (199) [28] suggested that cinnamon extract can activate hepatic glycogen synthase and insulin receptor kinase, increase glucose uptake, inhibit glycogen synthase kinase 3 and suppress the dephosphorylation of insulin receptors, thereby enhancing insulin sensitivity. Li et al. (208) [29] found that cinnamon polyphenols can reduce blood glucose and lipid levels by repairing pancreatic β - cells in diabetic mice, enhancing their antioxidant capacity, and alleviating cytotoxicity through inhibitory effects. Qin et al. (209) [30] used a diabetic Wistar rat model as the research object and fed them with cinnamon extract. They found that cinnamon extract can improve insulin resistance and increase glucose absorption by enhancing the insulin signaling transduction pathway in skeletal muscle. Kim et al. [31] further discovered that the compound 3,4 - dihydroxyphenylpropionic acid (DHH105) purified from cinnamon can increase the content of GLUT4 in adipocytes and enhance insulin sensitivity, thus promoting glucose absorption. In addition, DHH105 can enhance the phosphorylation of insulin receptor - subunits and insulin receptor substrate - 1 in adipocytes.

3.3. Inhibition of α-glucosidase Activity

Studies by Solomon et al. [32] have shown that cinnamon can activate glycogen synthase, inhibit glycogen synthase kinase, delay gastric emptying, increase glucosidase, and inhibit ATPase in the small intestine, thereby reducing the absorption of glucose in the small intestine and producing a hypoglycemic effect. Cinnamon extract can effectively inhibit the activity of α-glucosidase, and its inhibitory effect increases with the administration concentration, showing a dose - dependent relationship. Its IC50 is 529 μg/ml, while the IC50 value of the positive control drug Acarbose is 34.9 μg/ml. Regarding the inhibitory effect of cinnamon extract on α - glucosidase activity, kinetic analysis of the inhibition of α - glucosidase by cinnamon extract reveals that the Km value increases with the increase of the mass concentration of cinnamon extract, while the V - max value remains unchanged, indicating that the mode of action of cinnamon extract on α - glucosidase activity is competitive inhibition. Some studies have shown that cinnamon extract can strongly inhibit the activities of yeast α - glucosidase and mammalian α - glucosidase, suggesting that cinnamon extract contains active components with enzyme - inhibitory effects [33-34]. EKM analysis was performed on the data of enzyme kinetic studies, and the results showed that the mode of action of cinnamon extract on the inhibition of α - glucosidase is competitive inhibition, which is similar to that of Acarbose [35]. Using diabetic rats as a model, the changes in post - prandial blood glucose after maltose and sucrose loading were studied. Theoretically, α - glucosidase inhibitors can inhibit the digestion and absorption of maltose and sucrose, but not the absorption of monosaccharides (glucose). The research results showed that cinnamon extract can significantly reduce post - prandial hyperglycemia caused by maltose and sucrose loading. Considering that cinnamon extract may reduce post - prandial blood glucose through other mechanisms such as improving insulin sensitivity, the authors also observed the effect of cinnamon extract on post - prandial blood glucose after glucose loading in diabetic model rats. The results showed that cinnamon extract had no significant effect on post - prandial hyperglycemia after glucose loading. The above results suggest that cinnamon extract mainly inhibits post - prandial hyperglycemia caused by maltose and sucrose loading by inhibiting the activity of α - glucosidase in the small intestine. Cinnamon contains a variety of active compounds, including flavonoids, glycosides, etc.

3.4. Scavenging Free Radicals and Anti - Lipid Peroxidation

Anderson et al. believed that diabetic patients often

accompanied by an increase in the level of lipid peroxides (LPO) and a decrease in the activity of superoxide dismutase (SOD) which can scavenge free radicals. The increase of free radicals can exacerbate the occurrence and development of diabetic complications. Kim et al. administered 200 $mg \cdot kg^{-1} \cdot d^{-1}$ of Rhodiola and Cinnamon extracts to C57BL/Ks db/db diabetic model mice. After 12 weeks of administration, the blood glucose level of the mice decreased significantly and the lipid peroxidation reaction was significantly alleviated. Cinnamon also has the effect of reducing the levels of important adipocytokines leptin and resistin, thereby improving the disorder of glucose and lipid metabolism in insulin - resistant mice [36]. Li et al. [37] found that cinnamaldehyde can reduce the body weight of obese db/db mice, improve insulin resistance and regulate the disorder of glucose and lipid metabolism. Sheng et al. [38] found that the aqueous extract of cinnamon can reduce the disorder of glucose and lipid metabolism in diet - induced obesity (DIO) rats and db/db mice fed with high - calorie diet. At the same time, in the in vitro experiment on 3T3 - L1 cells, it was found that cinnamon increased the transcriptional activity of peroxisome proliferator - activated receptors gamma and alpha (PPARγ/α) and increased the mRNA expression of target genes LPL, CD36, GLUT4, and ACO in 3T3 - L1 adipocytes. Cao [39] used cinnamon extract to increase the GLUT1 mRNA expression level in 3T3 - L1 adipocytes and reduce the protein expression in the insulin signaling pathway encoded by downstream genes, including GSK3B, IGF1R, IGF2R, and PIK3R1. This regulation may contribute to improving the viability of adipocytes.

3.5. Potential Mechanisms of Cinnamon in Regulating Blood Glucose through Influencing Gut Microbiota and Metabolism

The balance of gut microbiota influences the host's health status. If the balance is disrupted, it can easily lead to disorders in the body's metabolism and immune system. In 2004, scientists discovered that gut microorganisms could directly affect the synthesis and storage of fat in the host's gut. Since then, research on the mechanism of action of gut microbiota in metabolic diseases such as diabetes has begun to attract people's attention. Multiple studies have found that diet, antibiotics, and exogenous substances are the main factors affecting the diversity of gut microbiota.

Cinnamon is a plant used both as medicine and food, and it has therapeutic effects on chronic diseases caused by intestinal flora imbalance, such as obesity and diabetes. Cinnamon is rich in cinnamaldehyde, which has a certain inhibitory effect on a variety of bacteria. Multiple studies have found that cinnamaldehyde can damage the bacterial cell membrane and cause changes in cell morphology, thereby inhibiting the activity of bacteria. After the structure of the microbial cell membrane is altered, the ions related to metabolism within the cell are lost, resulting in a decrease in the synthesis of biological enzymes, which further inhibits the metabolism of microorganisms. Peng Xichun et al. (2018) [40] confirmed that cinnamon essential oil can affect the quantity, species, diversity, and distribution of two types of intestinal flora, namely Clostridium cluster IV and Bacteroides. Among them, the changes in all aspects of Clostridium cluster IV bacteria are very significant. Liang Xiao et al. (2019) found in a mouse model study that cinnamaldehyde can affect the growth of lactic acid bacteria and regulate the host's intestinal function through lactic acid bacteria, thus improving diseases caused by intestinal flora imbalance.

Currently, the known studies only focus on the changes in the diversity and structure of gut microbiota caused by cinnamon, without involving its impact mechanisms on the host metabolic system and genetics. This study will systematically explore how cinnamon affects the host gut microecology, metabolic system, and gene expression through three dimensions: metagenomic sequencing, targeted quantitative metabolomics, and host gene expression profiling, aiming to further reveal the molecular mechanism by which cinnamon exerts a therapeutic effect on type 1 diabetes.

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