MEDS Clinical Medicine (2023)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2023.040306
ISSN 2616-1907 Vol. 4 Num. 3

Prevention Effects of Spices on Hyperglycemia and Diabetes Mellitus

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Keywords: Spices, Diabetes mellitus, Active compounds, Glucose uptake

Abstract: Diabetes mellitus is one of the human health problems since it causes multiple complications. The presence of hyperglycemia is one of the key signs of diabetes. According to recent research, spice extracts and their active compounds have a wide range of pharmacological actions, including anti-inflammation and anti-hyperglycemia properties. They can significantly reduce the effects of diabetes and alleviate its symptoms in a sea of ways. Clinical investigations have demonstrated that spice extracts and their active ingredients are effective in treating insulin resistance and problems of lipid metabolism. This review surveys and presents information about the active ingredients, traditional uses and antidiabetic effects of aromatic spices. As well as the potential pharmacological properties of aromatic spices and extracts.

1. Introduction

Diabetes is becoming more common worldwide as a result of the faster pace of life and poor eating habits. During the COVID-19 pandemic, diabetic patients may require strict control of blood glucose levels and prevention of diabetic complications in order to maintain low susceptibility and avoid the severe course of COVID-19. [1] The distinctive clinical features of diabetes are high blood glucose concentrations and disturbances in the metabolism of proteins, fats and carbohydrates due to a relative lack of insulin secretion and action. At the same time, complications of diabetes can lead to eye, nerve, kidney and vascular pathologies, and even premature death if left untreated. Hyperglycemia is one of the most important factors affecting the onset and course of diabetes. Hyperglycemia affects four of the body's capital pathways, including: increased flux of the hexosamine pathway, formation of advanced glycosylation end increase products, activation of protein kinase C (PKC) isoforms, and increased flux of the aldose reductase pathway.

Diabetes research is currently moving in a variety of directions. Currently, the main treatments for diabetes are insulin injections and oral medications, and oral treatments are more economical and convenient for most patients than insulin injections. However, the existing medication has certain toxic side effects, it will cause the body's response to drugs to weaken due to the cycle of taking and individual differences. In recent years, anti-diabetic and anti-hyperglycemic drugs and functional foods of plant origin have started to appear and have attracted consumers because of the safer and economical composition of products of plant origin.

Spices are another natural source of medicine in addition to vegetables and fruits. Spices are one of the seasonings that play an important role in food preparation and there are more than a hundred species of plants used as spices worldwide. They are usually taken from leaves, fruits, seeds, bark and roots, and these parts are aromatic when dried. Since ancient times, spices have not only been used as food additives to improve the flavor and quality of food, but also make preservatives used to delay the decay of food to extend its shelf life. Spice extracts that are commonly used are volatile oil, water extract, and ethanol extract. The extracts primarily contain phenols and terpenes, but they also contain aldehydes, acids, and lipids. In addition, 80 spices have been shown to have anti-glycation properties that help manage and prevent DM, and studies have shown that spices can affect glucose capitalization through a variety of mechanisms, such as regulating hepatic glucose release, stimulating insulin secretion from pancreatic beta cells, and activating insulin receptor sensitivity in tissues. This review surveys and presents information about the active ingredients, traditional uses and antidiabetic effects of aromatic spices. As well as the potential pharmacological properties of aromatic spices and extracts.

2. Methods

2.1 Protocol

We performed current systematic review based on the preferred declaring items for systematic reviews and meta-analysis guidelines. We registered the study protocol on the international prospective register of systematic reviews (PROSPERO) database (http://www.crd.york.ac.uk/PROSPERO), with a registration number CRD42021239810.

2.2 Search strategy and paper selection

We sought following electronic databases until February 2022: PubMed, Scopus, WOS, Embase, ProQuest, and a search engine Google Scholar. Also, we turned on search alert services in each database to recognize papers published following the primary search. We performed our search without any limitation in publication date and/or language using following MESH and non-MESH words in title, abstract, and keywords: “spices”, “spice”, "condiment", "spice seasoning", "spices extract", “aromatic condiment”, “flavoring materials”, “natural spices”, “seasoning” in combination with “diabetes”, “diabetes mellitus”, “d.millitus”, “honey pore-urine”, “glycuresis”, “hyperglycemia”, “hyperglycemic”, “hyperglycemia and glucsuria”, “diabetes glycosuria”, “experimental diabetic”, “diabetes”, “diabetics”. Additionally, we sought the references or citations of these studies and grey literature to find potential researches. We did not include reviews, book chapters, conference abstracts, and articles regarding pomegranate in health problems other than OA.

2.3 Data extraction

We prespecified outcomes and data to be collected. Following data were gathered from the selected articles: first author's name, publication year, subjects’ characteristics, type and dose of spices, treatment duration, and outcomes. Plausible disagreements were emended.

2.4 Risk of bias assessment

We performed risk of bias assessment by Checklist for Reporting In-vitro Studies (CRIS) guideline for in vitro studies, SYRCLE’s risk of bias tool for animal studies, and Cochrane Collaboration's tool for clinical studies, respectively.

3. Results

3.1 Hypoglycemic effect of spices extracts and its active components

The active substance in spice extract can inhibit hyperglycemia and diabetes via a drug-like action. The active ingredients in spice extracts, according to research, help to lower blood sugar levels by activating insulin receptors, increasing glycogen synthase, and other mechanisms. Spice extracts and their active components can also inhibit carbohydrate digestion in the digestive tract, increase glucose absorption in the body, regulate liver glycogen heterogenesis, regulate transporters, and act in other ways to provide a synergistic anti-hypoglycemic effect. [2] In a previous study, we extracted 24 spices with hot water and ethanol and measured glucose uptake in L6 myotubes, and we discovered that more than one spice extract can promote glucose uptake in L6 myotubes. [3] The mechanism of action of spices is shown in the fig. 1.

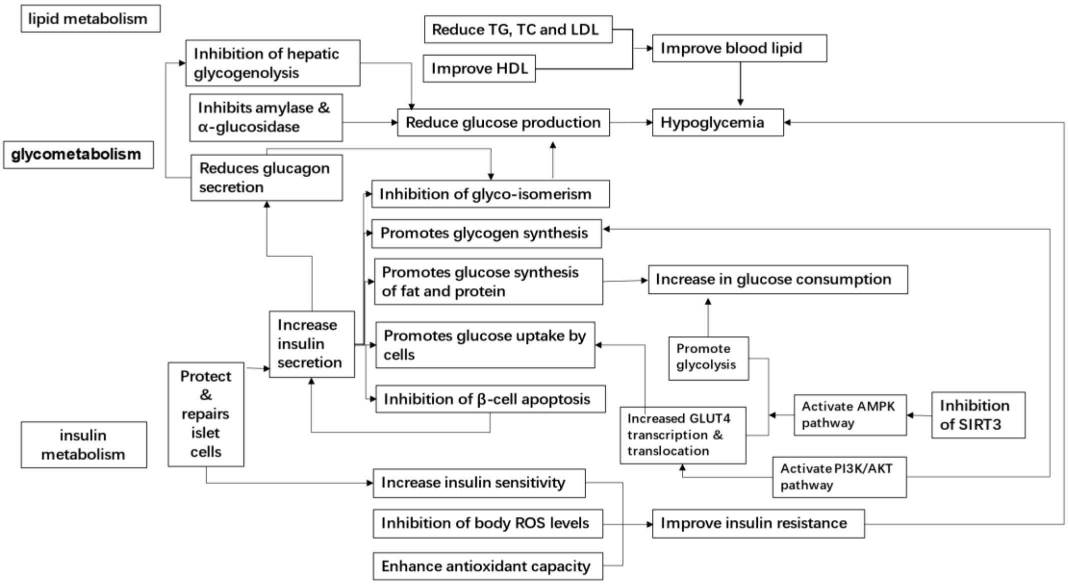

Figure 1: Anti-diabetic effect of spices

3.2 Anti-hyperglycemic activity by spices compounds

Skeletal muscle glucose metabolism accounts for 75% of total body glucose metabolism, and it is through this process that insulin regulates blood glucose levels by stimulating glucose uptake in peripheral tissues[4]. Controlling blood glucose levels is a critical step in the prevention and management of diabetes[5]. The cell surface glucose transporter 4 (GLUT4) regulates glucose uptake by adipose tissue. In a previous study, we used hot water and ethanol to extract 24 different spices, including nutmeg, fennel, clove, and nutmeg. Ethanol extracts of nutmeg, turmeric, nutmeg, black pepper, and white pepper all increased glucose uptake in L6 myotubes. Piperine was also investigated to see if it caused GLUT4 translocation to the plasma membrane. According to the findings, piperine promoted glucose uptake and GLUT4 translocation.

Hepatic gluconeogenesis is an important part of hepatic glucose metabolism. The disorder of hepatic gluconeogenesis increases hepatic glucose output, which is a major inducer of hepatic insulin resistance. Furthermore, a number of transcription factors regulate liver gluconeogenesis by inhibiting or enhancing transcription factor activity via a variety of signal transduction pathways, affecting the transcription of gluconeogenesis rate-limiting enzyme coding genes. Curcumin, derived from the spice turmeric, can increase the expression of two key hepatic gluconeogenesis genes, PEPCK and G6Pase, whereas HFFA-induced gluconeogenesis inhibits the expression of PEPCK and G6Pase, as well as gluconeogenesis and blood glucose control. [3]

3.3 Inhibit glycosylation by spices compounds

Diabetes complications are linked to glycosylation. Non-enzymatic reactions involving amino groups in proteins, lipids, nucleic acids, and reducing sugars produce it. To degrade toxic glycosylation compounds, it primarily inhibits glycosylation final product formation by acting on molecular pathways and key targets involved in glycosylation product formation. Cinnamon polyphenols, for example, reduced insulin resistance in rats. A polymer can significantly increase liver glycogen synthesis by regulating insulin signal. [6] Cinnamon extract can also inhibit the mRNA expression of genes related to glucose-6-phosphatase (G6P) and phosphoenolpyruvate carboxylation kinase (PECK), inhibiting glycogenogenesis and regulating blood glucose. [7] A study looked into the effect of clove bud on -amylase and -glucosidase activity.

3.4 α-glucosidase and α-amylase inhibition by spices compounds

Food carbohydrates are primarily hydrolyzed by -glucosidase and pancreatic -amylase. Pancreatic -starch is hydrolyzed to yield branched isomaltose oligosaccharides, which are then hydrolyzed further by intestinal -glucosidase to yield monosaccharide. After eating, the digestive tract's digestion and absorption of carbohydrates in food causes a rapid increase in blood glucose levels in diabetics. One of the most common spices is pepper. According to studies, the inhibitory activity of pepper ethanol extract on—glucosidase is 23-66%. Sweet pepper and pepper have the most inhibitory activity, while pepper has the least inhibitory activity. The inhibitory effects of the two enzymes were dose-dependent, and increased with the increase of pepper extract concentration.[8] The active ingredients in cinnamon extract inhibited the activity of -glucosidase by competitive inhibition, according to kinetic data analysis. [9] Through the study of diabetic rat models, cinnamon extract and its active components were found to inhibit the mRNA expression of genes involved in lipid and glucose metabolism, indicating that cinnamon extract and its active components could indeed participate in preventing the increase of postprandial blood glucose level. [10]

3.5 Reduction of blood glucose level by spices compounds

Improving IR activity can boost insulin receptor substrate signal transduction, resulting in better glucose metabolism. Skeletal muscle insulin resistance is closely related to type 2 diabetes because it completes the majority of the glucose metabolism involved in insulin in the body. Spice phenolic extracts have been shown in studies to induce insulin resistance in skeletal muscle via the NO pathway, improve insulin signal transduction in skeletal muscle, and increase glucose uptake by adipocytes, thereby lowering blood glucose. Spice heat measurement boosts antioxidant activity by changing the chemical structure of potent antioxidant compounds in spices. Turmeric, ginger, and garlic were found to be beneficial to the diet, and blood glucose levels were reduced when turmeric at 90mg/dL was fed versus the control group. [11] The insulin resistance, oxidative stress, biochemical parameters, and anthropometric results of 40 T2 D patients taking metformin and/or glibenclamide were evaluated with rosemary tea (2 g / 1 litre per day) as a supplementary therapy. This treatment is notable for lowering glycosylated hemoglobin percentage, insulin resistance, and pancreatic -cell function. Finally, the levels of lipid peroxide differed significantly. [12] Diabetic rats were given ginger orally for six weeks. Ginger reduced blood glucose levels, and the liver index was close to normal, as was metformin.

3.6 Other assay by spices compounds

Glucagon-like peptide-1 (GLP-1), encoded by the glucagon-like gene, is primarily released from intestinal endocrine L cells in response to hormones, nutrients, and neuronal stimulation. It can regulate the proliferation of -cells and protect them from metabolic stress in addition to acting as GLP-1 to regulate the effect of dietary consumption on insulin secretion[13]. The spices used in curry contain a plethora of active compounds. One study found that curry mixed with white rice in three different doses had an acute postprandial effect on GLP-1 concentration, which included ginger, onion, and garlic. Curcumin has been shown to stimulate intestinal GLP-1 secretion in spice turmeric, which may be beneficial to glucose homeostasis. [14]

The rise in blood glucose levels in diabetic patients is linked to an increase in free radicals in the body, as well as damage to the antioxidant defense system. Diabetes, particularly complications, are regulated by oxidative stress. Low levels of antioxidants in plasma are a risk factor for disease occurrence, and high levels of free radical scavengers must be monitored throughout the diabetes process. The spice extract contains antioxidants that can scavenge free radicals, protect cell membranes, increase cell viability, and regulate tissue and organ functions. The hypoglycemic effect of onion is primarily due to sulfur compounds such as S-methylcysteine and flavonoids such as quercetin. As well as boosting antioxidant enzyme activity and insulin secretion. By normalizing the activities of hepatic hexokinase, glucose 6 - phosphatase and HMG-CoA reductase, onion extracts have also been proved to have hypoglycemic and hypolipidemic effects.[15] Some studies revealed the phenolic content of key enzymes related to type 2 diabetes mellitus and hypertension in Latin American traditional medicinal plants, herbs and spices and the antioxidant activity related to DPPH radical scavenging through in vitro analysis. And in this experiment, all evaluated peppers showed good carbohydrate-regulated enzyme inhibition profiles, suggesting that peppers have potential for managing type 2 diabetes-related hyperglycemia. [16]

3.7 Spices extract and its active components improve diabetic complications

Diabetic patients with abnormal apolipoprotein metabolism can develop serious vascular complications. Apolipoprotein, as a component of plasma protein, is crucial in the transfer and metabolism of blood lipids. Furthermore, insulin resistance is associated with abnormal blood lipid levels, which are caused by excessive production of high triglyceride lipoproteins in the intestine and liver, as well as delayed clearance by the liver. Spice extracts can improve dyslipidemia and lower risk factors for cardiovascular disease. Ginger and garlic help to prevent dyslipidemia by increasing fat metabolism as well as bile acid synthesis, which helps to eliminate cholesterol. HDL levels increased significantly, indicating that it participates in reverse cholesterol transport. [17] Cinnamon extract's active ingredients have been shown in studies to inhibit apolipoproteins, improve vascular complications, and inhibit gene expression associated with elevated cholesterol and triglyceride levels. Therefore, spice extract and its active components are very favorable for improving diabetic vascular complications.[18]

Diabetes will cause central nervous lesions in the late stages of the disease, resulting in cognitive dysfunction and the development of some neurodegenerative diseases. Neurotoxicity can result from abnormal -amyloid protein expression, leading to severe neurodegenerative diseases such as Alzheimer's disease. According to research, the active ingredients in spices can form reversible interactions with the cystine residue of Tau protein, which may organize the abnormal phosphorylation of Tau protein, alleviate neurodegenerative disease symptoms, and improve cognitive dysfunction. Gingerol can effectively inhibit the intracellular accumulation of reactive oxygen species and/or nitrogen substances caused by A-25-35 and restore A-25-35. In addition, ginger treatment found increased habitual memory and decreased escape latency of behavioral characteristics because it improved cognition by enhancing cholinergic transmission. Moreover, the extractable chemicals in ginger protect another part of the brain through antioxidant properties. [19] As a microtubule protein, hyperphosphorylation of Tau protein can also lead to Alzheimer's disease. Cinnamon extracts can promote the complete decomposition of Tau protein filaments, and cause substantial changes in the morphology of paired helix filaments isolated from the brain of patients with Alzheimer ' s disease[20]. It was found that catechol and cinnamaldehyde, the active components in the extract, could form a reversible interaction with the cystine residue of Tau protein, which might prevent the abnormal phosphorylation of Tau protein, improve cognitive dysfunction and alleviate the symptoms of neurodegenerative diseases. [21]

4. Conclusion

Advances are being made in the pathophysiology and management of diabetes, but the disease and complications are also evolving. Spice extracts are rich in biologically active compounds that exhibit pharmacodynamic interactions in antidiabetic and antihyperglycemic settings and synergistic effects with some diabetes therapeutic agents.

This review describes that the diabetic effects of spices are activated by stimulation of insulin production and release from the pancreas, alteration of glucose uptake and insulin-protective effects of bioactive compounds, and that the antidiabetic mechanisms vary among spices. Therefore, further studies are needed to evaluate the antidiabetic effects of the active compounds in spices to determine their specific mechanisms. Also, the intake and bioavailability are crucial to evaluate their effects.

To summarize, spices contain a number of chemical components, each of which contains a number of active substances that can inhibit hyperglycemia and diabetes. Furthermore, it has a high potential for further development in inhibiting hyperglycemia and diabetes by inhibiting the formation of glycosylation end products or promoting glucose absorption, regulating a variety of insulin signaling pathways, improving anti-diabetes and promoting treatment.

However, some issues remain in the study of spices as functional foods for diabetes adjuvant treatment and hyperglycemia inhibition: First, the structure of bioactive components must be identified. The identification of active components ensures the development and quality of related products, as well as the identification of active monomer compounds in the extract to improve its utilization value and to establish clear research objectives. Second, the in vivo hypoglycemic mechanism of hypoglycemic active components was investigated. Several hypoglycemic mechanisms are still unknown. The internal environment of the body is complex, and efficacy is likely to be the result of a variety of internal environment factors. The majority of research has concentrated on the effects of extracts on in vitro glucose metabolism inhibition. As a result, it is necessary to combine in vitro and in vivo experiments to provide a more effective evaluation for the study of hypoglycemic bodies.

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