Is Cinnamon Efficacious for Glycaemic Control in Type-2 Diabetes Mellitus?

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Abstract

Diabetes is on the rise, and has become a major public health issue. In view of limitations of available glucose lowering therapy, there is a need to explore and develop natural remedies with anti-diabetic properties. Spices such as cinnamon, cloves, bay leaves, and turmeric display insulin-enhancing activity in vitro. Cinnamon or Dalchini is popularly use as a spice for its fragrance and flavour in wide variety of traditional foods. Among various types of cinnamon, C. zeylanicum is well known as effective substitute for diabetes. Cinnamaldehyde is one of the major constituents (65-80%) of bark oil extracted from C. Zeylonicum which seems to reduce plasma blood glucose concentration more effectively when it is compared with metformin. It enhances the expression of proteins involved in glucose transport, insulin signalling, and regulates dyslipidaemia. This review describes the basic and clinical pharmacology of cinnamon.

Keywords: Cinnamon, Glycaemic control, Type 2 Diabetes Mellitus

Prevalence of Diabetes

In 2019, 463 million number of people were estimated to be alive with diabetes which represents 9.3% of the global adult population (20–79 years). This number is expected to increase to 578 million (10.2%) by 2030 and 700 million (10.9%) by the year 2045. In 2045, the top three countries with the highest number of people with diabetes are expected to be China, India and Pakistan, with 147, 134 and 37 million, respectively.[1,2]

The risk of type 2 diabetes is determined by an interplay of genetic and metabolic factors. Ethnicity, family history of diabetes, and previous gestational diabetes combine with older age, overweight and obesity, unhealthy diet, physical inactivity and smoking to increase risk. If it is not well controlled, may cause blindness, kidney failure, lower limb amputation and several other long-term consequences that impact significantly on quality of life. There are no global estimates of diabetes-related end-stage renal disease, cardiovascular events, lower-extremity amputations or pregnancy complications, though these conditions affect many people living with diabetes.[3-5]

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Historical Perspectives

Ceylon Cinnamon (C. Verum or C. Zeylanicum), bushy evergreen tree of the family Lauraceous is native to Sri Lanka, the neighbouring Malabar Coast of India and Myanmar and is also cultivated in South America and the West Indies. Because of this, it is also called Mexican cinnamon. The spice, consisting of the dried inner bark, is brown in colour and has a delicately fragrant aroma and a warm sweet flavour. In Urdu, it is called Dalchini. Various related species are also cultivated as a source of cinnamon spice, including Chinese Cinnamon (C. aromaticum or Cassia), Vietnamese or Saigon cinnamon (C. loureiroi), Indonesian cinnamon (C. burmannii), Camphor laurel (C. camphora) and Malabar cinnamon (C. citriodorum or C. tamala, also known as tejpata, tejpat or Indian bay leaf).[6,7] Italians called it canella, meaning "little tube," which aptly describes cinnamon quills. Among two prime types: Ceylon and Cassia, Ceylon cinnamon is also named as True cinnamon, is easy to discriminate from others by its look of quill. It composed of soft and light colour roll of layers whereas the others are dark, hard and hollow and rolled in one layer. Its low coumarin levels and delicate taste make it a preferred species.[6,8] It is documented that cinnamon Cassia may be hepatotoxic because it contains high level of coumarin (0.8 to 10.63%); whereas cinnamon Ceylon has low level of coumarin content (about 0.2%), which makes its safer to use.[9] However, there is paucity of sufficient scientific evidence about it.

Chemical Composition

The different parts of the plant possess the same array of hydrocarbons in varying proportions, with primary constituents [Table-1].

Biochemical mechanism of action

- Disturbance in the balance between free radical and anti-oxidant defence causes tissue damage. Increased oxidative stress leads to insulin resistance, beta cell dysfunction, impaired glucose tolerance and ultimately leading to type 2 diabetes.[19] Cinnamon contains antioxidants that have the potential to protect against pre-diabetes.
- Water-soluble polyphenol compounds extracted from cinnamon, are insulin mimic, increase insulin sensitivity by inhibiting tyrosine phosphatase, an enzyme that

Table-1: Chemical compound in the cinnamon plant..

Part of plant	Primary constituent	Action against Diabetes
Leaves	1. Eugenol: (70 to 95%)[10] 2. Phenolic compound: rutin, catechins, quercetin, kaempferol, isorhamnetin.[11,12] 3. MHCP[15]	Eugenol cause lowering of blood glucose[13] Polyphenols activate insulin receptor kinase, increasing glucose uptake, do autophosphorylation of the insulin receptor.[14] Methylhydroxychalcone polymer (MHCP) is insulin mimetic and helps to stimulate glucose oxidation.[15,16]
Bark	1. Cinnamaldehyde: (65 to 80%)[10] 2. Cinnamyl-alcohol (alcohol form of cinnamaldehyde) 3. Cinnamic acid 4. Phenolic compound: procyanidins, MHCP[15], catechins[17]	Cinnamtannin B1, a proanthocyanidin isolated from the stem bark of Ceylon cinnamon, activates the phosphorylation of the insulin receptor β-subunit on adipocytes as well as other insulin receptors.[17] Hydroxyl- Cinnamic acid derivatives named naphthalene methyl ester has blood glucose-lowering effects.[18]
Root	Camphor[10]: 60.00%	
Fruit	Trans-Cinnamyl acetate (42.00 to 54.00%)[10]	
Flowers	Cinnamyl acetate[10]: 41.98%	

inactivates insulin receptors.[20] When insulin binds to α unit of insulin receptor, phosphorylation of tyrosine protein residue of β unit takes place. Phosphorylation means addition of phosphate from ATP. Kinase enzyme helps to phosphorylate tyrosine amino acid is termed as tyrosine kinase. There is an opposite enzyme protein tyrosine phosphatase that removes phosphate group from target molecule cause de-phosphorylation. De-phosphorylation of the insulin receptor by protein tyrosine phosphatase inactivates insulin receptors.[21] Water soluble polyphenol inhibits tyrosine phosphatase, inhibits de- phosphorylation and activates phosphorylation of insulin receptors.[22] Aqueous extract of cinnamon containing Polyphenol type-A polymers has demonstrated insulin-like activity on high performance liquid chromatography (HPLC).[23]

- A computational docking study has used Auto dock software to show high binding affinity and protein-ligand stability of cinnamaldehyde and cinnamic acid towards target protein tyrosine phosphatase which promote use of these as a conventional therapeutic molecule.[24] Negative regulation of protein tyrosine phospahtase-1B helps to improve in insulin action and also helps to control the storage of triglycerides in adipose tissues.[25]
- GLUT 4 is the major glucose transporter in skeletal muscle and adipose tissue which has a key role in uptake of glucose from blood stream, store it as glycogen and oxidizes it to produce energy. GLUT 4 is under control of insulin. It is well established that insulin promotes translocation of GLUT 4 from intracellular compartment to cell membrane.[21] In diabetes mellitus because of the absence or insufficient sensitivity of insulin, GLUT 4 is decreased, so blood glucose can't be stored and would be increased in blood stream. Cinnamon extract polyphenol improves type 2 diabetes by prompting GLUT 4 translocation.[26]
- AKT generates signal which trigger translocation of GLUT 4 to plasma membrane which facilitates glucose uptake. Mutation of AKT gene impairs glycogen synthesis causing a very rare form of T2 DM.[21] Cinnamon affect AKT along with the genes related to carbohydrate (PPECK, PK, GLUT-2 and IGF) and lipid metabolism (FAS, LPL. HSL and SREBP-1c) in a way to control the metabolic biohazards accompanied diabetes.[27,28] Cinnamon extract consumption also appears to regulate glucose uptake-related genes, such as glycogen synthesis 1, and glycogen synthase kinase 3β and mRNA expression in adipose tissue leading to increased insulin sensitivity.[29] Cinnamon also affects the expression of PKB, PDK1, PI3K, IRS-1 and INSR which accounts for the onset of insulin resistance and type-2 diabetes.[30-32]

Animal Studies

Anti-diabetic properties of cinnamaldehyde (20mg/kg bw) in streptozotocin induced male diabetic Wister rats reduced plasma blood glucose concentration, HbA1c, total cholesterol and triglyceride more effectively when it compared with metformin. At the same time it markedly increased plasma insulin, hepatic glycogen and HDL levels. In this study cinnamaldehyde has also restored the altered plasma enzyme, such as aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase and acid phosphatase levels near to normal.[33] Cinnamon extract improved insulin sensitivity in the brain and lowered liver fat in Mouse Models of Obesity.[34] Ethanolic extract of cinnamon cassia at 150 mg/kg and 200 mg/kg dose for 28 days has reduced fasting blood glucose concentration in Alloxan induced diabetic mice.[35]

Cinnamon cassia bark extract 200 mg/kg weight has lowered blood glucose, triglyceride, total cholesterol, intestinal α glycosidase after 6 weeks of administration in C57BlKsj db/db mice.[36] In another research, cinnamon bark extract improved glucose metabolism and lipid profile in

Table-2: Summary of clinical trials on effect of cinnamon on glycaemic control, and lipid profile in patients with diabetes type-2.

Author (year), place	Methods	Summary of results
Khan A et al. (2003) Peshwar, Pakistan[40]	Sixty patients were randomised in three experiential arms (1, 2 & 3 grams of cinnamon administration and placebo in control arms.	After 40 days, patients in all three arms cinnamon has reduced mean fasting serum glucose, triglyceride, LDL cholesterol and total cholesterol, while no significant changes were noted in the placebo groups.[40]
Crawford P (2009) Las Vegas, USA[41]	One hundred and nine patients (HbA1C >7.0) randomised in experimental arm (received cinnamon cassia 500mg 2 tabs daily for 90 days) and control arm with usual antidiabetic medications.	Cinnamon significantly lowered HbA1c ($P < .001$) compared with usual care alone ($P < .16$).[41]
Lu T et al. (2012) China[42]	Sixty-six patients were randomised into three groups (placebo, low dose- 120mg and high dose-360mg cinnamon group). Gliclazide was continued during the entire 3 months for all the patients.	HbA1c, FBS and triglyceride was significantly reduced in both low and high dose of cinnamon arms, where effect was relatively higher in high dose arm. However, no significant changes in placebo group.[42]
Sharma P et al. (2012), India[43]	One hundred and fifty newly diagnosed patients were randomised in three groups (cinnamon 3g, 6g and control with conventional antidiabetic treatment). Diet and exercise was continued for all three groups	After 3 months there was a significant improvement in FBG, HbA1c, lipid profile in both experimental arms.[43]
Vafa M et al (2012), Tehran, Iran[44]	A double blind randomized placebo controlled clinical trial on 44 patients randomized in experimental arm [3 g per day cinnamon zeylanicum supplement (n=22)] and a placebo (n=22), for eight weeks.	In experimental arm FBG, HbA1c, triglyceride, BMI decreased significantly compared to baseline, but not in placebo group. However, significant difference in glycaemic status, lipid profile was observed between the groups at the end of intervention.[44]
Al-Yasiry K et al. (2014), Kerbala, Iraq[45]	Forty male patients on oral antidiabetic drugs were administered 0.5 gm crude grind cinnamon 15 minutes after each meal (Total 1.5 gm daily) for 3 months.	Cinnamon had a significant antidiabetic effect in reduction of FBS, RBS, and HbA1c. However, there was no significant effect on body weight ($P>0.01$).[45]
Anderson RA et al. (2015), China[45]	A randomized double blinded placebo controlled trial on 137 Chinese participants. 250 mg cinnamon extract capsule BD was given to intervention group. Placebo group was taken 250 mg of dark brown (baked) wheat flour.	Supplementation with 500 mg of water-extract cinnamon for two months reduced fasting glucose, total and LDL cholesterol and enhanced insulin sensitivity of participants.[46]
Kizilaslan N et al. (2019), Turkey47	Forty-one healthy individuals randomised in three experimental arms (1 gm, 3 gm and 6gm/day of cinnamon administration)	Cinnamon consumption (3-6 gm/day) was found to be effective blood glucose after 40 days of intervention.[47]

the fructose-fed rat, an animal model of insulin resistance after 60 days of administration.[37] Mohammad HA et al had showed in their study that mean value of fasting blood glucose level in hyperlipidaemic rats (135.5±1.9mg/dl) and diabetic rats (401.8±3.5 mg/dl) was significantly decreased when hyperlipidaemic rats (123.2±1.9 mg/dl) and diabetic rats (221.1±3.5 mg/dl) were treated with cinnamon extract.[38] Al Jamal et al. found decrease of 29% in glucose level, 24% in cholesterol, 19% in triglycerides, 26% in LDL, and increase of 20% in HDL by administration of cinnamon in diabetic rats.[39]

Clinical trials

The clinical trials conducted on efficacy of cinnamon in glycaemic control, and lipid profile have shown significantly positive results as illustrated in Table-2.

Regulatory status

US Food and Drug Administration listed cinnamon as substances generally recognized as safe (GRAS) to consume.[48] Furthermore, according to the US Department of Health, cinnamon appears to be safe for most of the people when taken by mouth up to 6 grams daily for six weeks.[49] The European Food Safety Authority sets the "daily tolerable intake" at about a teaspoon per day or 0.1 mg/kg body weight.[50]

Pragmatic suggestion

Cinnamon use can be encouraged as metabolic modulator in persons with diabetes. Though it can be considered a complementary therapy, it should not be viewed as an alternative to established glucose lowering drugs. While the exact dose is not clear, one may recommend use of up to one teaspoonful of cinnamon powder as an adjunct to therapy.

Conclusion

There is currently growing interest in herbal remedies due to the side effects associated with oral hypoglycaemic agents and insulin used for the treatment of diabetes mellitus. Many herbs possess hypoglycaemic properties and are used as traditional folk medicine. One such product is cinnamon, which is generally recognized as safe (GRAS) by United States Food and Drug Administration. This review highlights the glucose lowering effect of cinnamon.

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