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Review Article

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The Probable Medicinal Usage of Cinnamon in Type 2 Diabetes Mellitus: An Overview

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ABSTRACT

Diabetes mellitus (DM) is a chronic disease which causes major public health problemand its estimated that in 2019, worldwide 463 million people were suffering from DM.The main goal for the therapeutics is to regulate the glycemic control and reduce the secondary complications. There are several plant-based products has been reported to have the antidiabetic effect in type 2 diabetes (T2DM). Herein we are discussing the role of cinnamon, an herb with more than 250 species known so far. Each species contains several volatile compounds, which seems to be highly bioactive and helpful in modulating various physiological functions, further improving various disorders. Cinnamon appearing to have mimetic effect of the insulin, reducing insulin resistance via reduction of lipolysis in the adipocytes, improving lipid profile, increases incretin hormones release and regulating the glycemic control. So, we can conclude that due to increased incretins, reduced insulin resistance and insulin mimetic effect, cinnamon helps healthy persons need to secrete less insulin and in T2DM same secreted amount of insulin will help to reduce hyperglycemia due to increased glucose uptake in adipocytes and skeletal muscles. Thus, cinnamon can be used as an adjuvant to the existing therapy for T2DM, which help them to improve their glycemic control and decrease the chances of secondary complications.

Key Words: *Diabetes, Insulin mimetic, Glycemic control, Insulin resistance*

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease which causes major public health problem and its prevalence growing rapidly globally. The International Diabetes Federation (IDF) estimated that worldwide 463 million people were suffering from DM by 2019 [1] and as per Global Burden of Diseases (GBD) report, in 2017, approximately 6.28% of the world's population had type 2 diabetes (T2DM) [2].T2DM is a progressive disease in which initially insulin resistance occurs that affect the insulin receptor signaling. Insulin resistance impact the peripheral tissues, including adipose, skeletal muscle, and liver, which do not respond appropriately to the existing level of insulin, causing the ineffective uptake of glucose from the blood circulation along with imbalanced carbohydrate, protein and lipid metabolism. To overcome this insulin resistance the pancreatic β-cells starts secreting more insulin to maintain the euglycemic state but later on hyperglycemia took place due to β-cells are exhausted and no longer can secrete excessive insulin [3, 4].This insulin resistance and hyperglycemic state affects the improper adipokines and cytokines release, causing macrovascular (ischemic heart disease, peripheral vascular disease, cerebrovascular disease) and microvascular (retinopathy, nephropathy and neuropathy) complications due to inappropriate regulations of several metabolic and physiological pathways [5, 6&7].Multiple factors have driven the global epidemic of T2DM, including ageing populations, sedentary lifestyles, obesity and unhealthy diets [8]. Many cases of T2DM could be prevented with lifestyle changes, including maintaining a healthy body weight, consuming a healthy diet, staying physically active, no smoking, and no alcohol consumption or in moderation [9, 10].The purpose of the pharmacotherapy/alternative medicine in T2DM patients is to protect or delay microvascular and macrovascular complications along with improvement in quality of life [11, 12, 13& 14]. In this review we are focusing on antidiabetic properties and mechanism by which Cinnamon (*Cinnamomum* genus) regulate the glycemic control.

About the Cinnamon

The cinnamon plant belongs to C*innamomum* genus, Lauraceae family and has around 250 species identified all over the world. People used the cinnamon (commonly dried inner bark) obtained from various *Cinnamomum* plants as an aromatic condiment and flavoring additive spice in a wide variety of cuisines and several household preparations. Cinnamon's therapeutic properties as traditional herbal medicine has been documented in various traditional healing systems along with ancient ayurvedic literature. Around the world various *Cinnamomum* species have been traditionally used for the treatment of muscle pain, cold and flu, urinary tract infections, abdominal discomfort, digestion related issues, neurological issues and diabetes [15]. Cinnamon has a peculiar fragrance and aroma which were used in the perfume industry since ages. A total of 127 chemical compounds has been reported from the various species and various parts of the cinnamon. All types of *Cinnamomum* species contain eugenol, cinnamaldehyde and trans-cinnamaldehyde that makes major content of their essential oils which is responsible for the fragrance and its various biological/therapeutic activities [15, 16& 17]. Cinnamaldehyde and cinnamic acid has been found to have antioxidant, anti-inflammatory, anti-diabetic, anti-microbial, anti-cancer, and lipid-lowering properties [16, 18& 19].It has also been observed that the cinnamaldehyde helps to improve the cognitive stimuli, memory and visual motor capacity, which can be helpful in depression, Alzheimer's and Parkinson's diseases [20].

In ayurvedic literature cinnamon has been described as Laghu (easily digestible), Ushnaverrya (hot in potency) hence absorbs more water, ruksha (dry), Katu (spicy), sweet (Madhur) with a bitter taste. It is described that the bark can be used to treat Vatadosha and Kaphadosha but as a side effect, increases pitta dosha. Furthermore, cinnamon is described as the best spice for detoxification (antioxidant property). Basically, it improves Agni which helps in digestion and eliminates ama, the body's toxins, hence named Vishapaha and Amahara. It is also recommended to be used in reducing flatulence, bloating sensation, increased secretion of mucus to acts as an expectorant. This spice has an anti-obesity property and used for lipid-lowering as it acts on Medha dhatu (Body fat) [21].

Anti-diabetic properties of Cinnamon

Cinnamon and many other herbs have been used as an antidiabetic agent traditionally since ages, but in last 3-4 decades several studies reported that the various components of the cinnamon have the potential for hypoglycemic, hypolipidemic and insulin sensitization activity [16, 22, 23, 24, 25& 26].It is observed that the cinnamon and its components help T2DM patients to metabolize sugar more easily, improves insulin resistance to transport glucose efficiently through the insulin sensitive glucose transporter (GLUT-4) to various tissues for metabolism and lowers the hyperglycemia [22, 24& 25]. It is also observed that cinnamon has the potential to improve glycemic control and insulin sensitivity in people with prediabetes/insulin resistance and metabolic syndrome [27,28]. In the experimental streptozotocin-induced diabetes rat model, it has been observed that cinnamon extracts lower blood glucose along with serum cholesterol and improving insulin resistance [29]. In last two decades, several compounds like eugenol, cinnamaldehyde, copane, cinnamic acid etc. derived from the cinnamon and hypoglycemic activities has been ascertained in different compounds, which has been observed to stimulate pancreatic β-cells, increase glycogenesis, inhibits α-glucosidases and α-amylases, transfer of GLUT-4 to the plasma membrane of skeletal muscle and adipose tissues, increased cellular uptake of glucose through GLUT-4, decreased gluconeogenesis, and improving insulin sensitivity to its receptor [30, 31& 32].

Cinnamaldehyde has been extensively investigated for its hypoglycemic properties by various studies. Subhash Babu*et al.* demonstrated that cinnamaldehyde significantly reduces the plasma glucose level in a dose-dependent manner in streptozotocin (STZ) induced male diabetic wistar rats. They also observed significantly decreased glycosylated hemoglobin (HbA1c), serum total cholesterol, triglyceride levels, along with markedly increased plasma insulin, hepatic glycogen and high-density lipoprotein-cholesterol (HDL-C) levels [30]. In animal studies, it's observed that aqueous solution of cinnamaldehyde exerts its activity by increasing the expression of peroxisome proliferator-activated receptors (PPARs), a transcriptional factor, involved in the regulation of insulin resistance and adiposity [33]. Cinnamon also observed in regulating protein tyrosine phosphatase 1B (PTP 1B) and insulin receptor kinase [34]. Hayward *et al.*, has compared the aqueous extract of cinnamon with other spices and found that cinnamon has a 20-fold higher potency to reduce blood glucose levels [35].

Potential mechanism for glycemic control

Insulin mimetic activity

The *in-vitro* and *in-vivo* studies observed that components of the cinnamon can elicit an insulin-mimetic effect through the regulation of insulin signaling pathways [36]. Anderson *et al.* isolated and characterized the polyphenol type-A polymers from cinnamon extract and demonstrated its insulin-mimetic biological activity in adipocytes. They observed that the hypoglycemic effect in epididymal adipocytes either in the presence of insulin or an aqueous extract of water-soluble constituent polyphenol type-A polymers from different species of cinnamon, like, *C. cassia, C. verum, C. burmmani, and C. loureinni* [24].Based on nuclear magnetic resonance and mass spectroscopy of water-soluble polyphenol polymers,the insulin-like activity has been specifically demonstrated in polyphenols having doubly linked procyanidin type A polymer whilecinnamic acid, cyanamide, cinnamyl alcohol, eugenol, and methoxy-cinnamaldehyde

demonstrated very little or no insulin-like activity nor there was any difference in different species of cinnamon [36, 37].Anand *et al.*, reported that incubation of islets from normal healthy rats with cinnamaldehyde in the presence of 10 mM glucose for 2 h resulted in significant release of insulin while the STZ induced diabetic rats have also increased insulin release after 60 days of treatment with cinnamaldehyde [38]. As per the studies we can conclude that cinnamon help for appropriate sensing of the glucose level and release insulin appropriate amount from the pancreas. These insulin mimetic compounds activate the insulin receptor's tyrosine kinase activity and autophosphorylation of tyrosine, which pass the signal for appropriate intake of glucose by translocation of GLUT-4 receptors to the plasma membrane (Figure 1) [3, 4, 5& 39].

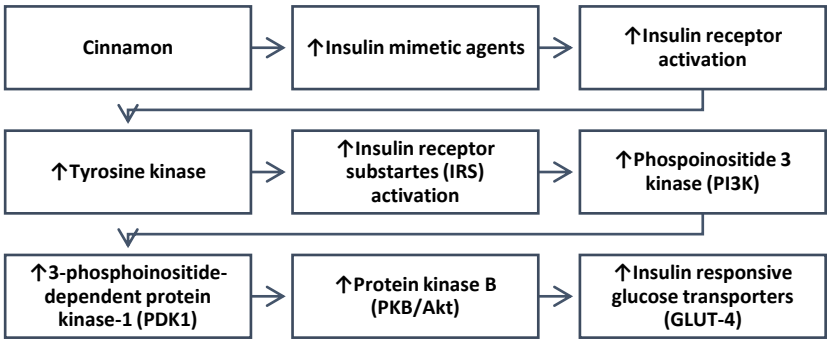

Figure 1: This figure explains how the insulin mimetic activity of cinnamon compounds help for the translocation of GLUT-4 to adipocyte cell membrane and inward movement of the glucose from the blood to adipocytes.

Effect on Incretin hormones

The two main incretin hormones; GIP (Gastric inhibitory peptide/ Glucose-dependent insulinotropic polypeptide) which release from L cells of the ileum and jejunum, and GLP-1 (Glucagon like peptide-1) which release from K Cells of the duodenum and jejunum. GIP and GLP-1 are both secreted within minutes of nutrient ingestion (food intake) from the mucosal cells of the small intestine and facilitate the rapid disposal of ingested nutrients [40]. Both peptides share common actions on β-cells of the pancreas and lead to glucose-dependent insulin secretion, induction of β-cell proliferation, and enhanced resistance to apoptosis. They also cause the satiety and slow down the gastric emptying. Dipeptidyl peptidase-4 (DPP-4) enzyme degrade these incretins which causes the increased glucagon release, more hunger, fast gastric emptying and increased lipolysis [41]. In T2DM, there is decreased incretin level due to DPP-4 activation [42]. Hlebowicz *et al.* observed that the intake of 6 g cinnamon with rice pudding reduces postprandial blood glucose and delays gastric emptying without affecting satiety in healthy subjects [43]. In their next study they observed that intake of 3 g cinnamon reduced postprandial serum insulin and increased GLP-1 concentrations without significantly affecting blood glucose, GIP, the ghrelin hormone, satiety, or gastric emptying in healthy subjects [44]. So, as per above studies, we can say that GLP-1 level may increase in T2DM with help of cinnamon then it will lead to glucose-dependent insulin secretion from pancreatic β-cells, induction of β-cell proliferation, and enhanced resistance to apoptosis. Same time as the level of insulin decreased in healthy subjects which must be due the insulin mimetic effects of the cinnamon (Figure 2).

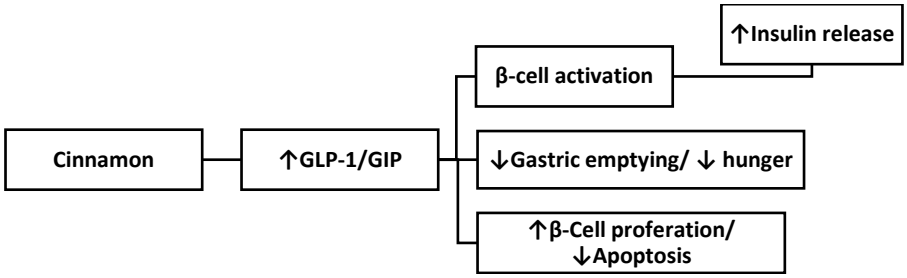

Figure 2: Cinnamon increase the level of GLP-1 and GIP, which help for various activities like, proper insulin release from pancreatic β-cells, increased β-cell proliferation and decreased apoptosis resultantly increased β-cells. GLP-1/GIP also delay the gastric emptying and hunger.

Peroxisome proliferator activator receptor (PPAR)

The peroxisome proliferator activator receptor (PPAR) gene is a type II nuclear PPARG gene that encodes a member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors. PPARs form heterodimers with retinoid X receptors (RXRs) and are responsible for the regulation of three isoforms od PPAR: PPAR-α, PPAR-γ, PPAR-δ/β [33].PPAR-α is expressed mostly in brown adipose tissue and liver and PPAR-γ is mainly expressed in adipose tissue, while PPAR-δ/β is expressed in several tissues. PPAR-α activation lowers the plasma triglycerides and increase

HDL-C levels, while PPAR-γ activation increases insulin sensitivity and yield antidiabetic effects via decreasing plasma glucose level [7, 45&46].

Sheng *et al.* demonstrated that treatment of cinnamon extract to the mouse 3T3-L1 adipocyte cell line (*in-vitro* study) can upregulate the expression of both PPAR-α and PPAR-γ and their target genes CD36, LPL, FAS, GLUT-4, and ACO. They also observed that in diet induced obese diabetic mouse (*in-vivo* study), the gene expression of PPAR-γ and its target genes CD36, low-density lipoprotein-cholesterol (LDL-C) in white fat tissue, and PPAR-α and its target gene ACO in liver were also upregulated, which indicates that cinnamon may act as a dual activator of PPAR-γ and PPAR-α resulting in improved insulin resistance and lowered serum lipids [33]. Recently, Nishikai-Shen *et al.*, reported that cinnamon significantly decreased PPAR-γ, C/EBP-α (CCAAT-enhancer-binding proteins), and FAS mRNA expression in a time-dependent manner and stimulated AMPK (AMP-activated protein kinase) phosphorylation in 3T3-L1 adipocytes. They further observed that cinnamon down regulated lipid synthesis by reducing ACSL1 (Acyl-CoA synthetase long-chain family-1), which have significant role in the regulation of lipid synthesis, and upregulated energy metabolism by phosphorylating AMPK [47].

Alpha-glucosidase inhibitory activity

α-glucosidase enzyme helps in the digestion of starch molecule. The first step of starch digestion took place in mouth where salivary amylase partially hydrolyzes endo-(1,4) bond and releases shorter oligomers (maltodextrins and maltooligosaccharides) [48]. The pancreatic α-amylase isozyme, which is secreted into the small intestine, extensively degrade the endo α-(1,4) glycosidic linkages to generate smaller oligosaccharides including maltose, maltotriose, and limit dextrin [49]. Additionally, this mixture of shorter oligosaccharides that have been digested passes through the mucosal layer's brush border membrane, where α-glucosidases finally cleaves the remaining linkages to release α-glucose monomers from the non-reducing end, which are then transported into the bloodstream by SGLT transporter [50, 51&52].

Adisakwattana *et al.*, studied the effect of the cinnamon content/extract on intestinal maltase, sucrase, pancreatic α-amylase and their combined effect in presence of acarbose. They observed that among studied cinnamon species, Thai cinnamon extract was the most potent inhibitor against the intestinal maltase while Ceylon cinnamon was the most effective intestinal sucrase and pancreatic α-amylase inhibitor. They further reported that cinnamon extracts produced additive inhibition against intestinal α-glucosidase and pancreatic α-amylase when combined with acarbose [53].

Mohamed Sham Shihabudeen *et al.*, *in-vitro* studies indicated dose-dependent competitive inhibitory activity of cinnamon extract against yeast α-glucosidase and mammalian α-glucosidase, while *in-vivo* animal experiments (STZ induced diabetic rats) indicated significant dampening of postprandial hyperglycemia with oral intake of the cinnamon [54]. These studies suggest that cinnamon extract may be potentially useful for the control of postprandial glucose levels in T2DM through inhibition of intestinal α-glucosidase and pancreatic α-amylase enzyme activities (Figure 3).

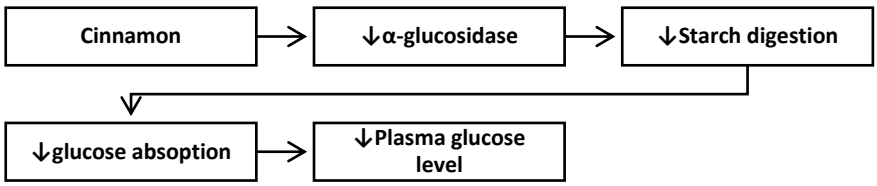

Figure 3: Cinnamon inhibits/decrease the α-glucosidase enzyme, which further decrease the starch digestion and release of glucose. Reduced glucose from starch digestion will send less glucose to blood circulation through the small intestinal enterocytes cell, which will reduce hyperglycemia after the food intake.

Effect on Glucose transporters 4(GLUT-4)

GLUT-4 is an insulin dependent transporter which is predominantly present in adipose tissues and skeletal muscles. When the glucose concentration increases in the blood after the food intake, insulin released from the pancreas and circulate in to the blood stream. The insulin binds to the insulin receptors at various tissues and its cytosolic domain which have tyrosine kinase activity, causes the phosphorylation of few tyrosine residues, which further pass the signal to the insulin receptor substrates (IRS). This IRS activate the phosphatidylinositol-3-kinase (PI3K) which signals the Phosphoinositide-dependent protein kinase (PDK1) and then this PDK1 activates protein kinase B (PKB/Akt), that help to mobilize the GLUT-4 containing vesicles to fuse with the plasma membrane for glucose uptake from the blood circulation (Figure 1) [36, 39]. In T2DM, the primary culprit is insulin resistance.In the adipocyte when the lipid stores are full,its endoplasmic reticulum is mechanically stretched and activates a heat shock protein that in turn activates a set of protein kinases (c-Jun amino-terminal kinases (JNKs). These JNKs phosphorylate serine and threonine residues of IRS and now these IRS cannot be activated by insulin signaling (Figure 4). So, the primary consequences are that insulin is unable to mobilize GLUT-4 and also unable to inhibit lipolysis [3, 4, 5&9].

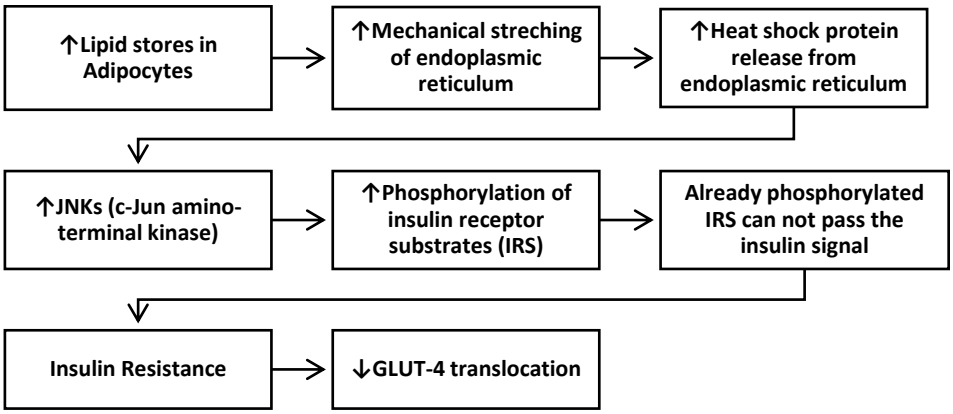

Figure 4: Cause of insulin resistance in adipocytes and other tissues. When lipid stores are filled in endoplasmic reticulum, it causes release of heat shock proteins (HSKs), which activates c-Jun amino-terminal kinases (c-JNKs) and further phosphorylation of insulin receptor substrates (IRS). Now these IRS cannot pass the signal even if insulin binds to the insulin receptor.

Nikazamir *et al.*, demonstrated a significant increase in the gene expression of GLUT-4 receptor and its mRNAin cinnamaldehyde-treated C2C12 skeletal muscle cell line in a dose dependent manner (*in-vitro* study) [55]. Shen *et al.*, demonstrated in STZ-induced diabetic rats that oral administration of a hot-water extract of cinnamon upregulates mitochondrial uncoupling protein-1 (MCP-1) and enhances GLUT-4 production and translocation in their brown adipose tissue as well as in the muscles. Further, they verified upregulated GLUT-4 translocation that increases the glucose uptake in 3T3-L1 adipocytes cell line with exposure to extract of cinnamon (*in-vitro* study) [56].Anand *et al.*, have also observed that the treatment with cinnamaldehyde resulted in the increase of glucose uptake viatranslocation of glucose transporter (GLUT-4) in muscle tissues [38].

Cinnamon on glycogen synthesis and Inhibition of gluconeogenesis

In T2DM, due to insulin signaling compromise, the glycogen synthesis and storage amount decreased [57, 58]. Couturier *et al.* and Anand *et al.*, observed that the hepatic and skeletal muscle glycogen contents were significantly decreased in STZ induced diabetic rats compared to healthy rat. However, treatment with cinnamon/cinnamaldehyde to these diabetic rats increased the liver and muscle glycogen contents albeit lesser than healthy control animals. These studiesindicate that the defective glycogen synthesis and storage of the diabetic state was improved with the treatment ofcinnamon/cinnamaldehyde due to upregulated insulin sensitivity and signaling [38, 59]. Improved insulin signaling activates Akt1/PKB which inhibits GSK-3 (Glycogen synthase kinase-3) thathelps to keep the glycogen synthase in dephosphorylated and active form [35, 36].

Hepatic gluconeogenesis is regulated by Pyruvate Kinase (PK) and Phosphophenolpyruvate carboxykinase (PEPCK). In T2DM, PK activity is reduced and PEPCK activity is elevated resulting in fasting hyperglycemia due to activated gluconeogenesis [36, 39]. Anand *et al.*, reported that the activity of total and active pyruvate kinase was significantly lowered in the liver of diabetic rats in comparison to the normal control while diabetic rats treated with cinnamaldehyde exhibited near to healthy control pyruvate kinase activity [38]. They further reported that PEPCK mRNA level was increased in untreated diabetic liver while treatment with cinnamaldehyde reduced the PEPCK levels near to the level of non-diabetic rat (Figure 5) [38].

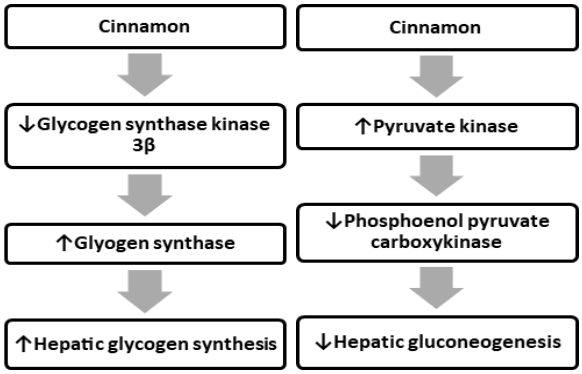

Figure 5: Effect of cinnamon on hepatic glycogenesis and gluconeogenesis. Cinnamon downregulate the Glycogen synthase kinase 3β (GSK3 β) which will not phosphorylate the glycogen synthase and keep them active for glycogen

synthesis in the liver. Cinnamon activate the pyruvate kinase (PK) enzyme and downregulate the phosphoenol pyruvate carboxykinase (PEPCK) enzyme which will help to decrease gluconeogenesis in liver.

Cinnamon usage as drug trial

Allen *et al.*, in 2013 published a meta-analysis of 10 randomized controlled trials (543 total participants) and reported that consumption of cinnamon is associated with a statistically significant decrease in levels of fasting plasma glucose, total cholesterol, LDL-C, and triglyceride levels, and an increase in HDL-C levels; however, no significant effect on HbA1c was found [60]. Namazi*et al.*, in 2019 published a meta-analysis of 18 randomized controlled trials and reported that the supplementation with cinnamon can reduce serum levels of glucose with no changes in other glycemic parameters and anthropometric indices [61]. Krittanawong *et al.*, in 2019 published a meta-analysis of 23 studies (1070 subjects) for risk of cardiovascular health and reported that the supplementation with cinnamon there is no association between cinnamon consumption and differences in LDL-C, HDL-C, and HbA1clevels [62].Kutbi*et al.*, in 2022 published a meta-analysis of 35 clinical trials of cinnamon supplementation dose ≤1.5 grams, among metabolic diseases and reported a significant reducing effect on total cholesterol, triglyceride, LDL-C, serum glucose, serum insulin, and waist circumstance, while increased HDL-C [63]. Another recent meta-analysis of 14 cinnamon supplementation as an adjunct therapy in T2DM published by Silva *et al.*, delineate that the ingestion of 1, 2, or 6 g of *C. cassia* after meals for 40 days decreased fasting glycemia and HbA1c while aqueous cinnamon extract intake for three or four months in different doses (250, 336, 360, and 500 mg) also decreased fasting hyperglycemia [39].

CONCLUSION

The etiology of diabetes and other syndromes have complex genetic, epigenetic and nutritional/environmental components [64-66]. Since ancient time healers tried various natural remedies to control them. Cinnamon has existed in a tropical climate since the evolution of human civilization and its medicinal property has been described in ancient ayurvedic and Chinese literatures. The most consistent observation on the medicinal property of cinnamon has been published in the last few decades on metabolic syndrome including obesity, dyslipidemia, and insulin resistance. There are validated data in clinical as well as laboratory studies that cinnamon decrease insulin resistance and improving insulin sensitivity by acting on the PPAR-γ receptor which modulate GLUT-4 translocation, enhance insulin signaling through Akt/PKB to improve glycogen synthesis and decreased gluconeogenesis. Cinnamon alsoimprove GLP-1 which help for appropriate insulin release, delayed gastric emptying and improving satiety to reduce hunger. It also inhibits α-glucosidase activity which delay the starch digestion and further delayed gastric emptying. All aforesaid mechanism helps T2DM to improve glycemic control and lipid profile, which has been suggested by several human clinical trials. Targeted delivery of active cinnamon compound has the potential to improve the quality life of T2DM and prediabetics. So, we can conclude that the cinnamon can be added (starting from lower dose and moving to higher dose) as an adjuvant along with current therapeutics among the T2DM to improve their glycemic control and lipid profile which will delay the major secondary complications.

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