Review

Dose-Response:
An International Journal
July-September 2023:1–12

DOI: 10.1177/15593258231200527
journals.sagepub.com/home/dos
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Prospective Nutraceutical Effects of Cinnamon Derivatives Against Insulin Resistance in Type II Diabetes Mellitus—Evidence From the Literature

Saima Naz Mohsin, MS[1], Faiza Saleem, PhD[2], Ayesha Humayun, PhD[3], Afifa Tanweer, PhD[4], and Ambreen Muddassir, FCPS[5]

Abstract

Apart from advances in pharmaceutical antidiabetic agents, efforts are being made toward hypoglycemic agents derived from natural sources. Cinnamon has been reported to have significant benefits for human health, particularly as an anti-inflammatory, antidiabetic, and anti-hypertriglyceridemic agent. The phytochemicals in cinnamon can be extracted from different parts of plant by distillation and solvent extraction. These chemicals help in decreasing insulin resistance and can act against hyperglycemia and dyslipidemia, inflammation and oxidative stress, obesity, overweight, and abnormal glycation of proteins. Cinnamon has shown to improve all of these conditions in *in vitro*, animal, and/or human studies. However, the mechanism of action of active ingredients found in cinnamon remains unclear. The current review presents the outstanding ability of cinnamon derivatives to control diabetes by various pathways modulating insulin release and insulin receptor signaling. It was also found that the type and dosage of cinnamon as well as subject characteristics including drug interactions are likely to affect the response to cinnamon. Future research directions based on this review include the synergistic usage of various cinnamon derivatives in managing and/or preventing diabetes and possible other relevant chronic diseases.

Keywords

cinnamon, diabetes mellitus, fasting blood glucose, hyperglycemia

Background

Diabetes mellitus (DM) is one of the most important and key public health issues which is affecting more than 400 million people globally.[1] Diabetes mellitus type 2 (T2DM) is more common with more than 90% diabetic patients suffering from it. DM is a metabolic disorder which gradually leads to other life-threatening and chronic complications including neuropathic, macrovascular, and microvascular disorders. It is caused by a number of factors including secretion of insulin, insulin resistance related to non-use of insulin, or damage of pancreatic β-cell. Other important risk factors of DM among people globally are unhealthy food habits, sedentary lifestyle, and obesity. The prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The number of diabetic patients is increasing on a daily

[1] NIH, HRI, Research Center NHRC, Shaikh Zayed Post Graduate Medical Institute, Lahore, Pakistan
[2] Department of Biotechnology, Lahore College for Women University, Lahore, Pakistan
[3] Department of Public Health and Community Medicine, Shaikh Zayed Postgraduate Medical Institute, Lahore, Pakistan
[4] Department of Nutrition & Dietetics, School of Health Sciences, University of Management and Technology, Lahore, Pakistan
[5] Department of Medicine, Shaikh Zayed Post Graduate Medical Institute, Lahore, Pakistan

Corresponding Author:
Afifa Tanweer, Department of Nutrition & Dietetics, School of Health Sciences, University of Management and Technology, Raiwind Road, Lahore 54000, Pakistan.
Emails: afifa.tanweer@umt.edu.pk and afifatanweer@yahoo.com

basis, and cases in elderly population (>65 years) are expected to rise up to 366 million in 2030.[2,3] In addition, the expected rise in the urban population in developing countries furthers the potential prevalence of this disease.[3]

T2DM is a chronic condition which is characterized by insulin resistance, reduced insulin production, failure of pancreatic β-cells, and failure of metabolic control.[4,5] The uncontrolled T2DM results in various life-threatening complications including cardiovascular disorders, microvascular complications, neuropathy, nephropathy, and renal complications with high mortality rates.[6]

Burden of T2DM

Diabetes is one of the largest public health concerns worldwide which imposes a great burden on health care resources and economy. The occurrence of diabetes in developing and developed countries has been on a rise.[7–9] Almost 537 million adults aged 20 to 79 years have diabetes. This accounts for 1 in every 10 adults of this age group suffering from this condition.[10,11] The number is expected to increase up to 643 million in 2030 and 783 million in 2045.[10,11] In every 5 seconds, around 6.7 million deaths have occurred due to diabetes in 2021.[10,11] Diabetes resulted in 316% increase in health expenditure of causing USD 966 billion in the last 15 years. Around 541 million adults are at a high risk of T2DM due to impaired and reduced glucose tolerance (IGT).[10,11]

A community-based survey was carried out in Pakistan which showed that the occurrence of T2DM was 16.98% and prediabetes was 10.91%.[12] The analysis of subgroup showed that the prevalence of diabetes in males was more than in females (13.1 vs 12.4%). It was lower in rural than in urban patients (15.1 vs 1.6%) and in HbA1c than in OGTT tests (23.9 vs 14.4%). On the other hand, the WHO and ADA criteria for diabetes were almost similar (13.8 vs 13.5%).[13,14]

Pathogenesis of Type 2 Diabetes and Insulin Resistance

T2DM is a complicated disorder which is characterized by reduced insulin secretion, insulin sensitivity, and action on the adipose tissue and skeletal muscles. Signaling of insulin results in a cascade of events begin by binding of insulin to the receptor of its cell surface (Figure 1). The receptor comprises 2 β- and 2 α-subunits that is linked through a disulfide bridge into a hetero-tetrameric complex. The β-subunit domain of intracellular tyrosine kinase is activated by binding of insulin to the extracellular α-subunits. After that, the activation of receptor tyrosine kinases along with receptor auto-phosphorylation happens which leads to phosphorylation of tyrosine of insulin receptor substrates (IRSs). These substrates include IRS1, IRS2, IRS3, IRS4, Shc, and Gab1.[15] The β-subunit causes serine/threonine phosphorylation that results in decreasing its capacity to auto-phosphorylate to start the phosphorylation of insulin receptor substrates of insulin-resistant humans and animal models. The glucose transporter 4 (GLUT4) is translocated to the cell membrane, and this process is induced by activation of AMP-activated protein kinase (AMPK).[16] Previous research has shown that the signaling pathways of AMPK and AMPK are possible molecular targets in drug development for the treatment of obesity and T2DM.[17]

Insulin-mediated GLUT-4 translocation from intracellular vesicles toward the plasma membrane occurs due to IRSs which facilitates the entry of glucose. In this process, receptor of insulin is inactivated by dephosphorylation which is done by tyrosine phosphatase protein. Therefore, the biological action of insulin is dependent on phosphorylation and dephosphorylation.

Phosphatidylinositol 3-kinase (PI3K) is an important factor of the insulin-signaling cascade, responsible for the metabolic effects of insulin on GLUT4 translocation and glucose transport.[15,18]

Diabetes and insulin resistance occur due to the downstream signaling and reduced activation of the phosphatidylinositol 3-kinase which is due to derangement of insulin signaling pathways.

Pharmacological Management of T2DM. Observational research studies demonstrate that higher risks of mortality and complication are associated with inpatient hyperglycemia with and without diabetes. Sufficient evidence demonstrates that mortality in critically ill patients postsurgery and general medicine as well as the hospital complications is reduced by alteration of hyperglycemia through insulin administration.[19]

T2DM can be treated by emergence of a number of non-insulin-based oral therapies. These are characterized as Biguanides, insulin secretagogues, Alpha Glucosidase Inhibitors, Insulin Sensitizers, Amylin antagonists, Incretin mimetics, and SGLT2 inhibitors[20] (Figure 2).

Pakistan has always met a great deal of health challenges due to diabetes because of its increased risk of complications and high prevalence. The Diabetic Association of Pakistan (DAP) recently established the National Clinical Practice Guidelines named "Pakistan's Recommendations for Optimal Management of diabetes from Primary to Tertiary care level" (PROMPT). The foremost agenda of this document is to develop National Guidelines in order to manage T2DM in Pakistan in resource-controlled settings.

According to the PROMPT guidelines, if there are no contraindications, all patients should be prescribed metformin along with the modifications in lifestyles, regardless of their weight status in terms of BMI.[21] These guidelines are illustrated in Figure 3. The most common side effects of this therapy are nausea, anorexia, metallic taste, and diarrhea. Metformin should be taken with meals in order to reduce these side effects. Sulphonylureas, insulin, or dipeptidyl peptidase IV (DPP4) inhibitors may be used as an alternative when metformin is contraindicated. Repaglinide, glucagon-like peptide 1 (GLP-1), alpha glucosidase inhibitor, and thiazolidinedione (TZDs) can also be used as alternative drugs (Figure 1).[22]

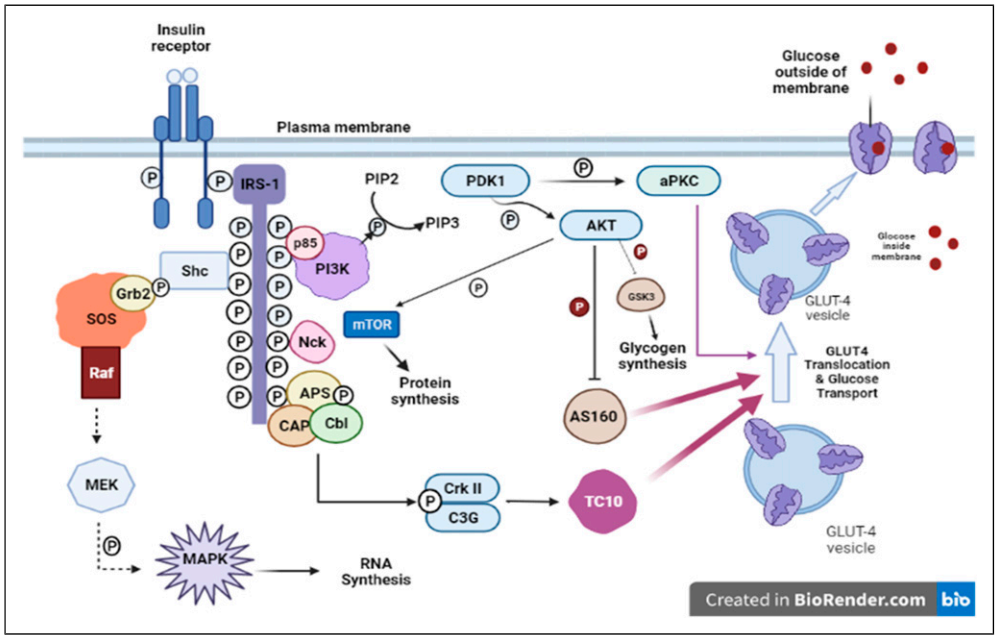


Figure 1. Insulin signaling pathway. Protein-tyrosine phosphatase 1B; PTP1B, insulin receptor substrate; IRS, ROCK, PIP, Rho-kinase; PTEN, phosphatase, phosphatidylinositol phosphate; and tension homologue deleted on chromosome 10; Pleckstrin homology domain; PDK, PH domain, GβL, phosphoinositide-dependent protein kinase; G-protein beta subunit like; mTOR, substrate; PKCλ/ζ, protein kinase C λ and mammalian target of rapamycin; AS160, 160 kDa Akt ζ; GLUT4, glucose transporter 4.[15]

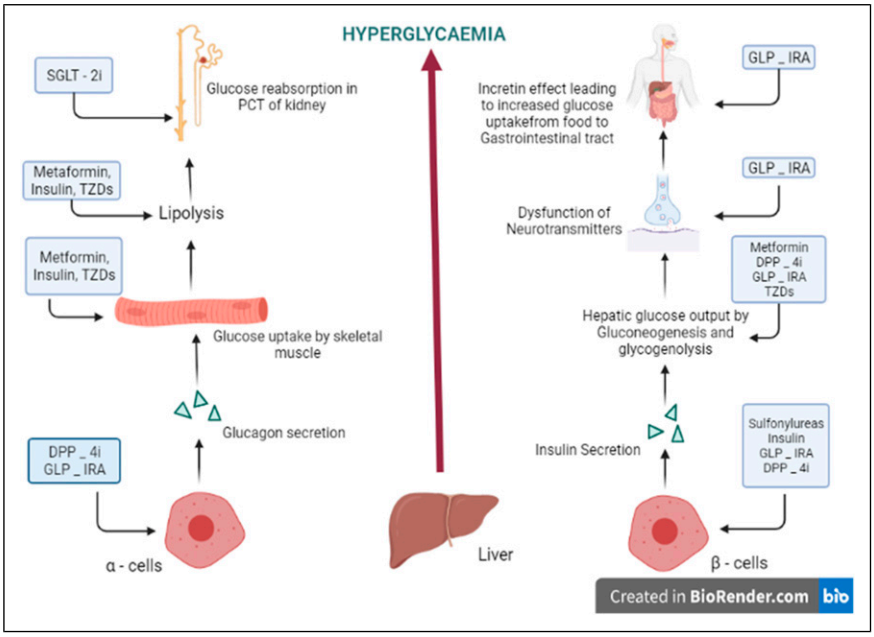


Figure 2. Target treatment for T2DM (DPP – 4i, dipeptidyl peptide – 4 inhibitor; TZDs, thiazolidinediones; SGLT-2i, sodium–glucose co-transporter 2 inhibitor; GLP-1RA, glucagon-like peptide – 1 receptor agonist).[20]

Side Effects of Conventional Antidiabetic Drugs

Several antidiabetic medicines can be used in order to manage a chronic disease like diabetes which is a metabolic disorder. Long-lasting medications are a requirement for diabetes. However, the therapeutic success is difficult to achieve due to long-term safety profile of patients. The medications which are available in the market have side effects such as weight gain, hypoglycemia, and gastrointestinal adverse effects[19,23] (Table 1).

There are some adverse effects which are uncommon but can be bothersome to some patients. The adverse effects may prevent patients to stick to medications which lead to the

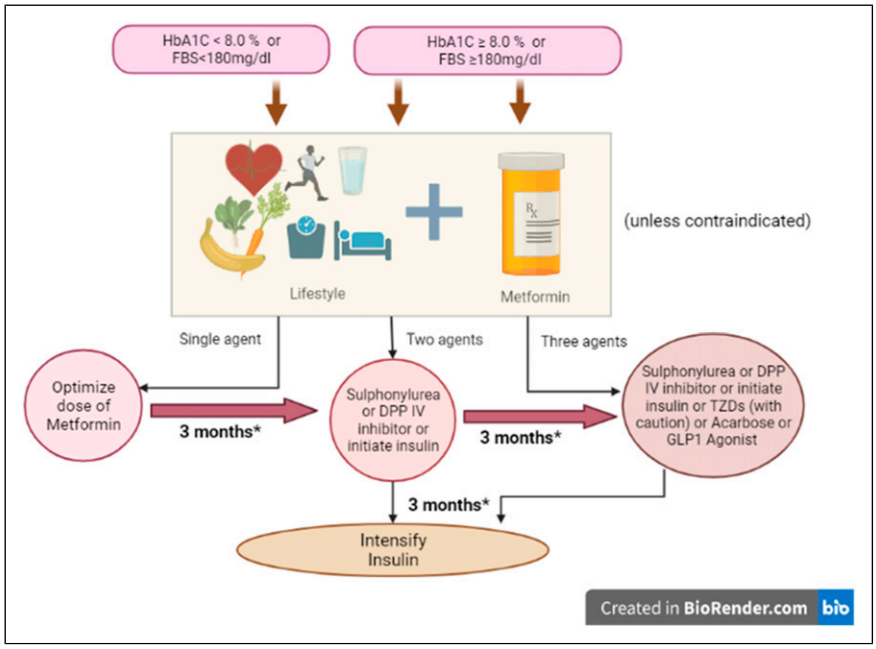


Figure 3. PROMPT guidelines for managing T2DM.[2]

failure of treatment. Few findings suggest that sulfonylureas are related with cholestatic jaundice and metformin is related with lactic acidosis. Pioglitazone may cause worse effect of pulmonary edema that may or may not result in congestive heart failure. Acarbose may result in ileus or subileus in many patients. Pancreatitis can be caused by glucagon-like peptide-1 receptor-like liraglutide.[19,24]

Nutraceuticals as an Alternative or Complementary Medicine

Nutraceutical is any ingredient or substance which is a part of food or a food particle and provides health or medical benefits. In the past, people have looked for nutritional and additional health benefits of food ingredients[25] such as minerals, vitamins, phytosterols, probiotics, and antioxidants.[26] Polyphenols, flavanone, and other natural chemical groups were examined as an adjuvant in the possible management of chronic diseases such as T2DM.[27]

There are Several Sources of Such Active Ingredients. This Review Focuses on the Impact of Cinnamon Consumption on Diabetes Control

Search Strategy Used for Current Review

A thorough search for the literature on "Cinnamon and diabetes" was done using Google Scholar, PubMed, and Clinical Trials.gov. Key word alternates used for searching the exposure variable included cinnamon, cinnamon extract, cinnamon oil, cinnamon phytochemicals, and cinnamon phenolic compounds while those for the outcome variable included diabetic control, insulin resistance, insulin signaling, and cellular glucose uptake. Published literature demonstrating the link of cinnamon with diabetes mellitus was included in this review.

Cinnamon. Cinnamon (genus *Cinnamomum* and family *Lauraceae*) is a spice which is utilized as a nutraceutical. It has rich contents of phytochemically active compounds which have diverse structures and antioxidant properties.[28] Cinnamon is defined as a sweet wood which comes from a Greek word. It is a part of inner bark of evergreen tropical cinnamon trees.[29]

Cinnamomum (cinnamon) belongs to *Lauraceae family,* and a lot of members of this family are utilized as spices.[30] Almost 250 cinnamon species have been known to date and 4 species are used to extract consumable cinnamon.

Cinnamomum verum (also famous as Ceylon cinnamon, *Cinnamomum zeylanicum*, or true cinnamon) is a small tree found in Chinese cassia and Sri Lanka. Other species such as Cinnamon (*Cinnamomum cassia*) are the most commonly accessible species in the entire world.[31] Although cinnamon is not produced in Pakistan, but people living in Pakistan commonly use cinnamon as a spice in their kitchens, around 90% of Pakistan's cinnamon. The other imports come from Sri Lanka (3%) and India (6.5%). Cinnamon is a most commonly used flavoring agent in the beverage and food industry.

Cinnamon is prepared when tree's outer bark is stripped and inner bark is dried. After that, the inner bark is curled into its cinnamon customary quills. It is very well known for its good medicinal properties.[32,33] In a research study, it was stated that after hydro-distillation, volatile fractions of common spices along with remains of spent material of plants may

Table 1. Conventional antidiabetic drugs and their major adverse effects.[19]

S. No.	Drug class	Example of drugs	Adverse effects
1	Insulin and analogues	Regular insulin	Hypoglycemia, weight gain, insulin allergy, and lipodystrophy at injection sites
2	Sulphonylureas	Glibenclamide	Hypoglycemia, weight gain, cardiovascular risk, rash, cholestatic jaundice, bone marrow damage, and photosensitivity
3	Meglitinides	Repaglinide	Hypoglycemia and sensitivity reactions
4	Biguanides	Metformin	Gastrointestinal effects and lactic acidosis
5	GLP-1 agonists	Exenatide	Gastrointestinal effects, pancreatitis risks for cancer, and cardiovascular events
6	DPP-4 inhibitors	Saxagliptin	Pancreatitis, risk for cancer, acute hepatitis, and kidney impairment
7	Thiazolidinediones	Pioglitazone	Hepatitis, cardiovascular risk, bladder cancer, water retention, and weight gain
8	Dual PPAR agonists	Saroglitazar	Gastritis, asthenia, and pyrexia
9	Alpha-glucosidase inhibitors	Acarbose	Gastrointestinal effects and hepatitis
10	Amylin analogues	Pramlintide	Hypoglycemia and allergy
11	SGLT 2 inhibitors	Canagliflozin	Glycosuria and cardiovascular concern

be viewed as rich sources of bioactive molecules along with multi-enzymatic and antioxidant inhibitory effects.[34]

Phytochemical Phenolic Composition of Cinnamon

Isolation of various bioactive compounds found in plants is a very time-consuming and laborious process. In a study, Jayaprakasha et al (2011) tried to isolate volatile oils present in the bark and leaves of cinnamon using hydro-distillation methods. Acetate, camphor, cinnamaldehyde, cinnamyl copane, and eugenol were some major constituents found in the extracted oils in addition to other compounds.[31] Essential oils can be easily extracted from barks of cinnamon using solvent extraction and distillation.[35–41] A number of factors can affect the chemical composition of volatile oils found in cinnamon. In a study, it was suggested that antioxidant activity and flavonoid content differ considerably in various cinnamon species.[42] However, no visible effect was noted in either antioxidant capacity or flavonoid content due to difference in growing method (conventional or organic).[42] Chemical compositions of volatile oils are considerably influenced due to age of leaves and bark of cinnamon plant.[43,44] In a study, it was confirmed that chemical constituents of essential oil extracted from leaves of cinnamon plants harvested on different dates were influenced.[45] The extraction method and solvent type have a significant effect on antioxidant activity and chemical composition of cinnamon-extracted oil.

Water-soluble polyphenol polymers that have the ability to enhance insulin-dependent in vitro glucose metabolism by approximately 20-fold and exhibit antioxidant activity were isolated from cinnamon and further characterized using mass spectroscopy and nuclear magnetic resonance. These polymers were made up of monomeric units having 288 molecular mass.[46] These compounds are known as tetramers and trimmers of catechin, epicatechin, and flavonoids. Contrary to other cinnamon components, cinnamon polyphenols with double-bonded procyanidin type-A polymers seem to exhibit insulin-like activity.[47] Other components like cinnamic acid, eugenol, cinnamide, 2-methoxy-cinnamaldehyde, and cinnamyl alcohol displayed little to no insulin-like activity. Difference in specie does not affect the insulin-like activity of cinnamon extract. The phytochemical and phenolic compounds extracted from cinnamon bark are described in Table 2 while the molecular structure is illustrated in Table 3.

Mechanism of Action of Cinnamon Polyphenols on Insulin Signaling Pathway

Insulin receptors (IRs) are activated by cinnamon-extracted polyphenols due to enhanced tyrosine phosphorylation activity and decreased phosphatase activity (responsible for receptor inactivation) facilitated by these polyphenols. Furthermore, cinnamon polyphenols also enhance the synthesis and accumulation of glycogen by increasing the amount of GLUT-4 proteins and insulin receptor-β. It also reduces glycogen synthetase (GS) kinase-3 β (GSK3β) activity and enhances the levels of tristetraprolin protein. Cinnamon polyphenols might inhibit GSK3β activity resulting in decreased phosphorylation of tristetraprolin protein subsequently leading to increase in its activity.[52]

Effect of Cinnamon for the Activation of Insulin Receptors

Major cause of metabolic syndrome, diabetes mellitus (type 2), and obesity is insulin resistance. Insulin receptor is responsible for mediating cellular response to insulin. It is a protein having two α-subunits (extracellular) which are responsible for binding insulin and two β-subunits which exhibit the activity of tyrosine kinase inside the cell.[53] Binding of insulin to α-subunit results in activation of tyrosine kinase in β-subunit leading to autophosphorylation of tyrosine residues in β-subunit.[54] Insulin sensitivity is enhanced when autophosphorylation increases and dephosphorylation decreases in

Table 2. Phytochemical and phenolic compounds extracted from cinnamon bark.

Species	Type of extract	Compounds	Ref
Cinnamomum cassia	60% Ethanol extract	Cinnamic acid, sinapic acid, p-coumaric acid, vanillin, caffeic acid, protocatechuic acid, and 3-4-dihydroxybenzaldehyde	40
C cassia	Boiling water extract	Quercetin-3-rhamnoside, kaempferol, coumaric acid, syringic acid, and tannic acid	48
Cinnamomum zeylanicum and *C cassia*	60% Ethanol extract	Gallic acid, p-hydroxybenzoic acid, p-hydroxybenzaldehyde, protocatechuic acid, salicylic acid, syringic acid, vanillic acid vanillin, caffeic acid, chlorogenic acid, ferulic acid, p-coumaric acid, cinnamic acid, and sinapic acid	49
C cassia	Essential oil	Trans-cinnamaldehyde (73.56%) benzene, 1,3-dimethyl, styrene, benzaldehyde, camphene, linalool, cis-cinnamaldehyde acetophenone, camphor, borneol, benzenepropanal, decanal decane, 3-ethyl-3-methyl-, 2-propen-1-ol, 3-phenylacetate, trimethyl-eugenol copaene, geranyl acetate, caryophyllene, benzene, and cinnamyl acetate	50
Cinnamomum verum	Essential oil	Trans-cinnamaldehyde (74.49%) benzene, 1,3-dimethyl, styrene, benzaldehyde, camphene, linalool, and cis-cinnamaldehyde acetophenone, camphor, borneol, benzene propanal, decanal decane, 3-ethyl-3-methyl-, 2-propen-1-ol, 3-phenylacetate, trimethyl-eugenol copaene, geranyl acetate, caryophyllene, benzene, and cinnamyl acetate	50
Cinnamomum loureiroi	Essential oil	Trans-cinnamaldehyde (81.97%) benzene, 1,3-dimethyl, styrene, benzaldehyde, camphene, linalool, cis-cinnamaldehyde acetophenone, camphor, borneol, benzenepropanal, decanal decane, 3-ethyl-3-methyl-, 2-propen-1-ol, 3-phenylacetate, trimethyl-eugenol copaene, geranyl acetate, caryophyllene, benzene, and cinnamyl acetate	50

the insulin receptor.[55] A proanthocyanidin (Cinnamtannin B1) extracted from the stem of Ceylon cinnamon facilitates the activation of β-subunit phosphorylation in various insulin receptors including adipocytes.[56] In a study, it was reported that cinnamon extract (CE) has the ability to enhance the insulin receptor (IR)-β (which is stimulated by insulin), IRS1/phosphoinositide 3-kinase (PI3K), and IR substrate-1 (IRS1) tyrosine phosphorylation levels in skeletal muscles of rats fed with chow diet. Furthermore, it was also revealed that utilization of glucose in rats fed high fructose diet (HFD) improved due to CE.[57]

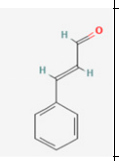
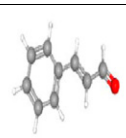
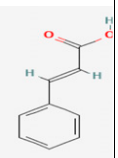
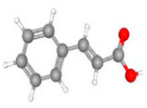
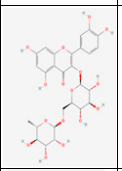
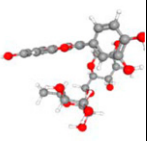
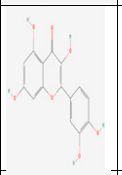
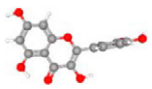
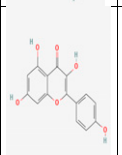
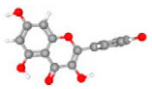
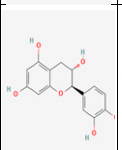
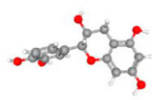
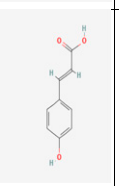
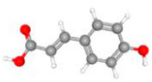
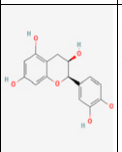
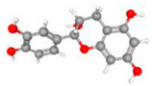
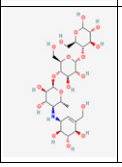
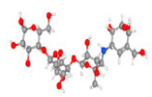
In HFD-fed rats, CE also improves the IRS1 associated with PI3K, IRS1 tyrosine phosphorylation levels, and reduced insulin-stimulated IRβ significantly. These findings suggest that insulin resistance development is prevented by CE to a certain extent by increasing insulin signaling and likely through NO pathway in skeletal muscle. In another research, it was reported that insulin sensitivity is improved due to an aqueous cinnamon extract in humans.[58] The mechanism is described in Figure 4.

Cinnamon Extract Upregulates GLUT4 Expression and Glucose Uptake

The transport of glucose in the adipose tissue and skeletal muscle is facilitated by GLUT4 (a transporter controlled by insulin). The transport of GLUT4 of cell membrane from intracellular compartments is promoted by insulin.[59] In diabetes mellitus, a decrease in GLUT4 is caused due to unavailability or deficiency of insulin sensitivity. In a study, it was reported that in C2C12 skeletal muscle cells treated with cinnamaldehyde, the GLUT4 receptor and its mRNA expression were upregulated in Real-Time PCR.[60] In various studies, the expression of GLUT4 and uptake of glucose in 3T3-L1 adipose cells were enhanced due to CE. It is also reported that a cinnamon water extract (Cinnulin PF®) facilitated the reduction of blood glucose, a novel insulin sensitivity marker known as soluble cluster of differentiation 36 (CD36) and plasma insulin.[61,62] Expression of retinol binding protein, which is an adipokine involved in insulin resistance in adipose and plasma tissues, is also inhibited by cinnamon extract.[63] Increased levels of RBP4 are observed in serum of rodents and human who are insulin resistant, subsequently affecting the production of glucose in liver and mediating resistance of insulin in muscle.[55,56,64] An inverse correlation is observed between levels of RBP4 in plasma and GLUT4 expression in the adipose tissue.[55,56,64] Regulation of genes involved in glucose uptake (expression of GLUT1, glycogen synthesis 1 GLUT4, and glycogen synthase kinase 3β mRNA in the adipose tissue) takes place due to the consumption of CE.[61]

In a recent research, it was testified that type 2 diabetes is improved by cinnamon extract due to its capability of translocating GLUT4 through the AMPK signaling pathway. It has also been reported that drugs for obesity and diabetes (type 2) can be potentially developed by targeting AMPK and the signaling pathway related to it because AMPK activation

Table 3. Molecular structure of compounds commonly found in cinnamon (the structures were retrieved from PubChem database.[51]

Ligand Name	Molecular formula	2D Structure	3D Structure
trans-Cinnamaldehyde PubChem CID 637511	Molecular Formula O Synonyms maldehyde Cinnamaldehyde 5-2 -10-9 mic aldehyde		
Cinnamic Acid PubChem CID 444539	Molecular Formula $C_9H_8O_2$ Synonyms Cinnamic acid Trans-Cinnamic acid 140-10-3 621-82-9 (E)-Cinnamic acid		
Rutin PubChem CID 5280805	Molecular Formula $C_{27}H_{30}O_{16}$ Synonyms RUTIN 153-18-4 rutoside Phytomelin Quercetin 3-rutinoside		
Quercetin PubChem CID 5280343	Molecular Formula $C_{15}H_{10}O_7$ Synonyms Quercetin 117-39-5 Meletin Sophoretin Xanthaurine		
Kaempferol PubChem CID 5280863	Molecular Formula $C_{15}H_{10}O_6$ Synonyms Kaempferol 520-18-3 Kempferol Robigenin Kaemphero		
Catechin PubChem CID 9064	Molecular Formula $C_{15}H_{14}O_6$ Synonyms (+)-catechin Cianidanol CATECHIN 154-23-4 Catechuic acid		
p-coumaric acid	Molecular Formula $C_9H_8O_3$ Synonyms 4-Hydroxycinnamic acid p-coumaric acid 501-98-4 p-Hydroxycinnamic acid trans-4-Hydroxycinnamic acid		
Epicatechin	Molecular Formula $C_{15}H_{14}O_6$ Synonyms (-)-Epicatechin Epicatechin 490-46-0 L-Epicatechin (-)-Epicatechol		
Acarbose	Molecular Formula $C_{25}H_{43}NO_{18}$ Synonyms Acarbose 56180-94-0 Glucobay Precose Acarbosum		

helps in translocating GLUT4 to the plasma membrane.[17] Amounts of Insulin Receptor (IR), Insulin Receptor substrates, and GLUT4 receptors are increased due to cinnamon which enables the entry of glucose into the cells.[56] A study revealed that *Cinnamomum zeylanicum* extracts enhance the translocation and production of GLUT4 to the plasma membrane in the adipose tissue.[65] This has been summarized in Table 4.

Cinnamon Extracts Upregulate the Expression of PPARs

Diabetes and dyslipidemia can be treated by targeting peroxisome proliferator-activated receptors (PPARs).[73] PPARs are nuclear hormones (ligand-activated) including 3 isoforms, that is, PPARα, PPARγ, and PPARδ/β. PPARα is mostly expressed in the liver and brown adipose tissue, PPARγ in the adipose tissue, whereas PPARδ/β in various tissues.[74] HDL cholesterol levels in plasma are elevated and triglycerides lowered when PPARα is activated.[75] Insulin sensitivity is enhanced when PPARγ is activated resulting in antidiabetic effects.[76] Expression of PPARα and PPARγ is enhanced by cinnamon which elevates the insulin sensitivity.[77] In the adipose tissue of mouse (in vivo and in vitro), cinnamon extract is capable of inducing PPARα and PPARγ expressions. Moreover, 3 T3-L1 pre-adipocytes were differentiated into adipocytes in mouse when treated with CE.[77]

Effect of Cinnamon Extracts on Enzyme Activity Inhibition

Extensive research has been conducted on antidiabetic usage of cinnamon. In vitro research has revealed that CE improves diabetes by enhancing glycogen synthesis, increasing uptake of glucose, modulating sensitivity and response of insulin, preventing the activity of gastro-intestinal enzymes, and gluconeogenesis.[78] In a study, four types of cinnamon species were tested for inhibitory effect on intestinal sucrase and maltase, pancreatic α-amylase separately, and in presence of acarbose. Intestinal maltase was potently inhibited by Thai cinnamon extract, whereas intestinal sucrase and pancreatic amylase were effectively inhibited by Ceylon cinnamon. However, acarbose was a lot more effective in inhibiting these two enzymes than Ceylon cinnamon. Yet, additional inhibitory effect was provided by these cinnamon extracts when used in combination with acarbose for all three enzymes.[67] A study revealed that pancreatic α-amylase and α-glucosidase are inhibited very effectively in a dose-dependent manner by Ceylon cinnamon.[66] Postprandial glucose can be potentially controlled in diabetic patients by using extracts obtained from the bark of cinnamon via inhibition of pancreatic α-amylase

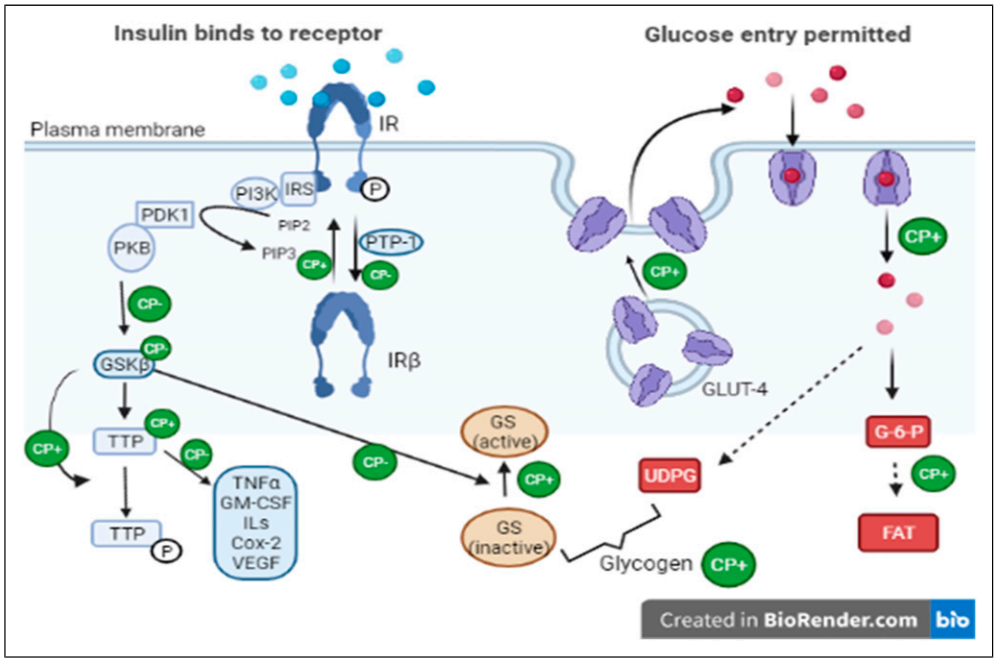


Figure 4. A model of actions of cinnamon polyphenols (CPs) in the insulin signal transduction pathway leading to beneficial effects in subjects with glucose intolerance or type 2 diabetes.[53] IRS, insulin receptor substrate; PI3K, 1-phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; PTP-1, protein-tyrosine phosphatase-1; PDK1, phosphatidylinositol-dependent protein kinase 1; FAT, fat; G-6-P, glucose 6-phosphate; PKB, protein kinase B; UDPG, uridine diphosphoglucose; GM-CSF, granulocyte–macrophage colony-stimulating factor; Cox2, cyclooxygenase-2; VEGF, vascular endothelial growth factor; –, negative effect; +, positive effect.[52]

Table 4. Summary of in vitro studies showing anti-glycemic effects of cinnamon.

Year	Extract	Type of cinnamon	Part used	Result
2007[52]	Ethanol extract	*Cinnamomum burmannii*		Increase in the amount of GLUT4 IRβ and TTP
2010[66]	Aqueous extract	*Cinnamomum zeylanicum*	Bark	Anti-α-glucosidase activity and inhibition of sucrase and maltase
2010[66]	Aqueous extract	*C zeylanicum*	Bark	Anti-α-amylase activity
2011[67]	Aqueous extract	*Cinnamomum aromaticum*	Bark	Anti-α-amylase activity
2011[67]	Aqueous extract	*C zeylanicum*	Bark	Anti-α-amylase activity
2011[67]	Aqueous extract	*C zeylanicum*	Bark	Anti-α-glucosidase activity and inhibition of sucrase and maltase
2011[67]	Aqueous extract	*Cinnamomum loureiroi*	Bark	Anti-α-glucosidase activity and inhibition of sucrase and maltase
2011[67]	Aqueous extract	*C loureiroi*	Bark	Anti-α-amylase activity
2011[87]	Aqueous extract	*C aromaticum*	Bark	Anti-α-glucosidase activity and inhibition of sucrase and maltase
2012[68]	Ethanol extract	*C zeylanicum*	Bark	Inhibitory activity of AChE and BChE
2012[69]	Methanol extract	*Cinnamomum verum*	Bark	Anti-glycation activity
2014[70]	Methanol extract	*C zeylanicum*	Leaf	Inhibitory activity of AChE and BChE
2014[71]	Hydro-alcoholic extract	*C zeylanicum*	Bark	Anti-α-amylase activity
2020[72]	Ethanol extract	*C zeylanicum*	Bark	Anti-α-glucosidase activity and anti-α-amylase activity

Table 5. Summary of clinical trials showing the effects of cinnamon on insulin resistance and T2DM.

Year	Extract/oil	Type of cinnamon	Part	Dosage	Model	Follow-up duration	Result
2010[81]	Powder	*Cinnamomum cassia*	Bark	2 g/d	Human	12 weeks	Reduction in HbA1C and FPG
2007[82]	Capsule	*C cassia*		1 g/d	Human	3 months	No significant effect on insulin levels, A1C, or fasting glucose
2009[83]	Capsule	*C cassia*		1 g/d	Human	90 days	Reduction in HbA1C
2018[84]	Powder filled in a capsule	*Cinnamomum verum*	Bark	1 g/d	Human	3 months	Improvement in FPG, HbA1C, insulin resistance, fasting insulin, and 2 hpp
2018[85]	Extract	*C verum*	Cinnamon stick	3 g/d	Human	90 days	-
2014[86]	Sticks	*C verum*	Inner bark		Human	8 weeks	Reduction in fasting blood sugar (FBS)
2020[87]	Extract encapsulated in a capsule	*Cinnamomum zeylanicum*	Bark	225 mg/d	Human	12 weeks	Reduction in FBS, HbA1C, and insulin resistance
2016[88]	Capsule	*C verum*	Bark	1 g/d	Human	12 weeks	Reduction in FBS and HbA1C
2015[89]	Alcohol extract	*C zeylanicum*		50 mg/kg to 200 mg/kg body weight	Rats	4 weeks	Reduction in glucose level
2015[90]	Aqueous extract	*C cassia*	Bark	60 mg/kg	Rats	15 days	Reduction in glucose level
2010[91]	Aqueous extract	*Cinnamomum tamala*	Leaf	125 mg/kg and 250 mg/kg body weight (twice a day)	Rats	20 days	Reduction in fasting blood glucose level and an increase in glycogen level

and intestinal α-glucosidase. A number of studies have witnessed the correlations between inhibitory effects of enzyme and polyphenol content found in natural products,[79] which is supported by another research where the inhibition of α-glucosidase by $r = -.90$; $P < .001$ and α amylase by $r = -.59$; $P = .045$ was correlated to polyphenol content obtained from natural extracts.[80]

Table 5 summarizes the effects of cinnamon on insulin resistance.

Conclusion

Cinnamon has been used as a natural traditional medicine in numerous cultures throughout the world. Cinnamon can be a promising natural medicine for the regulation of blood glucose levels. From the findings of various studies, it can be concluded that the oral administration of cinnamon extracts has a valuable nutraceutical effect on blood glucose levels through a range of metabolic pathways The incorporation of cinnamon powder or its phytochemical extract in nutraceutical preparations as well as in common food recipes would be of interest to future researchers. This opens up further research on the development of functional foods, incorporation of its powder as well as extract in local food recipes and the potential nutraceutical preparations for prevention and management of DM. Such adjunctive approach may inspire to reduce the burden of DM and possibly other related chronic illnesses.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Afifa Tanweer https://orcid.org/0000-0002-0174-2941

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