REVIEW ARTICLE

Cinnamon, a Promising Herbal Plant for Combatting Diabetes and Its Anti-Diabetes Mechanisms

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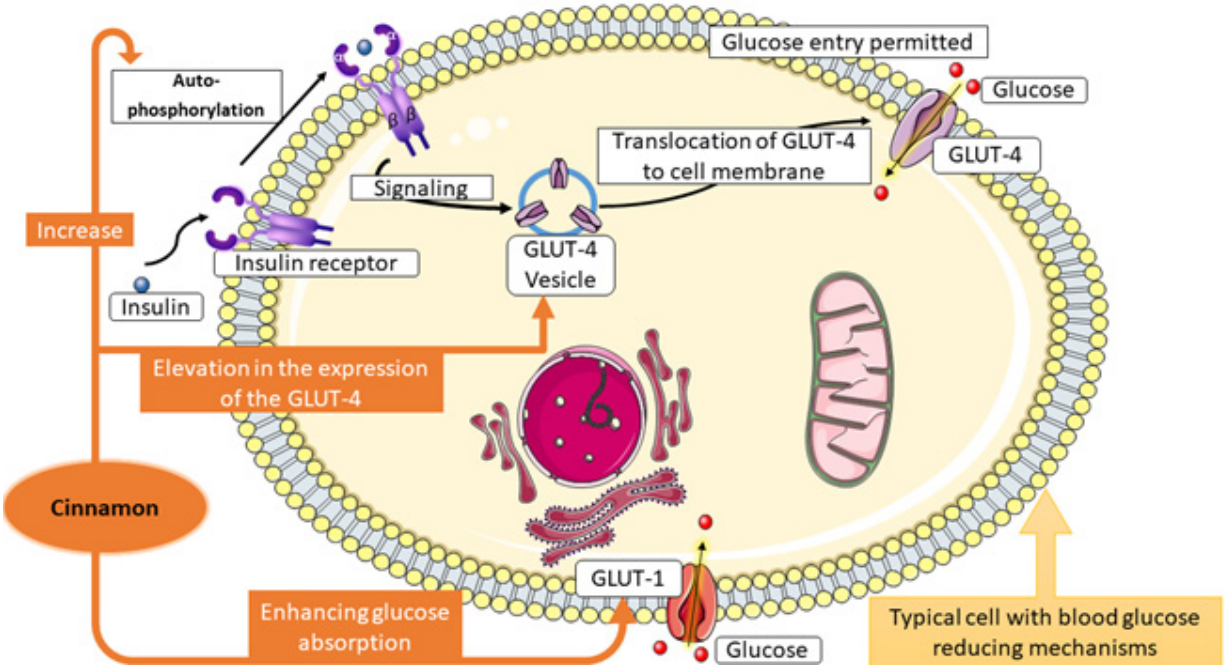

Highlights

- Diabetes mellitus has become a worldwide health burden.
- Cinnamon increase Auto-phosphorylation and decrease de-phosphorylation of insulin receptor.
- Cinnamon can elevate GLUT 4 activity by translocating GLUT 4.
- Cinnamon have an effect on GLUT1's glucose transport activity.
- This review evaluates scientific evidence for anti-diabetic properties of cinnamon.

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REVIEW ARTICLE

Cinnamon, a Promising Herbal Plant for Combatting Diabetes and Its Anti-Diabetes Mechanisms

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Abstract: Diabetes has affected the lives of over 537 million people aged 20 to 79 years by the year 2021. These statistics are anticipated to escalate to 783 million by the year 2045 according to the International Diabetes Federation. Diabetes leads to cardiovascular diseases, neuropathy, nephropathy, and retinopathy as complications. Therefore, there is an emerging global interest to find better treatment options or supplements which give a synergistic effect with the existing treatments. Some of such experiments based on medicinal herbs. In line with the concept of nutraceuticals and functional foods, considerable effort is being expended in the search for effective plant extracts with properties of controlling hyperglycemia. The genus *Cinnamomum* comprises 250 species of shrubs and trees that can be found in China, south-east Asia, and Australia. Out of many, two main varieties of cinnamon; *Cinnamomum zeylanicum* and *Cinnamon cassia* have been extensively studied to explore their anti-diabetes potential and the mechanism of action. Diverse secondary metabolites compositions have been reported for various parts of Cinnamon and out of many compounds, cinnamaldehyde, eugenol, coumarin, cinnamic acid, cinnamyl alcohol, benzaldehyde, and cinnamyl acetate are found as major compounds. The experimental evidence has been given on acting through the various mechanism to control and cure hyperglycemia, i.e.; Auto-phosphorylation and decreased de-phosphorylation of the insulin receptor, translocating glucose transporter 4 (GLUT 4), inhibition of α-glucosidase and α-amylase, etc. This review summarizes the scientific knowledge gathered by scientists in the past 12 years on cinnamon in its therapeutic potential and application in diabetes.

Keywords: Cinnamon, Diabetes Mellitus, Herbal Medicine, Therapeutic Potential.

INTRODUCTION

Diabetes mellitus can be defined as a non-communicable disease that is characterized by elevated blood glucose levels. In 2019, International Diabetes Federation reported that diabetes has affected the lives of nearly 463 million adults aged 20 to 79 years worldwide (International Diabetic Federation, 2019). According to the statistics of the 2021 report, the number has increased to 537 million. Further, it has been mentioned that the population with diabetes is concurred to increase by 46% by 2045, while the estimation of global population growth is at most 20%. In most countries, the proportion of Type 2 diabetes patients is rising and diabetes has been recognized as a rapid-growing public health crisis of the 21st century. Furthermore, diabetes has affected more individuals in urbanized areas than rural areas, with a prevalence of 12.1 % and 8.3 %, respectively in 2021. Moreover, one in every five people over 65 years old is diagnosed with diabetes and one in every two (232 million) remains undiagnosed (International Diabetic Federation, 2019).

Insulin which is synthesized by the pancreas β-cells plays a significant role in glucose metabolism. It allows glucose to be transported from the bloodstream to the cells of the body, where it is converted into energy or stored as glycogen in the liver (Forbes & Cooper, 2013). As a result of a shortage of insulin, or the lack of cells' response to it, blood glucose is increased. It is known as hyperglycemia, which is a clinical indicator of diabetes. There are two types of diabetes. Type 1 diabetes is due to deficiency in insulin production by beta cells of the pancreas (Salehi *et al*., 2019).As a result, insulin produced in the body is not adequate to regulate blood glucose. Type 1 diabetes occurs most frequently in children and adolescents (Petersmann *et al.,* 2019). Patients with Type 1 diabetes require daily insulin injections to keep their blood glucose levels within the normal range (Tran *et al.,* 2020). A variety of distinct pathophysiologic abnormalities have been linked to Type 2 diabetes. Amongst, insulin resistance plays a major role (Pearson, 2019). Characteristic features of insulin resistance are decreased peripheral glucose uptake which mainly occurs in muscle combined with elevated endogenous glucose production. Furthermore, increased lipolysis, augmented free fatty acid levels, and accumulated intermediary lipid metabolites also caused for increasing glucose output, reducing peripheral glucose utilization, and impairing beta-cell function (Solis-Herrera *et al., 2*021). Moreover, function of beta cell deterioration in response to chronic hyperglycemia and hyperlipidemia, non-alcoholic fatty liver, delayed transportation of insulin across the microvascular system, and inflammation are well known for the development of Type 2 diabetes (Solis-Herrera *et al.,* 2021).

Diabetes leads to cardiovascular diseases, neuropathy, nephropathy, and retinopathy as complications (Forbes & Cooper, 2013). Diabetic ketoacidosis and nonketotic

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hyperosmolar coma are acute life-threatening events due to uncontrolled diabetes (Belete, 2020). Further, it has been explored that there is a correlation between regulating insulin release and control of blood pressure in patients with diabetes (Hettihewa et al., 2008). In addition, a genetic association has been explored between total cholesterol and insulin resistance in Type 2 diabetes (Menik et al., 2005). Furthermore, insulin resistance is a major cause of Type 2 diabetes in its early stages and an independent risk factor for cardiovascular disease and metabolic syndrome (Hettihewa *et al.,* 2017). Therefore, it is noteworthy to report that diabetes has a possibility of giving rise to several other complications other than hyperglycemia.

At the moment, the most commonly used drugs in the treatment of diabetes are insulin, insulin analogs, and oral hypoglycemic drugs. Nonetheless, there is still no comprehensive therapy strategy for the management of diabetes due to inherent deficiencies in the drugs, side effects, and limitations in the route of administration, such as adverse reactions caused by long-term subcutaneous injection and various challenges in oral administration, such as chemical instability, enzymatic degradation, and poor gastrointestinal absorption (Zhao e*t al.,* 2020). As Type 2 diabetes is a multifactorial disease associated with many proteins, ranging from 30 to over 200 genetic loci and over 3,000 postulated associations", the effectiveness of the drugs is vary person to person (Hansson *et al.,* 2020). Therefore, exploring novel drug treatments for diabetes is a current trend in the world. Many studies have been focused to explore effective plant extracts that can be used for treatment or reducing the risk of diabetes (Ranasinghe *et al.,* 2017). As a supplement to the treatment, functional foods and nutraceuticals which are effective in diabetes have emerged as recent interest by researchers as well as the general public. Stephen DeFelice defined the word "nutraceuticals" as, "a food or part of a food that has medical or health benefits, including the prevention and treatment of diseases" (Daliu *et al.,* 2018). Nutraceuticals have both nutritional and pharmaceutical values. Nutraceuticals are supposed to be used beyond the diet and before the drugs are used in the prevention and treating diseases. Nutraceuticals contain biological substances which have a natural origin without denaturing their original properties without incorporating any synthetic substances (Corzo *et al.,* 2020). Cinnamon is one such plant extensively studied by scientists to explore its potential therapeutic effect on diabetes.

This review focus on cinnamon in its therapeutic potential in diabetes by exploring the scientific knowledge gathered by scientists in the past 12 years. Literature search was done with Google Scholar and PubMed® (U.S. National Library of Medicine, USA) for studies published until January 31, 2022. Subject headings and keywords were used by the authors are "Cinnamomum and Diabetes mellitus" and "Cinnamon and Diabetes". Results were restricted to English-language free journal articles.

Cinnamon

The genus *Cinnamomum* (Laureaceae family) comprises 250 species of shrubs and trees that can be found in China, south-east Asia, and Australia. It is a 10-15 m tall evergreen tree. The bark is extensively consumed as a spice for centuries (Cardoso-Ugarte *et al.,* 2016). There are two main species of cinnamon; *Cinnamomum zeylanicum* Blume (true cinnamon/ *Cinnamomum verum*/ Ceylon cinnamon) and *Cinnamon cassia* Presl (Chinese cinnamon / *Cinnamomum aromaticum)* which are widely available (Meena *et al.,* 2018). In addition, *Cinnamomum camphora, C. loureirii*, *C. tamala,* and *C. burmanni* are also popular cinnamon species related to *Cinnamomum cassia* (Costello et al., 2016). *C. zeylanicum* is indigenous to South India and Sri Lanka (Jayaprakasha & Rao, 2011). Cassia cinnamon is originated from a variety of sources, including Chinese cinnamon which natively grows in Vietnam and China; Indonesian cassia (*C. burmanni*) which belongs to the regions of Java and Sumatra, and Indian cassia (*C. tamala*) which is native to northern India and Myanmar (Leela, 2008).

Phytochemicals in cinnamon extracts

Cinnamaldehyde, coumarin, cinnamic acid, eugenol, cinnamyl alcohol, benzaldehyde, and cinnamyl acetate were discovered to be the key flavoring chemical agents of cinnamon bark (Khuwijitjaru *et al*., 2012). Fajar and colleagues have determined that cinnamaldehyde, cinnamyl acetate, cinnamyl alcohol, and cinnamic acid as the major components of *C. burmannii* oil which are present in 68.3 - 82%, 2.5 - 16%, 2.25 - 4.6%, and 3 - 8%, respectively (Fajar *et al.,* 2019). The existence of flavonoids, alkaloids, phenolic compounds, coumarin, terpenoids, saponin, anthrocyanin, tannins, and glycoside was observed in the aqueous, acetone and methanolic extracts of *C. verum* bark by Ahmed *et al.* (2020) while cinnamon essential oil extracted from the bark was found to be composed of 85.5% cinnamaldehyde and 3.69% stigmasterol (Ahmed *et al.,* 2020). In addition, ergosterol, cadinene, alpha-amorphene, alpha-cubebene, hydrocinnamaldehyde, and (E)-cinnamaldehyde were also identified as the major compounds of the *C. verum* bark essential oil (Ahmed *et al.,* 2020).

Wu *et al*. have successfully identified 20 chemical markers for discriminating *C. cassia* and *C. verum* (Wu *et al.*, 2021). According to their study, six procyanidin components (cinnamtannin B1, isocinnamtannin B1, procyanidin B2, Cinnamtannin B1+2H, etc.) were observed at a higher level in *C. cassia* than *C. zeylanicum* bark, while the content of three alkaloids (norboldine, norisoboldine and norboldine+O) were presented higher levels in *C. zeylanicum* than *C. cassia barks.* However, the difference in constituents has been reported by Ranasinghe and colleagues as *C. zeylanicum* bark oil contains 49.9-62.8% trans-cinnamaldehyde while *C. cassia* contains almost 95% cinnamaldehyde (Ranasinghe *et al.,* 2013). In addition, it is reported as *C. cassia* contains high levels of the potentially hepatotoxic constituent coumarin up to 1%, whereas *C. zeylanicum* contains coumarin only at undetectable levels (Krieger *et al.,* 2013). Therefore, long-term consumption of *C. cassia* can cause health risks (Ranasinghe *et al.,* 2013). According to that, it has been suggested that *C. zeylanicum* should be used instead of *C. cassia* for treating Type 2

diabetes (Shinjyo *et al.,* 2020).

However, the chemical composition of the cinnamon varies with the species (Figure 1), growth stage, maturity of the bark, and extraction method (da Silva et al., 2019). The results of Geng *et al.* confirmed that the quality of older dry bark is superior to younger bark (Figure 2) (Geng *et al.*, 2011).

The chemical substances present in cinnamon are known to have the ability to regulate blood glucose by insulin-mimetic properties, improve the lipid profile, demonstrate anti-inflammatory activity, and in-vitro antimicrobial properties (da Silva *et al.,* 2019). Gas chromatography-Mass spectrometry (GC-MS) analysis of methanolic bark extract of *Cinnamomum zeylanicum* has revealed the existence of the 39 bioactive compounds including major as Cinnamaldehyde (Hameed *et al.,* 2016). Identifying the chemical composition of plant extracts and their pharmaceutically active compounds is important for novel drug and nutraceutical development (Bulugahapitiya, 2013).

Anderson *et al*., (2004) isolated and characterized water-soluble polymers with polyphenol from cinnamon which has the ability to heighten insulin-dependent *in vitro* glucose metabolism. The isolated compound is approximately 20-fold and exhibits antioxidant activity. The polymers were made up of 288 molecular mass monomeric units (Anderson *et al.,* 2004). These cinnamon polyphenolic polymers have the ability to act as antioxidants, improve insulin activity, and aid in the management of glucose hypersensitivity and diabetes mellitus.

Geng *et al.,* (2011) extracted the essential oil of the cinnamon barks at different growth stages by hydrodistillation, and GC-MS analysis was used to detect chemical compounds (Geng et al., 2011). It can be clearly observed the difference in the chemical composition at different growth stages. (Detected trace compounds (<0.1%) were rounded off to 0.05% by the authors for graphical interpretation of the data.)

In-vitro evidence of glycemic control with cinnamon extracts

Inhibition of α-glucosidase and α-amylase

As a therapeutic approach for reducing postprandial glucose, inhibition of α-glucosidase and pancreatic α-amylase can be used (Adisakwattana *et al.,* 2011). The main function of α-amylase is hydrolyzing the glycosidic bonds in starch molecules which induce the conversion of complex carbohydrates (non-absorbable carbohydrates) to simple sugars (absorbable carbohydrates) (Akinfemiwa & Muniraj, 2021). α-glucosidase regulates the digestion of carbohydrates and as a result that postprandial blood glucose level increases (Nakamura *et al.,* 2014)

Many studies claim that cinnamon extracts can be possibly convenient for reducing postprandial glucose in patients with diabetes by inhibiting pancreatic α-amylase and intestinal α-glucosidase. However, the glycemic regulatory properties depend on the part of the plant, the maturity status of the plant, and the variety of the plant. As an example, it can be observed that glycemic control of immature, partly matured, and mature leaves of cinnamon fluctuated from 18.05 ± 0.24 - 36.62 ± 4.00% inhibition at 2.5mg/mL of methanol: dichloromethane (1:1, v/v) Ceylon cinnamon leaf extract (Abeysekera *et al.,* 2019)v/v. Table 1 shows the differences in enzyme inhibition activities according to the variety of cinnamon that was extracted from two different studies.

Inhibitors of α-glucosidase reduce postprandial hyperglycemia due to the digestion of carbohydrates

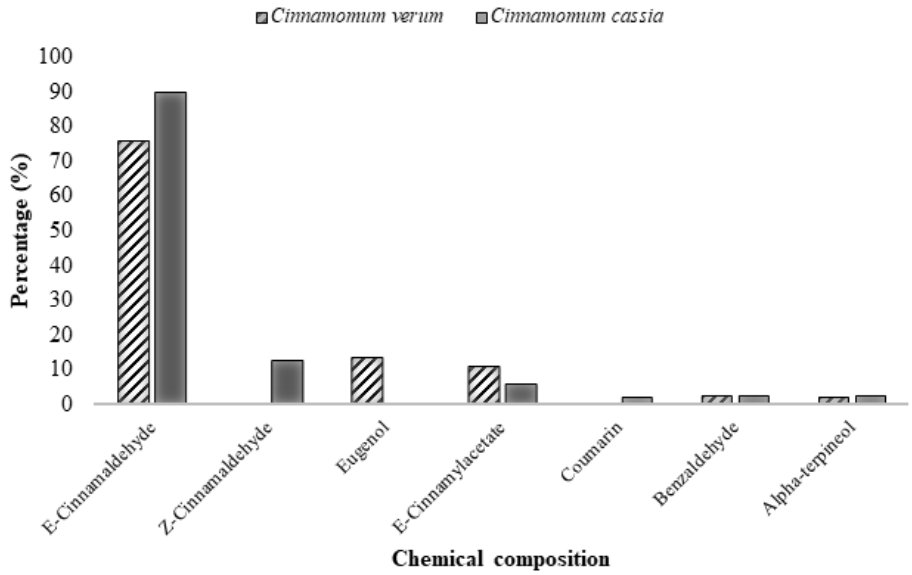

Figure 1: Comparison common constituents in cinnamon essential oil extracted from various plant parts of *Cinnamomum verum* and *Cinnamomum cassia* (Stevens & Allred, 2022).

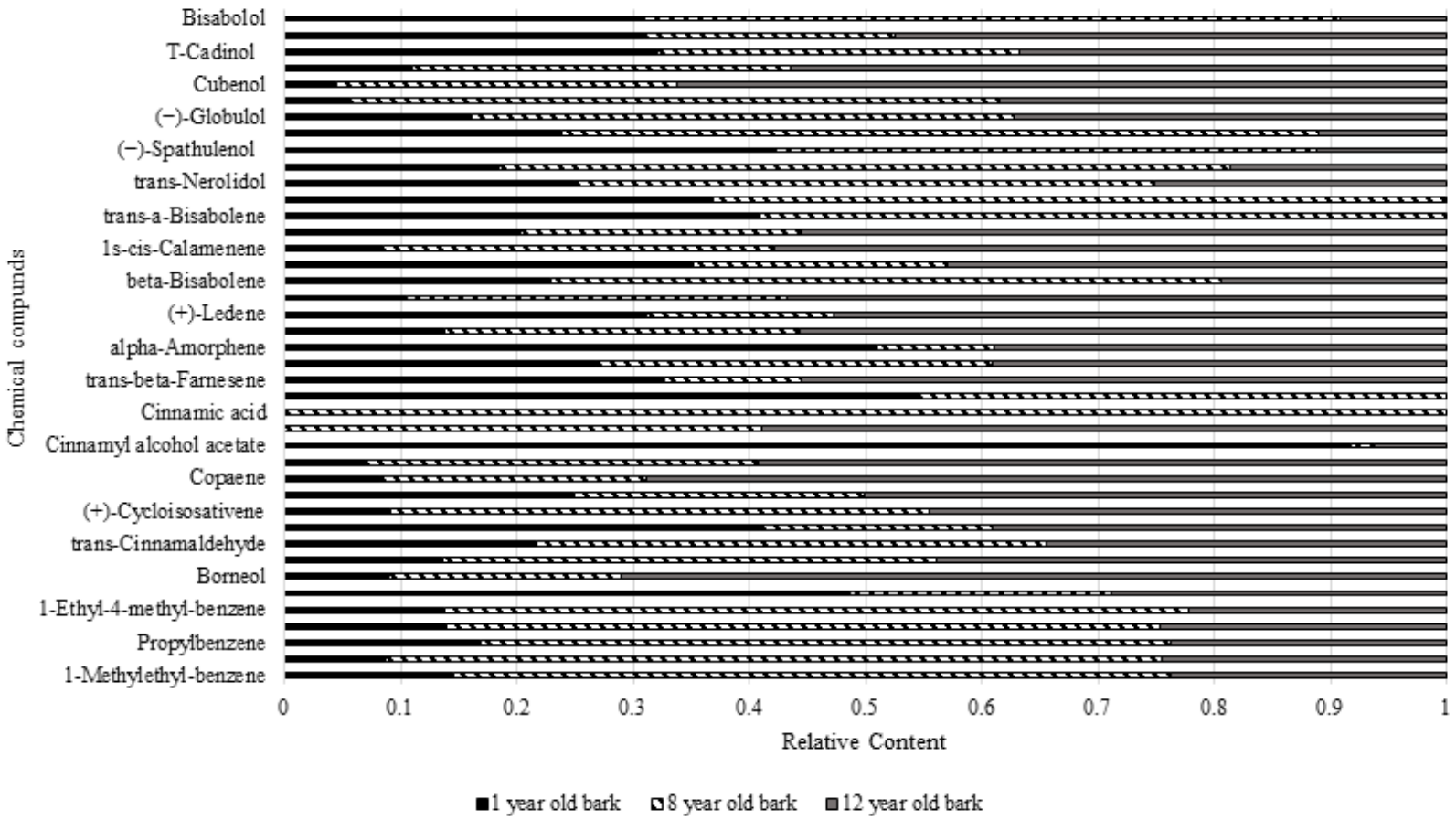

Figure 2: Chemical composition of essential oil extracted from bark of cinnamon at different ages.

Geng *et al*., (2011) extracted the essential oil of the cinnamon barks at different growth stages by hydrodistillation, and GC-MS analysis was used to detect chemical compounds (Geng *et al*., 2011). It can be clearly observed the difference in the chemical composition at different growth stages. (Detected trace compounds (<0.1%) were rounded off to 0.05% by the authors for graphical interpretation of the data.)

Table 1: IC_{50} values of α-amylase and α-glucosidase enzyme inhibition by cinnamon.

Cinnamon variety and extract	*IC_{50} value of α-amylase inhibition (µg/ml)	*IC_{50} value of α-glucosidase inhibition (µg/ml)
Cinnamomum zeylanicum Sri Wijaya (SW) quill aqueous extract (Wariyapperuma *et al*., 2020)	42 ± 13	78 ±7
Acarbose (Wariyapperuma *et al*., 2020)	173 ± 7	95 ±4
C. cassia bark aqueous extract (Vijayakumar *et al*., 2020)	790	910
C. cassia bark ethanol extract (Vijayakumar *et al*., 2020)	620	570
C. cassia bark methanol extract (Vijayakumar *et al*., 2020)	770	780
Acarbose (Vijayakumar *et al*., 2020)	560	500

*IC_{50} is an operational metric defined as the inhibitor (ligand) concentration necessary to achieve 50% inhibition (binding saturation) of the enzyme (receptor).

being controlled. It leads to reducing the diet-related acute postprandial glucose excursion (*Alpha-Glucosidase - an Overview | ScienceDirect Topics*, n.d.). An *in-vitro* study of Shihabudeen and colleagues has discovered that cinnamon bark methanol extracts have inhibitory activity against yeast α-glucosidase and mammalian α-glucosidase with the IC_{50} value of 5.83 µg/ml and IC_{50} value of 670 µg/ml respectively (Shihabudeen *et al.,* 2011). Further, they demonstrated the mode of inhibition of *C. zeylanicum* extract is indistinguishable from acarbose which is a competitive inhibitor by formulating a double reciprocal plot from the kinetic data (Shihabudeen *et al.,* 2011).

Anti-hyperglycemic characteristics of four substantial cinnamon types used throughout the globe were systematically compared in a study by Hayward and colleagues (*C. cassia*, *C. burmanii*, *C. loureirii,* and *C. zeylanicum* (Hayward *et al.,* 2019). According to the results, they have reported that all those commercial cinnamon types manifested overwhelming species-specific effects on α-amylase and α-glucosidase inhibition. *Cinnamomum cassia* was the most effective against the α-amylase enzyme. All four species exhibited strong inhibition of α-glucosidase compared to acarbose. It was determined that cinnamon is able to reduce starch digestion significantly during gastric and oral steps of gastro-intestinal digestion with *C. burmanii* and *C. zeylanicum* (Hayward e*t al.,* 2019). Furthermore, *C. burmanii*, *C. loureirii,* and *C. zeylanicum* were observed to have the highest potential to inhibit the advanced glycation end products (AGEs) genesis during digestion (Hayward *et al.,* 2019).

GLUT 4 translocation

A study has been conducted in 2014 to ascertain the exact mechanism by which *C. zeylanicum* extract increases glucose uptake in cell culture systems using 3T3-L1 adipocytes and C2C12 myotubes. For investigating the role of protein kinase B and AMPK in cinnamon extract-induced glucose uptake, researchers used specific enzyme inhibitors in the insulin signaling, AMPK signaling pathways, and small interference RNA. *C. zeylanicum* was found to stimulate the AMPK phosphorylation and phosphorylation of acetyl-CoA carboxylase (Shen *et al.,* 2014). Translocation of GLUT 4 to the cell membrane is induced by the AMPK activation. To discover drugs for treating Type 2 diabetes, AMPK and its signaling pathway can be identified as potential molecular targets. (Shen *et al.,* 2014). Furthermore, *in-vitro* incubation of pancreatic islets with cinnamaldehyde has elevated insulin secretion in comparison to glibenclamide. Moreover, the insulinotropic effect of cinnamaldehyde has been discovered to enhance glucose uptake in peripheral tissues via GLUT 4 translocation. The treatment also improved the enzyme activities of pyruvate kinase (PK) and phosphoenolpyruvate carboxykinase (PEPCK), as well as their mRNA expression (Anand *et al.,* 2010).

Effect on insulin secretion

Cinnamaldehyde and cinnamic acid were tested for insulin secretory activity in isolated mice islets by Hafizur *et al*., in 2015. They discovered that cinnamic acid has the ability to stimulate insulin secretion depending on the concentration (Hafizur *et al.,* 2015). Cinnamic acid at 50 µM significantly increased insulin secretion (3.76 ± 0.35 ng/islet/h) in comparison to 16.7 µM glucose alone (2.13 ± 0.11 ng/islet/h). Cinnamic acid-induced insulin secretion more efficiently (6.06 ± 0.83 ng/islet/h) at 100 µM, which is comparable to tolbutamide (6.56 ± 0.81 ng/islet/h) (Hafizur *et al.,* 2015). Furthermore, amelioration in insulin secretion was not observed over a 100 µM dose of cinnamic acid by the researchers.

Translocating glucose transporter 1 (GLUT 1) receptor is in charge of basal glucose uptake into cells. Plaisier *et al.* (2011) found that cinnamaldehyde inhibited GLUT 1-mediated glucose uptake when there is glucose distress in the culture medium (Plaisier *et al.,* 2011).

In-vivo evidence for glycemic control with cinnamon

Streptozotocin (STZ) induced diabetic rats were administered cinnamaldehyde orally (20 mg/kg/day) for 2 months and found a remarkable increase in glycogen amount of muscle and liver (Anand e*t al.,* 2010). Furthermore, it has been discovered that a hot-water extract of cinnamon at a dose of more than 30 mg/kg/day was upregulated mitochondrial uncoupling protein-1 (UCP-1) and it was able to increase the synthesis and translocation of GLUT 4 in muscle and adipose tissues (Shen *et al.,* 2010).

Shen *et al.,* (2014) have demonstrated that cinnamon extract ameliorated glucose tolerance in oral glucose tolerance tests in Type 2 diabetes rats treated with *Cinnamomum zeylanicum,* but there is not a significant difference in insulin sensitivity.

Li *et al*., (2012) have observed that the level of fasting blood glucose and serum insulin, and the bodyweight of db/db mice decreased by cinnamaldehyde at a dose of 20 mg/kg/day for 4 weeks. Furthermore, Hosni *et al.,* (2017) demonstrated that cinnamaldehyde has a safe anti-diabetic action on gestational diabetes of rats by administering a daily oral dose of 20 mg/kg of cinnamaldehyde one week prior to mating onwards.

Clinical trials with cinnamon on hyperglycemia

Anderson *et al.* (2016) conducted a placebo-controlled double-blind trial to study alterations in blood glucose level and insulin resistance after treating with cinnamon (*Cinnamomum cassia*) extracts. Men and women who have fasting blood sugar (FBS) level greater than 6.1 mmol/L or postprandial blood sugar levels greater than 7.8 mmol/L, were recruited for this study. Participants were randomly treated with either an aqueous extract of cinnamon, 250 mg/capsule, or a placebo twice daily for two months. Participants' mean ± SEM age was 61.3 ± 0.8 years, their BMI was 25.3 ± 0.3, and their male/female ratio was 65/72. It was determined that fasting glucose decreased after 2 months in the cinnamon extract-supplemented group (from 8.85 ± 0.36 to 8.19 ± 0.29 mmol/L) in contrast to the placebo group (from 8.57 ± 0.32 to 8.44 ± 0.34 mmol/L) (Anderson *et al.,* 2016). They also observed that cinnamon extract reduced blood sugar, 2 hours after a 75 g carbohydrate amount significantly. While it was reduced from 15.09 ± 0.57 to 13.3 ± 0.55 mmol/L in the cinnamon extract-supplemented group, the placebo group showed a non-significant difference from 14.18 ± 0.60 to 13.74 ± 0.58 mmol/L (Anderson *et al.,* 2016).

A randomized, double-blinded clinical study was performed by Lu *et al.* (2012) to determine whether cinnamon extract has an effect on fasting blood sugar levels and HbA1c in Type 2 diabetes patients. Recruited 66 Type 2 diabetes patients who had HbA1c higher than 7.0% and fasting blood sugar greater than 8.0 mmol/L. The patients were randomly allocated to three groups: placebo, low-dose (120 mg/day), and high-dose (360 mg/day) supplementation with cinnamon extract for three months (Lu *et al.,* 2012). Cinnamon extract has been prepared from the bark of *Cinnamomum aromaticum*, using methods previously reported by Sheng *et al. (*2008). The HbA1c levels were reduced in both the low-dose group and the high dose group from 8.90% to 8.23% with an average depletion of 0.67%, and from 8.92% to 8.00% with an average depletion of 0.92%, respectively. The fasting blood glucose showed a significant reduction from 9.00 to 7.99 mmol/L in the low-dose group with an average depletion of 1.01 mmol/L. The high-dosed group also demonstrated a significant reduction from 11.21 to 9.59 mmol/L with an average depletion of 1.62 mmol/L. Therefore, at the end of three months, authors have concluded that cinnamon supplementation has the ability to significantly reduce the blood sugar level in selected Type 2 diabetes patients *(Lu et al.,* 2012).

A randomized, double-blind, placebo-controlled trial was conducted by Sengsuk *et al.,* to investigate the effect of cinnamon supplementation on hyperglycemia in Type 2 diabetes mellitus patients (Sengsuk *et al.,* 2016). There were 49 patients with Type 2 diabetes in the cinnamon group and 50 patients in the placebo group. Throughout the 60-day study period, all participants were given either cinnamon or a placebo capsule which were purchased from the Government Pharmaceutical Organization, Thailand. At the termination of the study, median blood glucose levels were significantly lower in patients treated with cinnamon. Therefore, the authors determined that cinnamon supplementation may be beneficial for those with Type 2 diabetes control diabetes. Further, another study has revealed that a single supplement intervention of 3 g ground cinnamon bark showed a significant improvement in fasting blood glucose, HbA1c, and body mass index after16 weeks of continuous supplementation (Jain *et al.,* 2017).

In contrast, Hasanzade *et al. (*2013) conducted a randomized clinical trial together with 70 patients with Type 2 diabetes and they were divided into two similar groups for treating with *Cinnamomum cassia* for 60 days besides their routine treatment. Fasting blood glucose and HbA1c of patients were measured on the first day and 1 and 2 months after the treatment. The mean fasting blood glucose levels before and one and two months after the intervention were 174 ± 59 mg/dl, 169 ± 43 mg/dl, and 177 ± 45 mg/dl, respectively (Hasanzade *et al.,* 2013). HbAlc levels in the cinnamon group were reported as 8.9 ± 1.7% before and 8.9 ± 1.6% after the intervention. Levels of fasting blood sugar and HbAlc did not differ significantly between the two groups (Hasanzade *et al.,* 2013). The results of this study determined that using cinnamon 1000 mg/day for 60 days did not affect controlling hyperglycemia. As a result, the authors have tended to conclude that cinnamon cannot be recommended to treat patients with Type 2 diabetes.

In a study by Ranasinghe *et al.* (2017), 30 healthy volunteers were administered 85 mg of freeze-dried aqueous *Cinnamomum zeylanicum* daily for 30 days during the first month, 250 mg daily for 30 days during the second month, and 500 mg daily for 30 days during the third month. The mean fasting blood sugar level after 3 months follow-up period was 92.7 ± 9.6 mg/dl and it was not significantly different from the baseline fasting blood sugar level. Further, a study by Talaei *et al.* (2017) was conducted to ascertain the effect of administrating three grams of finely ground-cinnamon (*Cinnamomum zeylanicum*) daily for eight weeks. They have concluded that cinnamon supplementation did not affect glycemic or inflammatory indicators in Type 2 diabetes patients.

According to the literature, the effectiveness of cinnamon to control hyperglycemia is not definite (Table 2).

Table 2: Summary of the clinical trials with cinnamon to control hyperglycemia

Cinnamon Variety	Clinical trial	No of participants	Study Period	Dose	Whether Significantly reduced the blood glucose (Yes/No)
Cinnamomum cassia	Placebo-controlled double-blind trial by Anderson *et al*. (Anderson *et al*., 2016)	137	02 months.	Spray-dried water extract of cinnamon 500 mg/day	Yes ($p < 0.001$) FBS decreased in the cinnamon supplemented group (8.85 ± 0.36 to 8.19 ± 0.29 mmol/L)
	Randomized, double-blind, placebo-controlled trial by Hasanzade *et al*. (Hasanzade *et al*., 2013)	70	02 months	Grounded cinnamon bark 1000 mg/day	No ($p <0.05$) The mean levels of FBS before, and 1 and 2 months after the intervention were 174 ± 59 mg/dL, 169 ± 43 mg/dL and 177 ± 45 mg/dL respectively
	Randomized, double-blind, placebo-controlled trial by Sengsuk *et al.* (Sengsuk *et al*., 2016)	99	02 months	1500 mg cinnamon/day	Yes ($p < 0.005$) FBS decreased in the cinnamon group 8.53 (7.26-10.56) mmol/L to 7.32 (6.52-9.85) mmol/L
	Randomized, double-blind, placebo-controlled trial by Lu *et al*. (Lu *et al*., 2012)	66	03 months	*Cinnamomum cassia* tablet 120 mg/day	Yes ($P = 0.002$) FBS levels were reduced from 9.00 ± 1.23 mmol/L to 7.99 ± 1.05 mmol/L
				Cinnamomum cassia tablet 360 mg/day	Yes ($P = 0.00008$) FBS levels were reduced from 11.21 ± 2.21 mmol/L to 9.59 ± 1.66 mmol/L
Cinnamomum zeylanicum	Double-blind, randomized, placebo-controlled clinical trial study by Talaei *et al*. (Talaei *et al*., 2017)	44	08 weeks	*Cinnamomum zeylanicum* tablet 3 g/day	No ($p > 0.05$) FBS levels were reduced from 183.85 ± 36.16 mg/dL to 172.20 ± 44.86 mg/dL, but there was no significant difference ($p =0.09$)
Commercially available cinnamon capsule	Randomized double-blind placebo-controlled trial by Jain *et al*. (Jain *et al*., 2017)	116	16 weeks	Cinnamon commercial tablet 3g/ day	Yes ($P < 0.05$) FBS decreased significantly from 5.7 ± 0.6 mmol/L (baseline) to 5.2 ± 0.3 mmol/L (16 weeks); $p = 0.001$
	Randomized, triple-blind, placebo-controlled trial by Zare *et al*. (Zare *et al*., 2020)	140	03 months	1000 mg/day capsule of cinnamon bark powder	Yes ($P < 0.001$) FBS was improved in patients receiving cinnamon supplementation compared to placebo group (-13.1 ±1.7, -1.7 ±1.9,$P < 0.001$ for change in FBS)

Potential mechanism of action of cinnamon on diabetes

According to the previously discussed in-vitro, in-vivo evidence, and clinical trials, the following potential mechanism of actions of cinnamon has been suggested.

Auto-phosphorylation and decreased de-phosphorylation of the insulin receptor

The insulin receptor is a tetrameric protein composed of two identical extracellular alpha subunits and two beta subunits. After the alpha subunits bind to insulin, the identical transmembrane beta subunits initiate intracellular tyrosine kinase activity to mediate the cellular insulin response. As a result, auto-phosphorylation occurs in residues of beta subunit tyrosine. Insulin sensitivity is increased by the mechanism of increased auto-phosphorylation and decreased de-phosphorylation of the insulin receptor. It has been discovered that cinnamtannin B1 which has been isolated from the bark of *Cinnamomum zeylanicum*, stimulates the phosphorylation of the insulin receptor-subunit on adipocytes and insulin receptors (Medagama, 2015).

Translocating glucose transporter 4 (GLUT 4)

GLUT 4 which is regulated by insulin hormone, is the primary glucose transporter in adipose tissue and skeletal muscle. Alteration of GLUT 4 distribution from the intracellular compartment to the cell membrane is stimulated by insulin (Govers, 2014). GLUT 4 is reduced during diabetes mellitus due to a lack of or insufficient insulin sensitivity. Using Real-Time PCR, Nikzamir and coworkers discovered a substantial elevation in the expression of the GLUT 4 receptor when C2C12 skeletal muscle cells were treated with cinnamaldehyde (Nikzamir *et al.,* 2014). Further, it is considered cinnamon extracts have the ability to enhance the phosphorylation of Adenosine monophosphate-activated Protein Kinase (AMPK) and acetyl-CoA carboxylase, according to the findings of Shen et al., (Shen *et al.,* 2014). For this study, cinnamon sticks have been soaked in 2.5 l of water for 24 h at room temperature and heated for 30 min at 100 ◦C to prepare the cinnamon extract. Cinnamon extract-induced glucose absorption was suppressed by an AMPK inhibitor and LKB1 siRNA. Furthermore, Shen et al., discovered that insulin inhibited AMPK activation in adipocytes (Shen *et al.,* 2014). These findings suggest that cinnamon extracts can be useful to develop naval methods for uplifting the lives of people with Type 2 diabetes by translocating GLUT 4 through the AMPK signaling pathway (Shen *et al.,* 2014).

Effect on GLUT1's glucose transport activity

The GLUT1 gene is found on human chromosome 1 (1p35-31.3), and it encodes the glucose transport protein 1 (GLUT1) (Shah e*t al.,* 2012). It is highly present in proliferating cells of the developing embryo, cardiac muscle, human erythrocytes, and astrocytes and can be found in all tissues of the body and helps in the basal uptake of glucose (Pragallapati & Ravikanth, 2019) histopathology was used as major method in clinical routine. Of all oral subsites, buccal mucosa squamous cell carcinoma is aggressive in nature with poor survival. Therefore, the aim of the present study was to evaluate the relation of tumor histopathological grade with disease recurrence of buccal squamous cell mucosa carcinoma. Materials and Methods: A retrospective study was carried out in regional cancer research institute, Tamil Nadu. Demographic, histopathological and participant's follow-up details were collected from medical records. Results: Of 198 participants, high frequently encountered with well-differentiated squamous cell carcinoma (n = 98, 49.5%. GLUT1 is localized at the plasma membrane predominantly (Lu *et al.,* 2013)because GLUT1, the sole glucose transporter between blood and retina, transports more glucose when blood glucose is high. This is the ultimate cause of diabetic retinopathy. Knockdown of GLUT1 by intraocular injections of a pool of siRNAs directed against SLC2A1 mRNA which codes for GLUT1 significantly reduced mean retinal glucose levels in diabetic mice. Systemic treatment of diabetic mice with forskolin or genistein, which bind GLUT1 and inhibit glucose transport, significantly reduced retinal glucose to the same levels seen in non-diabetics. 1,9-Dideoxyforskolin, which binds GLUT1 but does not stimulate adenylate cyclase had an equivalent effect to that of forskolin regarding lowering retinal glucose in diabetics indicating that cyclic AMP is noncontributory. GLUT1 inhibitors also reduced glucose and glycohemoglobin levels in red blood cells providing a peripheral biomarker for the effect. In contrast, brain glucose levels were not increased in diabetics and not reduced by forskolin. Treatment of diabetics with forskolin prevented early biomarkers of diabetic retinopathy, including elevation of superoxide radicals, increased expression of the chaperone protein β2 crystallin, and increased expression of vascular endothelial growth factor (VEGF. Further, GLUT 1 plays a major role in the production of glucose for energy production in red blood cells and the brain in adults and it aids in the transport of glucose during the basal state in muscle and adipose tissue (Pragallapati & Ravikanth, 2019)histopathology was used as major method in clinical routine. Of all oral subsites, buccal mucosa squamous cell carcinoma is aggressive in nature with poor survival. Therefore, the aim of the present study was to evaluate the relation of tumor histopathological grade with disease recurrence of buccal squamous cell mucosa carcinoma. Materials and Methods: A retrospective study was carried out in regional cancer research institute, Tamil Nadu. Demographic, histopathological and participant's follow-up details were collected from medical records. Results: Of 198 participants, high frequently encountered with well-differentiated squamous cell carcinoma (n = 98, 49.5%. Plaisier and colleagues discovered that cinnamaldehyde affects the GLUT1 glucose transport activity in either basal or glucose deprivation conditions using L929 fibroblast cells (Plaisier e*t al.,* 2011). The findings showed that cinnamaldehyde has the ability to act on GLUT1's glucose transport activity in two ways (Plaisier *et al.,* 2011). Cinnamaldehyde enhances glucose absorption under basal conditions and reaches the utmost stimulation at 2.0 mM concentration (Plaisier *et al.,* 2011). On the other hand, cinnamaldehyde has played a role in the inhibition

of glucose absorption by glucose deprivation in a dose-dependent manner (Plaisier *et al.,* 2011). These functions rely on the alpha, beta-unsaturated aldehyde structural motif in cinnamaldehyde, according to experiments with cinnamaldehyde analogs.

LIMITATIONS

Even though, evidence to prove the possible effect on glycemic control with cinnamon, there are some limitations too. Some studies have utilized a cinnamon extract while other studies have utilized individual compounds known to be present in cinnamon. The optimum concentrations of the compounds which are important for effective action, might not be present when using the crude extract. Therefore, it can be the reason for the negative results of some studies which were conducted using crude extracts or ground cinnamon bark capsules. As the chemical composition of the cinnamon varies with the geographical location, the results which were observed using crude extracts are hard to presume conclusions of the studies and generalize the findings. However, the availability of cinnamon bark harvest to commercialize the product may be a limitation even though they have efficient glycemic control ability.

CONCLUSION

This review has explored anti-diabetes studies reported in the past with suggested mechanisms through scientific evidence, and also the main chemical compositions present in various extracts of Cinnamon. Dynamic properties of cinnamon include reduction of dephosphorylation of the insulin receptors, translocating glucose GLUT 4, and effect on GLUT1's glucose transport activity suggests that cinnamon is beneficial in controlling diabetes. However, more clinical trials have to be conducted to introduce cinnamon as a treatment for Type 2 diabetes as in vivo studies and clinical trials have given both negative and positive results in controlling hyperglycemia. Therefore, future research must be focused on the isolation of exact chemical compound/compounds/combination of compounds that are responsible for glycemic control, and understanding the mechanism of action are important. Further, structural elucidation of those compounds and finding out whether those compounds are able to manufacture synthetically will be the next step of future research.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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