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Review Article

Cinnamomum zeylanicum Linn. The spice with multi potential

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ABSTRACT

Cinnamomum zeylanicum Linn. has been used as a spice and flavoring agents. It is one of the healthiest spices and possesses useful medicinal benefits. It has been recognized as the medicinally essential phytoconstituents, such as phenolic, flavonoid and carotenoid. It is loaded with rich amount of polyphenols, which are the powerful antioxidants. It inhibits the growth of certain bacteria and fungi. It dramatically reduce insulin resistance, there by helps insulin to reduce blood glucose. It also slow down the break down of carbohydrate by interfering with carbohydrate digesting enzymes and decreases the entry of glucose from intestine to bloodstream. It reduces the growth of cancer cells. Numerous pharmacological investigations have confirmed that the ability of this plant is to exhibit hepatoprotective, cardioprotective, and neuroprotective activities and it supports the traditional uses. Present review gives a detailed information on recent literatures describing the multipotential uses of *C. zeylanicum* available for the treating various ailments.

Key words: *Cinnamomum zeylanicum*, Cinnamon, Antidiabetic, Antioxidant, Hepatoprotective, Anticancer.

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INTRODUCTION

The World Health Organization (WHO) has estimated that about 80% of the populations use the extracts of plant and their active components for treating their primary health problems.[1] Medicinal plants have been conventionally occupied a vital position in the social, spiritual as well as medicinal arena of both rural and tribal people of India. These plants are usually cheap, easily available and consumable. But their mode of action in treating various ailments and their respective role are yet to be discovered in most of the ailments. They are easily prepared and hence arbitrate the positive effect of the phytoconstituents present in them in treating the diseases.[2] Therefore, an enormous effort has been focused on using available experimental techniques to identify and isolate the natural antioxidants from plants. Results are promising their benefits in prevention as well as in therapy for many of the aforesaid diseases.

CINNAMON

Cinnamon has been used as a spice and an agent enhancing the flavours. The use of a variety of pharmacological effects in ailments are observed. *Cinnamomum zeylanicum* Linn. bark (family: Lauraceae) is commonly called as cinnamon, in French it is known as cannelle; ceylonzimt, in German as kaneel; in Italian as cannella; in Spanish as canela; in Chinese as yook gway; in India as dal-chini, darchini, dhall cheene and in Tamil Nadu as karuvappadai. It is also known as Ceylon or true cinnamon. Cinnamon is extensively used as spice and flavoring agent in commercially available products and it is almost entirely obtained from cultivated plants.

C. zeylanicum is a small and evergreen tree, most well-known for its bark, which offers the world with the normally recognized spice, cinnamon. The origin of the name cinnamon is from the Hebraic and Arabic term "amomon" which stands for fragrant spice plant. The name *C. zeylanicum* means "true cinnamon" in Latin. This review focuses on the phytochemical and pharmacological benefits of cinnamon from the internet data base PubMed and the most relevant articles are considered for review.

PHYTOCHEMISTRY

Cinnamon consists of various resinous compounds, including numerous essential oils, cinnamaldehyde, cinnamic acid and cinnamate.[3] The spicy taste and fragrance of the cinnamon is mainly due to the compound Cinnamaldehyde. It becomes darkens and improving the resinous compounds as cinnamon ages.[4] Tung *et al.*[5] reported the presence of cinnamyl acetate, *trans*-cinnamaldehyde, L-borneol, E-nerolidol, b-caryophyllene, eugenol, L-bornyl acetate, caryophyllene oxide, α-cubebene, terpinolene, α-terpineol, and α-thujene.

Unlu *et al.*[6] identified nine constituents of *C. zeylanicum* which are derived from the essential oil present in the bark. Some important compounds are benzaldehyde (9.94%), (E)-cinnamyl acetate (7.44%) and (E)-cinnamaldehyde (68.95%). Cao *et al.*[7] confirmed the presence of polyphenol in the aqueous extract of cinnamon. The greatest concentrations of polyphenols found in cinnamon is rutin (90.0672%) followed by kaempferol (0.016%), catechin (1.9%), isorhamnetin (0.103%) and quercetin (0.172%).[8,9]

ANTIMICROBIAL ACTIVITY

The essential oils of cinnamon are found to have antimicrobial activities which are reported in earlier studies.[10-13] Goni *et al.*[14] illustrated that the combination of clove oil and cinnamon are effective Gram-negative bacteria (*Escherichia coli, Pseudomonas aeruginosa, Yersinia enterocolitica* and *Salmonella choleraesuis*) and Gram-positive organisms (*Enterococcus faecalis, Listeria monocytogenes, Bacillus cereus* and *Staphylococcus aureus*).

The essential oil from the bark of *C. zeylanicum* showed strong antimicrobial activity against 4 candida species and 21 bacteria.[6] Recently, Parthasarathy and Thombare[15] reported the activity of the aqueous extract of cinnamon and *Azadirachta indica* and *Syzygium aromaticum* against oral microorganism. The antimicrobial activity of the essential oil from cinnamon is found to be more effective than *A. indica* and *S. aromati-*

cum.

Varalakshmi *et al.*[16] experimented the antimicrobial activity of the bark extracts of the *C. zeylanicum.* The results showed that the extract is effective against the gram negative and gram positive bacteria.

ANTIDIABETIC ACTIVITY

Khan *et al.*[17] coined the term "insulin- potentiating factor" for a compound which was isolated from cinnamon. Broadhurst *et al.*[18] concluded that the insulin- potentiating effect of cinnamon extract is 20 times higher than other species. Methyl-hydroxy-chalcone, a purified polymer, which stimulates the oxidation of glucose.[19] Anderson *et al.*[20] isolated and characterized the polyphenol type-A polymers from cinnamon. This substance acts as insulin-like molecules. Kim *et al.*[21] identified naphthalenemethyl ester which is the derivatives of hydroxycinnamic acid which has glucose-lowering effects.

Postprandial hyperglycemia is regulated by α-glucosidase inhibitors by hindering the digestion rate in the small intestine and so impedes the diet related acute glucose excursion. *C. zeylanicum* potentially reduce the glucose absorption of post-prandial intestine by inhibiting pancreatic α-glucosidase and α-amylase. This stimulates the cellular uptake of glucose by the glucose transporter-4 (GLUT4), stimulates glucose metabolism as well as glycogen synthesis, inhibits gluconeogenesis and stimulates insulin secretion and also potentiates receptor activity of insulin by *in vitro* models. Alanine plays an essential role in gluconeogenesis. The aqueous extract of cinnamon significantly reduced the absorption of alanine in the rats,[22] further confirming the anti-diabetic activity of cinnamon.

The extract of *C. zeylanicum* effectively inhibits α-glucosidase which suppresses postprandial hyperglycemia in rats induced by streptozotocin, loaded with sucrose and maltose. This bark extract have reversible and competitive inhibition on α-glucosidase. *C. zeylanicum* extract could be used as a possible nutraceutical compounds for treating postprandial hyperglycemia.[23] Cinnamon might be helpful for lowering the fasting blood glucose and serum glycosylated hemoglobin (HbA1C) in type 2 diabetes with HbA1C greater than 7.0 in additions to usual care.[24] Davis and Yokoyama[25] found that cinnamon intake significantly lowering the fasting blood glucose.

Hoehn and Stockert[26] observed a greater decrease in blood glucose values in patients under a 12-week trial using the cinnamon when compared to those using the dietary changes alone. Lu *et al.*[27] examined around a total of 66 patients affected by with type 2 diabetes and randomly divided them into 3 groups: placebo and low-dose (120 mg/d) and high-dose (360 mg/d) supplementation with cinnamon extract. Patients also received gliclazide for 3 months. The HbA1C and fasting blood glucose levels found to be significantly less in patients taking both doses, whereas they were not changed in the placebo group. This signifies that supplementation of cinnamon is able to control blood glucose level in patients with type 2 diabetes. Akilen *et al.*[28] observed that consumption of cinnamon for short term in patients with prediabetes and type 2 diabetes are found to be associated with a notable reduction in systolic blood pressure and diastolic blood pressure.

Peroxisome are the proliferator-activated receptors, which are transcriptional factors concerned in the regulation of insulin resistance and adipogenesis. Sheng *et al.*[29] confirmed that the expression of peroxisome proliferator-activated receptors gamma and alpha and their target genes such as GLUT4, LPL, ACO and CD36, are increased in presence of cinnamon in 3T3-L1 adipocyte. Therefore, this may be an alternative to peroxisome proliferator-activated receptors gamma activator in managing diabetes related to obesity and hyperlipidemia.

Absalan *et al.*[30] examined that GLUT4 translocation into the cytoplasmic membrane from the intracellular compartments of nuclear or endoplasmic eticulum membrane is enhanced by the hydro-alcoholic extract of cinnamon. GLUT4 contents were higher in cytoplasmic membrane and lower in dimethyl sulfoxide (DMSO) treated myotubes. For nuclear or endoplasmic reticulum membrane reverse results were obtained. This shows that the GLUT4 translocation happens from intra-cell into cell surface. Therefore, cinnamon can be chosen to treat type 2 diabetes mellitus as it improves GLUT4 contents in cytoplasmic membrane where the entry of glucose into the cell is facilitated.

Jiao *et al.*[31] reported that, the aqueous extract of cinnamon inhibits the amyloid formation of human islet amyloid polypeptide (hIAPP). Proanthocyanidins are the major anti-amyloidogenic compounds obtained from cinnamon extract which could affect the secondary structures of hIAPP and can delay the structural transition of β-sheet-rich structure from unstructured coils. Thus the membrane damaging is attenuated and the cytotoxic effect is made possible by hIAPP aggregation. Hence the obtained results proposed a promising way of using cinnamon against diabetes.

Lee *et al.*[32] illustrated a suitable doses of cinnamon (5 mg/kg, 10 mg/kg and 20 mg/kg) with the chemotype of linalool is found to help with glycemic control in diabetics by enhancing insulin secretion. Procyanidin B2, catechin and epicatechin are isolated from cinnamon, and they are shown to have inhibitory effect on the formation of advanced glycation end products.[33,34] In animal model *C. zeylanicum* attenuates the diabetes related weight loss; reduce blood glucose, HbA1c and low-density lipoprotein (LDL) cholesterol as well as increase high-density lipoprotein (HDL) cholesterol and circulating levels of insulin. *C. zeylanicum* also considerably enhanced metabolic derangements found to be associated with insulin resistance. It also exhibited positive effects against diabetic neuropathy and nephropathy, with no apparent toxic effects.[35] This might have a way for new therapeutic approach to treat diabetes and its related complications.

CARDIOPROTECTIVE ACTIVITY

Cinnamaldehyde produces hypotensive effects and expands rat vascular smooth muscle in an endothelium in dependent way.[36,37] Cinnamophilin is derived from *Cinnamomum philippinensis* which have the thromboxane A2 (TXA2) receptor blocking activity in animal models and thromboxane receptor-mediated proliferation of vascular smooth muscle cell.[38,39] Cinnamophilin is a potential TXA2 receptor antagonist and thromboxane synthase inhibitor. This is useful in the treating diseases involving TXA2 disorders [38], like platelet aggregation.[40]

Amin *et al.*[41] investigated the activity of cinnamon and atorvastatin on serum lipid profile, hepatic enzymes activities, antioxidant capacity, oxidative stress, nitric oxide (NO) as well as homocysteine in hypercholesterolemic rats. The levels of serum total cholesterol (TC), triglycerides (TG), LDL cholesterol, aspartate transaminase (AST), alanine transaminase (ALT) and hepatic malondialdehyde (MDA) levels are significantly low meanwhile, serum HDL cholesterol, NO values and antioxidant activities in liver were significantly higher in atorvastatin and cinnamon-treated group than untreated. The administering atorvastatin or cinnamon provides protection against the lipemic-oxidative disorder and reduce cholesterol and act as hepatoprotective agent and also improve the function cardiovascular system by modulating the oxidative stress, NO and homocysteine. Song *et al.*[42] isolated cinnamic aldehyde and cinnamic acid from *Cinnamon cassia* have the potential effect against myocardial ischemia. This provides evidence for cinnamon which can be used to treat cardiovascular disease.

NEUROPROTECTIVE ACTIVITY

Lee *et al.*[43] concluded that cinnamophilin (80 mg/kg) provides defense against ischemic damage of brains in rats at different time intervals (2, 4, and 6 h) after insult. It has shown a considerable effect (by 34-43%) on abridged brain infarction and further improves neurobehavioral outcomes.

C. zeylanicum aqueous extract reduces the filament formation and tau aggregation, which are the main features of Alzheimer's disease. *C. zeylanicum* extract can lead to complete fragmentation of tau filaments and modify the morphology of paired helical filaments from Alzheimer's disease brain.[44] Thus proves the potential benefits of cinnamon in treating the Alzheimer's disease.

Substance inhibits the buildup of amyloid-beta (Abeta) lump in the brain of Alzheimer's disease subject may be the potential therapeutic agents. Cinnamon may have the marginal affinity for Abeta (1-42) and may be effective clinically.[45] Panickar *et al.*[46] derived the compound procyanidin type-A trimer (trimer 1) from water-soluble extract of cinnamon. Trimer 1 is found to decrease the swelling of cell by controlling the movement of intracellular calcium [Ca2+]i.

Cinnamon and sodium benzoate (metabolite) increases the neurotropic factors brain-derived neurotropic factors and neurotrophin-3 in the mouse central nervous system.[47] Frydman-Marom[48] extracted a compound from cinnamon extract which is found to reduce the formation of toxic β-amyloid polypeptide oligomers and also prevents the toxicity of β-amyloid polypeptide oligomers on neuronal pheochromocytoma cells.

HEPATOPROTECTIVE ACTIVITY

Moselhy and Ali[49] investigated the hepatoprotective activity against carbon tetrachloride ($CC1_4$) of ethanolic and aqueous extracts of cinnamon and stimulated lipid peroxidation (LPO) and hepatic injury in animal models. The increased serum levels of AST and ALT enzyme activities induced by $CC1_4$ was restored to almost normal by oral administration of either extracts (200 mg/kg) once daily for 7 days, when compared to untreated rats. There was a significant change in the level of liver MDA, while the activities of antioxidant enzymes superoxide dismutase (SOD) and catalase (CAT) were significantly less in $CC1_4$ intoxicated rats. The hepatoprotective properties were also recognized by the data obtained by the histopathological analysis. The possible way of this action may be due to the free radical-scavenging effect of polyphenol compounds.

Acute alcohol intake may cause a >20-fold rise in the accumulation of lipids in hepatic cells. Pretreatment with extract of cinnamon considerably decreased the accumulation of hepatic lipids. This protective effect may be related to inhibition of the stimulation of the myeloid differentiation primary response gene (MyD) 88, plasminogen activator inhibitor 1 mRNA expression, inducible NO synthase (iNOS) and found in the liver of alcohol treated animals. *In vitro* with cinnamon extract suppresses the lipopolysaccharide induced MyD88, iNOS, and TNF alpha expression and NO formation almost completely.[50]

Couturier *et al.*[51] found that in cinnamon added to the high-fat/high-fructose (HF/HFr) diet fed rat has highly significant increase of liver glycogen. Cinnamon is found to decrease the gene expressions of the HF/HFr diet for the insulin receptor due to supplementation and its substrates 1 and 2, glycogen synthase 1 and glucose transporters 1 and 2 (GLUT1 and 2). In muscle cell, the reduced expressions of these genes and GLUT4 were also restored by cinnamon. The more expression of glycogen synthase 3β messenger RNA levels and also protein levels are observed in the muscle of HF/HFr fed rats was reduced in animals taking cinnamon. These suggest that, cinnamon improves insulin sensitivity and also enhances the liver glycogen through regulating insulin signaling and glycogen synthesis in insulin-resistant rats.

ANTIOXIDANT ACTIVITY

Nair *et al.*[52] found that high flavonoid content (>100 mg/100 gm) is found in drinks (tea and coffee), fruits (apple and guava), seeds (fenugreek seeds and mustard seeds), barks (terminalia bark and cinnamon), and powders (red chili powder, turmeric and cloves). Dhuley[53] found that the cardiac and hepatic enzyme activities which are antioxidants were significantly enhanced and reduced glutathione (GSH) content was noticeably restored in rats provided with fat diet with cinnamon and cardamom. Besides, these spices moderately found to increase in lipid conjugated dienes and hydroperoxides, which are the major products in LPO reaction.

Shobana and Naidu[54] evaluated the antioxidant activities of water and alcoholic extracts of commonly used spices such as onion, garlic, ginger, cloves, mint, pepper and cinnamon. The comparative antioxidant activities decreased as cloves>cinnamon>pepper> ginger>garlic>mint>onion. These results suggest that these spices are imparting flavor to the food as well as they have pivotal health benefits by inhibit the LPO.

Peng *et al.*[32] identified several phenolic compounds, like epicatechin, catechin and phenol polymers, and procyanidin B2 from the aqueous extract of cinnamon sub-fractions. These compounds showed inhibitory effects on formation of advanced glycation end products. The antiglycation activities of these phenolic compounds were not only carried out by their antioxidant activities but also found to be associated to their entrapping capabilities of reactive carbonyl species like methylglyoxal, an intermediary reactive carbonyl of advanced glycation end products formation.

Misharina *et al.*[55] studied the antioxidant potential and constancy throughout the storage of hexane solutions of 14 essential oils. The essential oils of garlic, clove bud, ginger and cinnamon leaves have the maximal efficacy of inhibition of hexenal oxidation (80-93%). Roussel *et al.*[56] determined the effects of cinnamon aqueous extract on antioxidant profile in persons with impaired fasting glucose. The levels of plasma MDA is found to decrease in subjects receiving the cinnamon extract treatment. There was also a positive correlation between plasma glucose and MDA. The risk factors associated with diabetes and cardiovascular disease are decreased by treating with the inclusion of water soluble cinnamon in the diet.

Dudonne *et al.*[57] investigated that aqueous extracts of 30 different medicinal plants and their antioxidant properties using 2,2-Diphenyl-1-picryl hydrazyl (DPPH) and 2,2'-azino-bis-3-ethyl benzthiazoline-6-sulphonic acid (ABTS) radical scavenging capacity assay, SOD assay, oxygen radical absorbance capacity (ORAC) assay, and ferric reducing antioxidant potential (FRAP) assay. Using Folin-Ciocalteu method is used to determine the total phenolic content. The aqueous extracts of oak, pine and cinnamon possessed the highest antioxidant capacities and can be the possible wealthy sources of natural antioxidants in most of the methods used. All these extracts presented the highest phenolic content and a significant association between antioxidant capacity and total phenolic content were determined.

Mishra *et al.*[58] examined the ameliorative effect of the cinnamon oil at different concentration (5, 10, 20 mg/kg) at the early stages of diabetic nephropathy due to its antidiabetic and antioxidant effect. The level of fasting blood glucose, thiobarbituric acid reactive substances, urea, CAT, GSH, TC and HDL cholesterol were significantly changed and protect against diabetic nephropathy and the results were compared with glipizide (10 mg/kg). The kidney's histopatholgical studies confirmed the protective efficacy of cinnamon oil by lowering the expansion of glomerular, removing hyaline casts, and also by reducing the dilatations of the tubules. The cinnamon oil contains 98% cinnamaldehyde and that it confers significant protective effect against alloxan-induced renal dam-

age in dose-dependent manner.

Wei and Shibamoto[59] tested twenty-five essential oils for antioxidant activities. The leaf oil from cinnamon showed strong activities 100% and 84% in the aldehyde/carboxylic acid assay and DPPH assay respectively, but only modest activities in the conjugated diene assay and malonaldehyde/gas chromatography assay 24% and 48% respectively. The leaf oil of cinnamon has high levels of cinnamaldeyde and it acts as a most important compound for its antioxidant activity.

Varalakshmi *et al.*[60] performed an *in vitro* study for determining the antioxidant activity of the phenolic compound found on the bark of *C. zeylanicum.* The results of the study showed great effects in scavenging the free radicals present in the test sample thus proving the anti-oxidant activity of the extract.

Yuce *et al.*[61] investigated the long-term effects of cinnamon bark oil ingestion on testicular antioxidant values, the quality of sperm and apoptotic germ cell in adult rats. A significant decrease in MDA level and marked increases in CAT, GSH level and glutathione peroxidase (GPx) activities were observed in rats treated with cinnamon bark oil compared with the control group. Cinnamon bark oil have a rise in weights of testes and epididymides, the concentration of epididymal sperm, motility of sperm and diameter of seminiferous tubules compared to the control group. However, cinnamon bark oil also decreases the apoptotic germ cell count and abnormal sperm rate, but it is not significant.

ANTICANCER ACTIVITY

Kwon *et al.*[62] have synthesized cinnamaldehydes and tested as inhibitors against angiogenesis. Treatment with cinnamaldeyde and ethanolic extract of *C. cassia* upregulate the levels of Nrf2 and established Nrf2 targets which is involved in the antioxidant response by means of gamma-glutamyl-cysteine synthetase and heme oxygenase 1in human colon cancer cells such as, HCT116 and HT29 as well as the non-immortalized primary fetal colon cells. Pretreatment also upregulate the cellular GSH levels and protect HCT116 cells against genotoxicity induced by hydrogen peroxide and oxidative insult induced by arsenic. Taken together, the cinnamaldeyde is a powerful activator of the Nrf2-orchestrated antioxidant activity in human cultured epithelial colon cells and may show an underappreciated chemopreventive dietary factor for targeting colorectal carcinogenesis.[63]

The target for anti-angiogenesis treatment is vascular endothelial growth factor (VEGF). Lu *et al.*[64] found that aqueous extract from cinnamon was a potent natural inhibitor of activity of mitogen-activated protein kinase, VEGFR2 kinase, and Stat3-mediated signaling pathway in endothelial cells. This can potentially be used in the prevention and treatment of cancer.

The anti-cancer activity of cinnamon bark tested by Varalakshmi *et al.*[16] showed that the process of apoptosis was increased on treating with the methanolic extract in the human hepatoma cancer cells.

CONCLUSION

The pharmacological investigations carried out on *C. zeylanicum* validate the immense potential of this plant in treating numerous diseases. Additional research and clinical trials are needed for the product development to strengthen the use of *C. zeylanicum* for the future generations.

CONFLICTS OF INTEREST

No funding source and there is no conflict of interest.

ABBREVIATION USED

ABTS: 2,2'-Azino-bis-3-ethyl benzthiazoline-6-sulphonic acid; **ALT:** Alanine Transaminase; **AST:** Aspartate Transaminase; **CAT:** Catalase; **CC14:** Carbon Tetrachloride; **DMSO:** Dimethyl Sulfoxide; **DPPH:** 2,2-Diphenyl-1-picryl hydrazyl; **FRAP:** Ferric Reducing Antioxidant Potential; **GLUT:** Glucose Transporter (GLUT1, GLUT2 AND GLUT4); **GPx:** Glutathione Peroxidase; HbA1C: Glycosylated Hemoglobin; **HDL:** High-Density Lipoprotein; **HF/HFr:** High-Fat/High-Fructose; **hIAPP :** Human Islet Amyloid Polypeptide; **LDL:** Low-Density Lipoprotein; MDA- Malondialdehyde; **NO:** Nitric Oxide; **ORAC:** Oxygen Radical Absorbance Capacity; **SOD:** Superoxide Dismutase; **TC:** Total Cholesterol; **TG:** Triglycerides; **TXA2:** Thromboxane A2; **VEGF:** Vascular Endothelial Growth Factor; **WHO:** World Health Organization.

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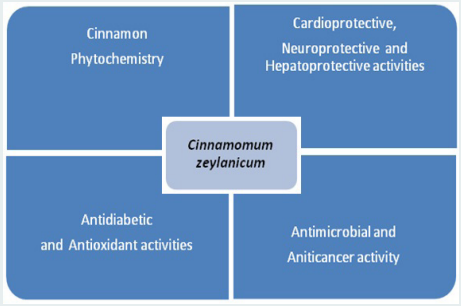
PICTORIAL ABSTRACT



SUMMARY

• *Cinnamomum zeylanicum* is a spicy which enhances the flavours.
• It consists of medicinally essential phytoconstituents.
• This review validates the possibility of this plant in treating numerous diseases.

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