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The Potency of *Cinnamomum Zeylanicum* to Prevent Diseases: A Review

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A B S T R A C T

Plants are an important source of traditional medicines that can be used to improve health. Cinnamon (Cinnamomum zeylanicum) has long been recognized to have many benefits. Cinnamon was used traditionally as a remedy for arthritis, diarrhea, allergies, and ulcers. This literature review aimed to identify the bioactive compounds and bioactivity of cinnamon. Literature searches used PubMed and Google Scholar. A total of 55 full-text articles met the inclusion criteria of the review. The extract or essential oil of cinnamon contains many bioactive compounds, such as eugenol, cinnamic acid, linalool, β-caryophyllene, coumarin, and trans cinnamyl acetate, and 1.8 cineole. These compounds have several bioactivities including anti-cancer, anti-arrhythmia, anti-inflammatory, anti-diabetic, anti-atherosclerosis, anti-cholinesterase, and anti-lipid oxidation. Cinnamon extract has excellent potential as an antioxidant and antidiabetic agent. Its potential and unique taste have contributed to its wide use in herbal remedies.

1. Introduction

The use of cinnamon as traditional herbal therapy or alternative complementary medicine has spread all over the world. Cinnamon was used traditionally as a remedy for arthritis, diarrhea, allergies, and ulcers. Plant extracts are often used for the treatment of various diseases because of their potentially beneficial bioactivities, such as antibacterial, antifungal, antiviral, antioxidant, anticancer, antidiabetic, immunomodulatory, analgesic, and anti-inflammatory.[1,2] Cinnamon is one of the potential plant medicines. Cinnamon is in the family of Lauraceae.[2] The Latin names are Cinnamomum zeylanicum or Cinnamomum verum which is also known as "true cinnamon".[3] Cinnamon has major bioactive compounds in every part of the tree including its bark, roots, leaves, and fruit.[4] Three major bioactive compounds present in cinnamon bark essential oil are eugenol, trans-Cinnamaldehyde, and linalool. These compounds make up almost 85% of the total composition.[5] Other bioactive compounds found are cinnamaldehyde, β-caryophyllene, and eucalyptol.[6] This herb is also one of the oldest in the herbal medicine pharmacopeia and was mentioned in Chinese Materia medica texts more than 4.000 years ago.[7] This literature review aimed to identify the bioactive compounds and bioactivity of cinnamon (*Cinnamomum zeylanicum*).

2. Methods

PubMed and Google Scholar were used as the search engine in this study. The search was conducted up to May 21, 2020, using the keywords "Cinnamomum zeylanicum" and "antioxidant" or "Cinnamomum zeylanicum" and "α-glucosidase". The articles selected were all published within the past ten years. Duplicate articles were excluded. From PubMed and Google Scholar, 125 and 41 results were obtained, respectively. Inclusion criteria for this review were: the relevant articles written in English related to Cinnamomum zeylanicum and the study of antioxidant and antidiabetic agents. There were 111 irrelevant titles excluded due to duplication and outside of the scope. As many as 55 full-text articles were included in the review.

3. Results and Discussion

Based on the results from the reviewed studies, we found that cinnamon extract (*Cinnamomum zeylanicum*) has several powerful bioactive compounds (Table 1).

Bioactive compounds from *Cinnamomum zeylanicum*

Cinnamaldehyde

Cinnamaldehyde (C9H8O) is a derivative compound of the volatile chemical, aldehyde that gives cinnamon its flavor and aroma. It is a natural flavonoid. As much as 90% of the total essential oil is cinnamaldehyde. This bioactive compound is commonly found in the bark of the cinnamon tree.[8]

Kallel et al. and Behbahani et al. reported that the main bioactive compound in Cinnamomum zeylanicum essential oil is cinnamaldehyde with the content percentage around 71.5% -77.34%.1.6 Meanwhile, Seroyi et al. also found cinnamaldehyde as much as 82.6% in the water extract.[9] It is also found in the methanol and ethanol extracts in lesser amounts. Cinnamaldehyde of the ethanolic and methanolic extracts are 14.63 ± 1.1 mg/g and 38.78 ± 0.78 mg/g, respectively.[10-12]

Babu et al. conducted translational research on antidiabetic compounds, especially cinnamaldehyde. In their study, diabetic rats were given cinnamaldehyde and glibenclamide. It found that cinnamaldehyde can be used as an antihyperglycemic, to reduce total cholesterol and triglyceride levels simultaneously, and increase high-density lipoprotein (HDL) in diabetic rats.[13]

A study also found that cinnamaldehyde increases the activity of glucose transporter 4 (GLUT 4) which transports blood glucose into cells to diminish the blood glucose levels.[14] Cinnamaldehyde also has antioxidant activity.[15]

Eugenol

Eugenol (C10H12O2) is a widely known and volatile component in clove extracts, but it is also found in cinnamon, especially in the leaves.[16,17] The study conducted by Rao et al. compared the bioactive compounds in the essential oil of cinnamon leaves and reported that eugenol compounds were found mostly on the top and larger leaves. Apart from the leaves, eugenol is also found in the bark of cinnamon.17 Eugenol was also found in the essential oil of cinnamon bark between 4.6 % - 7.45 %.[6,18.] The eugenol of essential oil of cinnamon leaves is as much as 58.10 %.[19]

The methanolic extract of cinnamon bark contains as much as 10.97 % of eugenol. Eugenol has strong antioxidant activity but also has cytotoxic effects when used in high doses. Further research is needed to confirm eugenol's use as a safe pharmacological agent.[12] Eugenol is not found in the ethanolic extract.

Cinnamic acid

Cinnamic acid (C9H8O2) is a compound found in cinnamon bark, derived from phenylalanine deamination.[20] Cinnamic acid has low toxicity and a broad spectrum of biological activity.[21] Generally, it is used as an antimicrobial agent.[22] Cinnamic acids are found in the cinnamon water extracts as much as 1.0 mg/g.[23] The methanolic and ethanolic extracts contain 0.68 ± 0.01 mg/g and 8.99 ± 0.5 mg/g, respectively. 10-12 Cinnamic acid derivates have phenolic hydroxyl

groups, so they are often associated with antioxidants. Cinnamic acid has been reported as an antioxidant, antibacterial, antiviral, and anti-fungal agent.[12]

Linalool

Linalool (C10H18O) is the main bioactive compound in cinnamon essential oil.[18,24] The concentration of linalool in the essential oil of the leaves is around 85.7%.[19,25,26] Linalool in the essential oil of the bark is 7%.6 The presence of a higher linalool content will give the essential oil more flavor and aroma.[27]

β- caryophyllene

β-caryophyllene (C15H24) is found in various essential oils, especially cloves.[28] Many studies have proven that this compound is also present in cinnamon. β-caryophyllene has content around 2.8 % - 6.4 %.6,18,24 β-caryophyllene has been reported as an anti-inflammatory, antibiotic, antioxidant, and anti- carcinogenic.[29]

Coumarin

Coumarin is found in aqueous and methanolic extracts of cinnamon. The methanolic extract contains 4.4 ± 0.10 mg/g of coumarin and the water extract contains as much as 4.8 mg/g of coumarin.[11,23]

Trans-cinnamyl acetate

Cinnamyl acetate (C11H12O2) is an acetate ester produced by the condensation of cinnamyl alcohol and acetic acid. This compound is found in cinnamon leaf oil. This compound has the potential as a fragrance, metabolite, and insecticide.[30] The cinnamon essential oil of leaves and bark contain cinnamyl acetate as much as 23.7% and 4.98%, respectively.[1,31]

1.8-cineole

1.8 cineole (C10H18O) or often called eucalyptol is a natural constituent in some aromatic plants.[32] This compound can be found in essential oils of the fruit, roots, bark, and leaves of cinnamon. 1.8 cineole has different content percentages: in the root, it is 6.39%, while in the bark, it is around 3.19% - 5.4%.[1,6,33] The water extract also contains 1.8 cineole as much as 3.4%.[9]

Pharmacological activities of Cinnamomum zeylanicum

Anti-cancer activity

There is a strong relationship between antioxidant activity and antiproliferative activity. The cinnamon essential oil has potential as an antiproliferative agent against HeLa cells (cervical cancer epithelium) and Raji cells (cells from Burkitt lymphoma), due to the antioxidant compounds.[1] The IC50 of the cytotoxicity is <30μg/mL. It is also considered an anti-tumorigenesis agent that prevents the development of certain cancers. Cinnamaldehyde and hydrocinnamic acid can be used to prevent oxidative damage.[34] Antiproliferative action could occur through various mechanisms such as diminished integrity of cell membranes, depolarization, increasing permeability, decreased activity of membrane-bound enzymes, or inducing apoptosis.6 Some of its compounds have anticancer activities and cytotoxic activities, especially carvacrol, linalool, and cinnamaldehyde.[35]

Eugenol and cinnamaldehyde have the ability to inhibit the proliferation of breast (T47D) and lung (NCI- H322) cancer cell lines.[15] Cinnamaldehyde inhibits cyclin-dependent kinases (CDKs) that are involved in the regulation of the cell cycle.[36] Figure 2 shows the mechanisms of flavonoids as an anti-cancer phytochemical. The mechanisms are inactivation of carcinogens, triggering termination of the cell cycle, triggering apoptosis, and inhibition of angiogenesis.[37]

Flavonoids inhibit the proliferation of tumor cells through inhibition of reactive oxygen species (ROS) formation and suppression of 5-LOX, COX-2, and xanthine oxidase, which are the main catalysts for tumor development and promotion. Many types of cancer are related to CDK hyperactivation, due to mutations in the CDK inhibitor gene or CD gene. Flavonoids cause the cessation of cell cycle checkpoints in the G1/S and G2/M by inhibiting CDK inhibition in human melanoma cells and breast

cancer.[38]

Inhibition of lipid oxidation

Lipid oxidation that occurs in food causes reduced shelf life and quality of the foods. Lipid oxidation is also involved in the pathogenesis of diseases.[39] Cinnamon ethanolic extract is associated with inhibition of lipid oxidation and has strong antioxidant activity, so it can be used as a substitute for synthetic antioxidants in processed food. This extract improves nutrition and health by decreasing harmful oxidative derivatives and free fatty acids (FFA).[2] Cinnamon essential oil also has vigorous antioxidant activity and can potentially suppress lipid oxidation.[6] Eugenol, cinnamaldehyde, and linalool have powerful antioxidant activity. They reduce nitrotyrosine formation by reducing peroxynitrite which promotes lipid oxidation.[2]

Anti-arrhythmia

Ventricular arrhythmias occur mostly due to damage, which can be caused by surgery or myocardial infarction. Cinnamon has been used in traditional herbal medicines to treat various health conditions including heart failure.[40]

The cinnamon ethanolic extract has high antioxidant activity. Antioxidant compounds have the potential to protect the heart against arrhythmias caused by ischemia. Further research is needed to develop cinnamon extracts into new anti-arrhythmic drugs. Cinnamon extract is able to reduce the QT interval. The decreasing amplitude of the R waves indicates the reduction of cardiac contractility. Cinnamon ethanolic extract can be used as a negative inotropic agent because it reduces contractility. It also significantly reduces markers of heart damage, such as cTnI and LDH. cTnI is a significant marker of myocardial infarction.[10]

Anti-inflammatory

Cinnamon has strong antioxidant and anti-inflammatory activities.[23] Its antioxidants contribute to anti-inflammatory activity.[41] Cinnamon inhibits the synthesis of COX-2 and prostaglandins.[41,42]

Cinnamaldehyde and linalool play an important role as anti-inflammatory agents. Cinnamon essential oil prevents systemic inflammation in endotoxin-induced mice. The protective effect was confirmed by the proinflammatory cytokines that were significantly reduced. Cinnamaldehyde demonstrated its inhibitory activity against Interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) production. Cinnamaldehyde and linalool can be used as prophylactic agents against inflammation caused by the overactivity of TLR4 and or NLRP3 signaling pathways.[43]

Anti-diabetic

Antioxidant compounds of the cinnamon extract improve oxidative stress and reduce blood glucose levels in diabetic-induced mice.[44] Figure 3 shows the potential of antioxidants in the type 2 diabetes mellitus pathway induced by oxidative stress. The existing ROS and reactive nitrogen species (RNS) cause oxidative stress in diabetes which leads to insulin resistance and endothelial and β cell dysfunction. It occurs by exposure to prolonged high glucose or FFA levels or a combination of both, and lower secretion of insulin and dysfunction of mitochondrial products.[45]

Cinnamon reduces blood glucose levels by reducing insulin resistance and increasing liver glycogenesis.[46,47] Phenolic acid in cinnamon is also proposed as an active compound in the modulation of insulin signals. Cinnamaldehyde has antihyperglycemic and antihyperlipidemic activity in diabetic animals. Cinnamon extract ca be used to be a potential antidiabetic agent, but the molecular target of this solvent from cinnamon or cinnamaldehyde is still unclear.[13,48] α-glucosidase inhibitors have an important role as antidiabetic agents. The α-glucosidase inhibitor activity found in the cinnamon extract is reversible, so this enzyme will still remain intact post inhibition. Cinnamon extract suppresses postprandial hyperglycemia associated with disaccharides.[49]

The cinnamon extract significantly inhibits the enzymatic activity of pancreatic α-amylase and intestinal α-glucosidase.[50] It contributes to the lowering of the level of HbA1c in diabetic patients and decreases the incidence of vascular chronic complications, both macrovascular and microvascular.[51] As well-known in translational research, acarbose has already been studied clinically in type 2 diabetes mellitus.[50]

Anti-atherosclerosis

The antioxidant activity of the cinnamon water extracts suppresses the incidence of atherosclerosis. Cinnamaldehyde and eugenol inhibit the activity of the cholesteryl ester transfer protein (CETP). The activity of CETP involves promoting the development of atherosclerosis by decreasing the HDL level. The inhibition of CETP promotes the production of HDL and prevents the development of atherosclerosis.[9]

Anti-cholinesterase

Antioxidants of cinnamon extract and the essential oil are related to the anticholinesterase activity.[12] This cholinesterase inhibition is linked to neurodegenerative diseases such as Alzheimer's.52 The cinnamon bark and leaves show an acetylcholinesterase inhibitory activity, so it is useful for managing Alzheimer's.[53] Alzheimer's disease is characterized by inadequate production of acetylcholine in the brain.[54] This cholinergic system plays a vital role in memory. The loss of cholinergic neurons from Meynert's basal is an important factor in memory deficits in people with Alzheimer's.[55]

Table 1. Summary of journal search results

Extract	Bioactive compounds	Bioactivity	Literature
Aquadest	Cinnamaldehyde, trans-cinnamyl acetate, 1.8 cineole, linalool, β-caryophyllene, eugenol, cinnamic acid, coumarin, eugenol acetate	Antioxidant, antiproliferative, antimicrobial, antidiabetic, anti-inflammatory	Kallel I et al[1], Behbahani BA et al[6], Seroyi J, et al[9] Kachaniova M, et al[18], Mahomodally F, et al[19], Durak A et al[23], Loizzo M, et al[24], Baker I, et al[41]
Ethanol	Cinnamaldehyde, methyl-eugenol, cinnamic acid	Antioxidant, cardioprotective, anticholinesterase	Shahid MZ, et al[2], Sedighi M. et.al[10]
Methanol	Cinnamaldehyde, coumarin, cinnamic acid, cinnamyl alcohol, eugenol, oleic acid	Antioxidant	Khuwijitjaru P et al[11], Abdeen A et al[12]

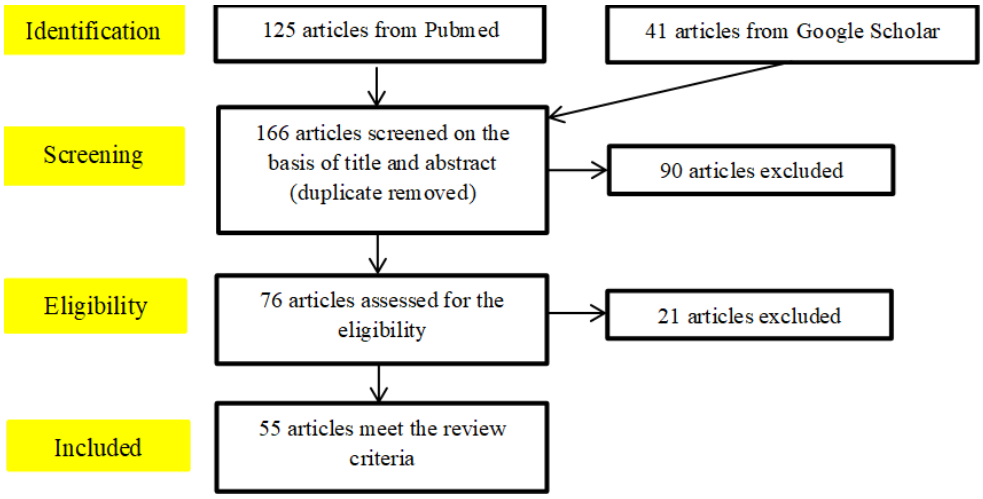

Figure 1. Journal selection process

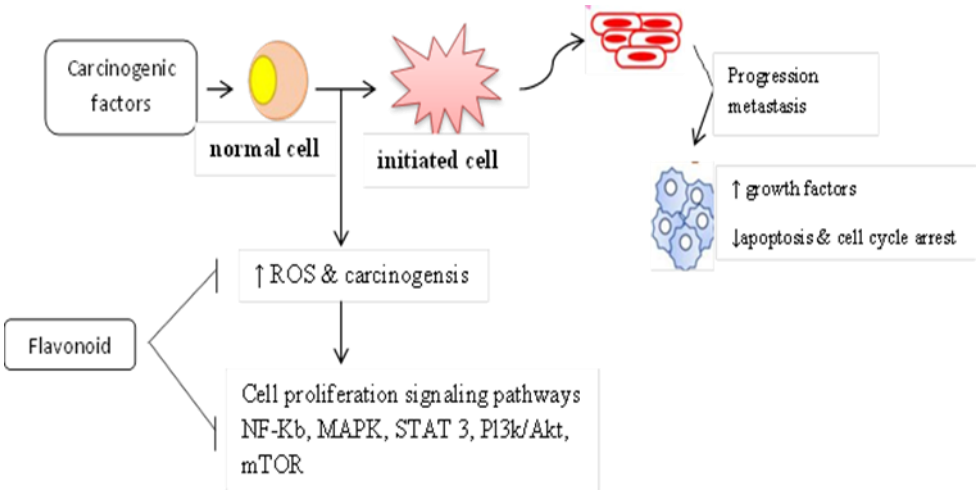

Figure 2. Role of flavonoids in cancer[37]

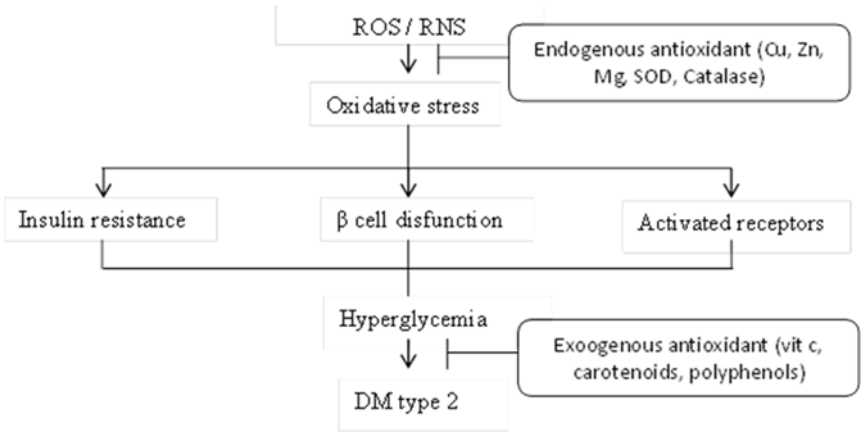

Figure 3. Antioxidants in the treatment of type 2 DM[45]

4. Conclusion

Bioactive compounds of the cinnamon extract are cinnamaldehyde, eugenol, cinnamic acid, linalool, β-caryophyllene, coumarin, trans-cinnamyl, and 1,8 cineole. Each compound has its own powerful bioactivity potential, such as anticancer, lipid oxidation inhibitor, anti-arrhythmia, anti-inflammatory, antidiabetic, anti-atherosclerosis, and anti-cholinesterase.

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