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Review article

Cinnamon from the selection of traditional applications to its novel effects on the inhibition of angiogenesis in cancer cells and prevention of Alzheimer's disease, and a series of functions such as antioxidant, anticholesterol, antidiabetes, antibacterial, antifungal, nematicidal, acaracidal, and repellent activities

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ABSTRACT

The purpose of this article is to use search engines such as PubMed and Scifinder to locate scholarly articles and reports pertaining to *Cinnamon* (肉桂 ròu guì), its novel effects, preparation, analysis, and use in the prevention and treatment of serious illnesses, such as diabetes, cardiovascular diseases, Alzheimer's disease, and cancer. Cinnamon has been used traditionally in food preparations and as an herbal medicine to treat a variety of ailments and their symptoms. Cinnamon is known to have antioxidant, antibacterial, anti-inflammatory, and other therapeutic properties. New studies reaffirm the importance of cinnamon as a spice but also suggest that it may be a natural remedy to treat serious diseases such as type 2 diabetes, chronic digestion problems, cardiovascular diseases, and even cancer and Alzheimer's disease. This article presents a comprehensive analysis of the botanical, chemical, and pharmacological aspects of cinnamon.

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1. Introduction

Cinnamon (肉桂 ròu guì), which is derived from a Greek word that means sweet wood, comes from the inner bark of tropical evergreen cinnamon trees.¹ *Cinnamomum* (cinnamon) is a genus of the Lauraceae family, many of whose members are used as spices.² There are two main varieties of cinnamon: the Ceylon or true cinnamon (*Cinnamomum zeylanicum* Blume), which is grown in Sri Lanka and Southern India (Fig. 1A), and cassia (*Cinnamomum aromaticum* Ness), which is grown in China, Indonesia, and Vietnam (Fig. 1B). Cassia, when dried, rolls into a tubular form known as a quill or cinnamon stick.^{1,3}

Cinnamon has been used in food preparations and in traditional medicine by the Egyptians and the Chinese since ancient times.⁴ In addition, this spice has been found to have strong antioxidant, antibacterial, antipyretic,⁵ and anti-inflammatory properties, which play an important role in tissue repair.⁶ The bark of cinnamon has been used as a spice and to make tea and also as an herbal remedy for the treatment of common colds, cardiovascular diseases, and chronic gastrointestinal and gynecological disorders in oriental herbal medicine.⁷ Cinnamon has likewise been used for treating sore throats, cough, indigestion, abdominal cramps, intestinal spasms, nausea, flatulence, and diarrhea.¹ Moreover, it has been found that cinnamon slows down food spoilage and displays antifungal properties.⁸

One study has found that cinnamon bark water extract enhances glucose uptake by increasing insulin sensitivity. Several studies have also found that cinnamon extract (CE) displays anticancer activity⁵ and inhibits angiogenesis by blocking vascular endothelial growth factor (VEGF) 2 signaling. These results indicate that the observed pharmacological activities may have originated from the polyphenolic compounds in cinnamon water extract.⁷

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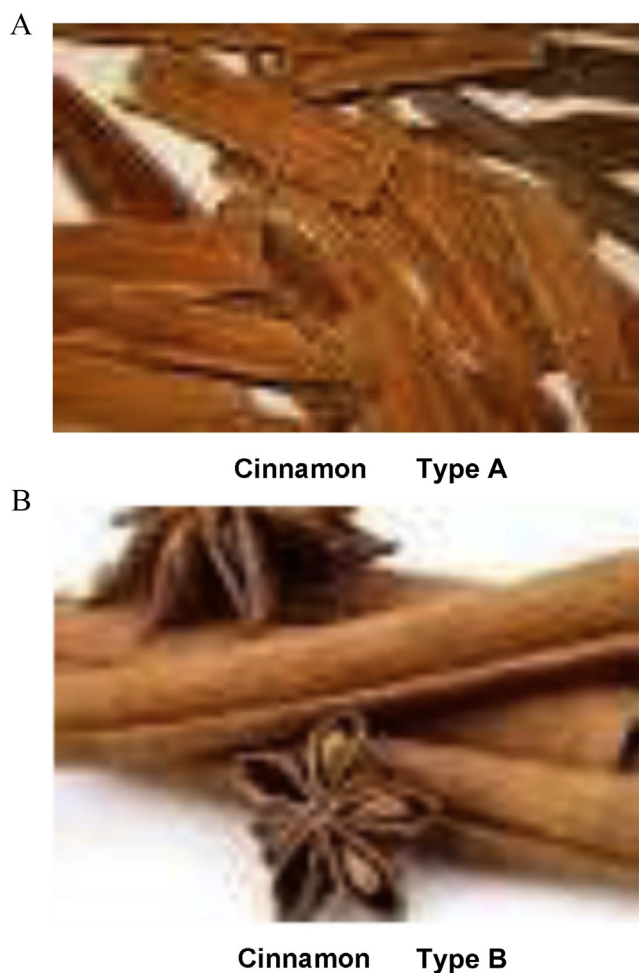


Photo by Pars Bioscience, LLC, Leawood Kansas

Fig. 1. (A) True cinnamon. (B) Cassia cinnamon. (Photographs by Pars Bioscience LLC, Leawood, KS, USA).

2. Components

Cinnamon (肉桂 ròu guì) is a plant with many uses as an herbal medicine and it contains mucilage, tannin, sugar, resin, and essential oil, among which essential oil is the most important constituent. The major portion of the essential oil is made up of cinnamaldehyde or cinnamic aldehyde.⁶ Cinnamaldehyde is responsible for the flavor and aroma of cinnamon.⁹ A study found that cinnamaldehyde is the major volatile component of cinnamon sticks, with 83.6% of essential oils extracted from cinnamon stick powder.² The essential oils from *Cinnamon cassia* also contain 80–90% cinnamaldehyde with little or no eugenol, which is different from *C. zeylanicum* bark, which contains 60–80% cinnamaldehyde and approximately 2% eugenol, however, essential oils from its leaves were found to be rich in eugenol (70–75%).² The study showed that the crude extracts of cinnamon stick also contained high levels of nonvolatile compounds (mainly condensed tannins), which consist of 23.2% proanthocyanidins and 3.6% catechins in addition to cinnamaldehyde (64.1%).²

3. Diabetes

Diabetes mellitus is a chronic disorder of glucose metabolism caused by the dysfunction of pancreatic beta cells and insulin

resistance. Diabetes is a serious health problem that affects both sexes in all age groups and all over the world.¹⁰

Cinnamon (肉桂 ròu guì) has been shown to have insulin mimetic properties because its biologically active substances enhance glucose uptake by activating insulin receptor kinase activity, autophosphorylation of the insulin receptor, and glycogen synthase activity.¹¹

In one study, a factor called methyl hydroxyl chalcone polymer, which was isolated from cinnamon, was observed to increase insulin-dependent glucose metabolism approximately 20-fold *in vitro*. Safdar et al¹⁰ explained that methyl hydroxyl chalcone polymer made fat cells more responsive to insulin by activating the enzyme that causes insulin to bind to cells and inhibiting the enzyme that blocks the process leading to maximal phosphorylation of the insulin receptor, which is associated with increased insulin sensitivity.

Cinnamon is rich in polyphenolic components, and it was shown that an intake of 500 mg/d for 12 weeks decreased oxidative stress and improved impaired fasting glucose.¹²

Another finding also indicated that the consumption of 500 mg/d of a specific aqueous extract of cinnamon (Cinnulin PF) for a 12-week period significantly improved some metabolic syndromes such as fasting blood sugar, systolic blood pressure, and body composition, and because there is a relationship between metabolic syndrome and cardiovascular disease, these results can have an important effect for the improvement of public health.¹³

4. Anticholesterol

The compounds present in *Cinnamon* (肉桂 ròu guì) have shown to be beneficial for glucose uptake, insulin regulation, and blood lipid profile. A study was performed on patients with type 2 diabetes consuming cinnamon. The results showed that there were significant decreases in fasting serum glucose (18–29%), triglycerides (23–30%), total cholesterol (12–26%), and low-density lipoprotein cholesterol (7–27%) for patients who consumed 1 g, 3 g, or 5 g of cinnamon for 40 days.^{4,14}

5. Antioxidant

Polyphenols, which are among the natural dietary antioxidants found in *Cinnamon* (肉桂 ròu guì), have been shown to reduce oxidative stress in a dose-dependent manner via the inhibition of 5-lipoxygenase.¹⁵ Specific antioxidant phytochemicals that have been identified in cinnamon include epicatechin, camphene, eugenol, gamma-terpinene, phenol, salicylic acid, and tannins.¹⁶

Today, natural antioxidants are the focus of considerable attention and efforts are ongoing for the replacement of synthetic ones. In addition, these natural antioxidants can be formulated as functional foods and can help prevent oxidative damage from occurring in the body.⁴

6. Cancer

Plants have been used as a source of effective anticancer agents, and 60% of currently used anticancer drugs are derived from natural sources such as plants, marine organisms, and microorganisms.¹⁷ Several studies have been conducted on herbs that possess anticancer properties and these have been used as potent anticancer drugs.¹⁷ Recently, the antitumor activity of *Cinnamon* (肉桂 ròu guì) has been shown to inhibit the proliferation of several human cancer cell lines including breast, leukemia, ovarian, and lung tumor cells.¹⁷

It is well known that metastasis, one of the major causes of mortality in cancer, involves cell adhesion, invasion, and migration.

In one study, the effect of CE on the migration of SiHa (human cervical tumor) cells was examined. The result showed that cinnamon significantly reduced the migration of cancer cells, demonstrating its potential use as an anticancer drug in cervical cancer.¹⁷ CE, which contains a mixture of polyphenols together with cinnamaldehyde as the major bioactive component, plays a therapeutic role in cervical cancer cells by depolarization of the mitochondrial membrane potential, resulting in cellular apoptosis.¹⁷

In another study, CE was shown to inhibit the growth of hematologic tumor cells. Moreover, the treatment of melanoma cell lines with CE also induced a decrease in Cox-2 and HIF-1 α expression in the tumor tissues that mediate the potent antitumor activity of cinnamon. Cox-2 and HIF-1 α are well known as master regulators in cancer progression to aggravate angiogenesis and metastasis.¹⁸

The use of herbal medicine is supported by scientific studies for potent anticancer drugs. However, the use of an herbal medicine as an anticancer agent requires extensive research and strict criteria for standardization, safety, quality control, toxicity, and clinical trials.¹⁸

7. Angiogenesis inhibitor

Angiogenesis is the development of new blood vessels in a mechanism used by tumors to promote growth and metastasis. VEGF is one of the most critical and specific angiogenesis factors. Various approaches for the inhibition of VEGF are currently being reviewed and studied in clinical trials.⁵

Currently available anti-VEGF agents have been shown to have serious side effects such as hypertension, bleeding, and gastrointestinal perforation. There has been a renewed interest in identifying natural anti-VEGF agents, given their advantage of being safe for human use. Additionally, consumption of a plant-based diet has been effective in the prevention of cancer development.⁵

One study has shown that *Cinnamon* (肉桂 ròu guì) is a natural diet-derived source of anti-VEGF agents.⁵ It was found that cinnamon and its components (such as type A procyanidin trimer and tetrameric procyanidins) effectively inhibited the activity of VEGFR2 kinase as well as VEGF signaling in endothelial cells. The various aspects of angiogenesis, including endothelial cell proliferation, migration, as well as tumor-induced blood vessel formation in mice, were inhibited by CE. Further research is required to determine the major components responsible for the anti-angiogenic property of CE. As a natural inhibitor of VEGFR2, CE has the potential to be a routine diet-based strategy for cancer prevention and treatment.⁵

8. Alzheimer's disease

Alzheimer's disease (AD) is a progressive, neurodegenerative, and irreversible brain disorder with symptoms such as memory loss, confusion, impaired judgments, and loss of language skills.¹⁹ Many studies have proven that the accumulation of soluble oligomeric assemblies of β -amyloid polypeptides [amyloid-beta (A β)] play a key role in AD development.¹⁹ Compounds made from natural sources have been reported in many studies to inhibit the formation of A β plaques.¹⁹ A study found that *Cinnamon* (肉桂 ròu guì) extract (CEppt) inhibits the formation of toxic A β oligomers and prevents the toxicity of A β on neuronal PC12 cells. In another study, the oral administration of CEPpt to an aggressive AD transgenic mice model led to the reduction of plaques and improvement in cognitive behavior. The results showed that the use of natural compounds such as cinnamon can inhibit toxic oligomeric A β species formation in AD.¹⁹

Extracellular plaques (such as A β) and also intracellular neurofibrillary tangles of tau can cause the emergence of AD. Tangles are formed in later stages in relation to amyloid formation and are effective in the process of neurodegenerative progression.⁹

Most of the drugs used for the prevention or treatment of AD are aimed to inhibit cholinesterase function or amyloid plaque formation. The agents capable of preventing the tau aggregation may be a key factor in the development of new drugs.⁹

Tau is a protein that displays little to no structure in regular conditions, and the molecule contains significant polyrich regions. The effects of an aqueous extract of cinnamon containing proanthocyanidins was examined on tau aggregation, and it was found that the extract of the whole cinnamon effectively inhibited the aggregation of human tau *in vitro*, and this could be attributed to both proanthocyanidin tinner and cinnamaldehyde in CE.⁹

9. Antigastric ulcer

Helicobacter pylori is a major cause of chronic gastritis, peptic ulceration, and gastric cancer. Probiotic bacteria have been used for the inhibition of *H. pylori* and intestinal pathogens, prevention of inflammatory bowel diseases, reduction of the risks associated with mutagenicity and carcinogenicity, and improvement of the immune system.²⁰ Yogurt containing bifidobacterium and *Lactobacillus acidophilus* can suppress the growth of *H. pylori* in infected clinical patients.²⁰ Behrad et al²⁰ showed that cinnamon yogurt exerted the strongest inhibitory effect on *H. pylori* growth *in vitro* in comparison with licorice yogurt and control yogurt for both strains tested.²⁰

The study showed that cinnamon preparations traditionally used for the treatment of gastrointestinal disorders are effective on suppressing *H. pylori* with little or no adverse reactions. These preparations could provide a potent anti-*H. pylori* effect that overcomes the problem of resistance to antibiotic treatments.²¹

Simethicone is the medication most commonly used in treating dyspepsia. A study showed that the use of a cinnamon stomachic mixture is effective in alleviating the symptoms of dyspepsia by 70% and is similar to simethicone. The longer use of cinnamon stomachic mixture can increase the favorable response up to 80%, and it is considered safe, effective, and affordable compared to simethicone.²²

10. Antibacterial, antifungal

Cinnamon (肉桂 ròu guì) oil has the most potential bactericidal properties.¹⁶ The antibacterial activity of cinnamon oil has been demonstrated, and it has been shown that cinnamon oil alone or in combination with triclosan, gentamicin, or chlorhexidine can effectively inhibit biofilm formation, detach existing biofilms, and kill bacteria in biofilms of clinical *Staphylococcus epidermidis* strains. Another advantage of the essential oil over antibiotics may be that bacteria do not develop resistance to essential oils.²³ However, further study is needed to clarify the complex mode of action of cinnamon and its components against biofilms of *S. epidermidis* and other clinically relevant microbes.²³

Cinnamaldehyde is one of the main components of cinnamon oil.²³ Cinnamaldehyde has been shown to destroy the cytoplasmic membrane of both Gram-positive and Gram-negative bacteria and induce depletion of the intracellular ATP concentration. Cinnamaldehyde inhibits the growth of fungi, including yeasts, filamentous molds, and dermatophytes, as well as the eggs and adults of human head lice, *Pediculus humanus capitis*. Aqueous and alcohol extracts of cinnamon also have demonstrated antibacterial effects against *H. pylori*.¹⁵

Cinnamomum osmophloeum Kaneh (Lauraceae), named as “indigenous cinnamon tree,” is one of the hardwood species that possesses significant antifungal activity. *C. osmophloeum* is an endemic tree that grows in Taiwan’s natural hardwood forest, and the chemical constituents of the essential oils found in its leaves are similar to those of *C. cassia* bark oil. The leaf essential oils of *C. osmophloeum* were found to have strong inhibitory effects on the growth of fungi.²⁴ Cinnamaldehyde, the major compound in leaf essential oils, had the strongest antifungal activities compared with the other components. People can simply harvest the leaves to obtain a large amount of natural bioactive essential oils or cinnamaldehyde without debarking the trees; this could potentially lead to the development of wood decay preservation agents or fumigants in the future.²⁴

11. Nematicidal

There is a growing public concern for the environmental effects of pesticides on human health and the increase of undesirable effects on nontarget organisms by repeated applications of chemical pesticides.²⁵ Natural alternative sources such as plant essential oils have been suggested because they degrade to nontoxic products and have few harmful effects on nontarget organisms and the environment.²⁵

Pine wood nematode, *Bursaphelenchus xylophilus*, is associated with dead or dying conifers such as pines throughout North America and Japan.²⁵ In one study, the nematicidal activities of two cassia oils and four *Cinnamomum* (肉桂 ròu guì) oils were evaluated, and the results showed that they are active against adult *B. xylophilus* and might be a good choice as a natural control agent.²⁵ The study showed that cinnamaldehyde is the most toxic compound against adult *B. xylophilus*, followed by (*E*)-2 methoxy cinnamaldehyde and (*E*)-cinnamic acid.²⁵

12. Acaricidal and repellent effect

House dust mites (*Dematophagoides farina*, *Dematophagoides pteronyssinus*) are a major source of allergy in human households causing symptoms such as atopic dermatitis, asthma, perennial rhinitis, and even infant death syndrome. The use of chemical methods or treatment with repellents such as DEET and benzyl benzoate are related to the control of mite species.²⁶ However, the repeated use of these chemicals has resulted in the development of resistance against such chemicals and raised concerns regarding their effect on human health.²⁶

It is more effective to repel than to kill house mites because the allergen does not come from living dust mites but from their dead bodies or fecal particles.²⁶ To control house dust mites, it is better to find natural repellent materials such as plants with a range of bioactive chemicals.²⁶ The concentrated essential oil of *Cinnamomum* (肉桂 ròu guì) has been tested for its acaricidal and repellent effect against house dust mites and has been shown to be a very effective material for this particular purpose, and could also reduce chemical resistance and harmful effects on human health.²⁶

13. Safety

Cinnamomum (肉桂 ròu guì) has been used in food preparation and as medicinal remedies from ancient times. It is the most frequently consumed spice and is both safe and relatively inexpensive.¹⁴ In one study, the intake of up to 6 g/d of *C. cassia* for > 40 days did not show any adverse effects. The most common adverse effects related to the excessive use of cinnamon were irritation and allergic reaction in skin or mucus membranes.¹⁵

According to the United States Food and Drug Administration, *Cinnamomum* spp., including common cinnamon and cassia cinnamon, are generally safe and well tolerated in amounts commonly found in food.¹⁵ Cinnamon oil has also been listed and recognized as safe and is exempt from toxicity data requirements by the US Environmental Protection Agency.²⁵

14. Conclusion

Cinnamomum (肉桂 ròu guì) has been used as a spice for flavoring foods and as a natural traditional remedy in many cultures throughout the world. From the findings of various studies, it can be concluded that cinnamon possess many specific functional properties such as antioxidant, anti-inflammatory, antimicrobial, and acaricidal activities, in addition to its medicinal values in relieving and treating a number of serious illnesses such as diabetes, hyperlipidemia, gastrointestinal disorders, AD, and cancer. Further studies are required to determine the effectiveness of the active principles of cinnamon and their therapeutic effects in the prevention and treatment of such diseases.

Conflict of interest

I Rafie Hamidpour Sign on behalf of all authored and as Corresponding authored that we have no conflict of interest with anyone and any agency at all.

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