Advances in Experimental Medicine and Biology 929

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Drug Discovery from Mother Nature

Springer

Advances in Experimental Medicine and Biology

Volume 929

More information about this series at http://www.springer.com/series/5584

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ISSN 0065-2598 ISSN 2214-8019 (electronic)
Advances in Experimental Medicine and Biology
ISBN 978-3-319-41341-9 ISBN 978-3-319-41342-6 (eBook)
DOI 10.1007/978-3-319-41342-6

Library of Congress Control Number: 2016947753

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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Cinnamon and Chronic Diseases

Mitra Hariri and Reza Ghiasvand

Abstract Cinnamon (*Cinnamomum zeylanicum* and Cinnamon cassia), the eternal tree of tropical medicine, belongs to the Lauraceae family and is one of the most important spices used daily by people all over the world. It contains a lot of manganese, iron, dietary fiber, and calcium. Cinnamon contains derivatives, such as cinnamaldehyde, cinnamic acid, cinnamate, and numerous other components such as polyphenols and antioxidant, anti-inflammatory, antidiabetic, antimicrobial, anticancer effects. Several reports have dealt with the numerous properties of cinnamon in the forms of bark, essential oils, bark powder, and phenolic compounds, and each of these properties can play a key role in human health. Recently, many trials have explored the beneficial effects of cinnamon in Alzheimer's disease, diabetes, arthritis, and arteriosclerosis, but still we need further investigations to provide additional clinical evidence for this spice against cancer and inflammatory, cardioprotective, and neurological disorders.

Keywords Cinnamon · Cinnamaldehyde · Cinnamate · Cinnamic acid · Chronic disease

1 Introduction

According to Malaysian researchers and researchers from the United States (US) Department of Agriculture, cinnamon is one of the most important spices used daily by people all over the world. It contains about 38 % of your daily requirement

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S.C. Gupta et al. (eds.), *Drug Discovery from Mother Nature*,
Advances in Experimental Medicine and Biology 929,
DOI 10.1007/978-3-319-41342-6_1

of manganese and contains 10 % of your daily requirement for iron and dietary fiber [1]. It also is high in calcium. Beyond this, there are several other reasons why cinnamon is a must-have spice. Cinnamon primarily contains vital oils and other derivatives, such as cinnamaldehyde, cinnamic acid, cinnamate, and numerous other components such as polyphenols [2]. In addition to being an antioxidant, anti-inflammatory, antidiabetic [3], antimicrobial [4], anticancer [5], lipid-lowering [6], and cardiovascular disease-lowering compound [7], cinnamon has also been reported as useful for metabolic syndrome, insulin sensitivity, polycystic ovary syndrome, increasing lean body mass, and gastric emptying [8, 9]. It is useful against neurological disorders, such as Parkinson's and Alzheimer's diseases [10].

Cinnamon is a common ingredient used in tea for nausea during pregnancy. It is also used following delivery to decrease hemorrhage. The health benefits of cinnamon can be attributed to its antibacterial, antifungal, antimicrobial, astringent, and anticlotting properties [11].

Researchers in Europe, the Middle East, India, China, and the United States are not necessarily using the same type of cinnamon when they do their research. This sometimes leads to confusion and to contradictory research findings. There is overwhelming evidence that cinnamon has numerous therapeutic benefits; however, these benefits are not universally reported by researchers in all countries. Also, cinnamon powder rapidly loses its freshness, which means that its active components may volatilize into the air. Thus, research that was done with different types of cinnamon, with an old inventory of cinnamon, with irradiated cinnamon, or cinnamon that was given with certain pharmaceutical drugs may not produce the same results when compared to other cinnamon studies.

In the United States, the word cinnamon can refer to spices that come from various parts of the world and from quite different varieties of plants. Thus, not all cinnamon or all cinnamon essential oil is the same.

This is important, because the different plant varieties do not have the same composition of active components. Ground cinnamon and cinnamon sticks are made from the bark of several related tropical evergreen trees in the Lauraceae (laurel) family. Cinnamon essential oil is distilled from the bark, stems, and leaves of these trees [12].

Most cinnamon spice sold is actually not true cinnamon. It is a closely related spice called cassia. Cassia (*Cinnamomum cassia*): also known as "Chinese Cinnamon," is what is usually sold as cinnamon.

True cinnamon is Ceylon Cinnamon (*Cinnamomum zeylanicum* or sometimes *Cinnamomum verum*). This "true cinnamon" is the preferred variety in Europe and Mexico. It is milder than cassia, but has a more subtle and complex flavor than cassia.

Most of the scientific studies that we will review in this chapter have used ground cinnamon or specific components of cinnamon that have been derived from cinnamon by use of a water process. Some studies have used essential oil of cinnamon, which is produced from distillation.

Conflict between studies about useful effect of cinnamon may be related to various methodological factors such as the use of different varieties of cinnamon, to the use of an old stock of ground cinnamon, to using an inappropriately high or low

dose of cinnamon, to using irradiated cinnamon, to the simultaneous use of pharmaceutical medications, or to other problems in research methodology.

2 Physiochemical Properties of Cinnamon

Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils [13] (Table 1). Singh et al. [14] reported that the spicy taste and fragrance are due to the presence of cinnamaldehyde and occur due to the absorption of oxygen. As cinnamon ages, it darkens in color, improving the resinous compounds [14]. Sangal reported various physiochemical properties of cinnamon (Table 2). The presence of a wide range of essential oils, such as trans-cinnamaldehyde, cinnamyl acetate, eugenol, L-borneol, caryophyllene oxide, b-caryophyllene, L-bornyl acetate, E-nerolidol, -cubebene, -

Table 1 Chemical constituents of different parts of cinnamon

Part of the plant	Compound
Leaves	Cinnamaldehyde: 1.00–5.00 % Eugenol: 70.00–95.00 %
Bark	Cinnamaldehyde: 65.00–80.00 % Eugenol: 5.00–10.00 %
Root bark	Camphor: 60.00 %
Fruit	Trans-Cinnamyl acetate (42.00–54.00 % and caryophyllene (9.00–14.00 %)
C. zeylanicum buds	Terpene hydrocarbons: 78.00 % alpha-Bergamotene: 27.38 % alpha-Copaene: 23.05 % Oxygenated terpenoids: 9.00 %
C. zeylanicum flowers	(E)-Cinnamyl acetate: 41.98 % Trans-alpha-Bergamotene: 7.97 % Caryophyllene oxide: 7.20 %

Table 2 Physicochemical properties of cinnamon

Parameter	Leaf oil	Bark oil
Specific gravity (20 °C)	1.030–1.050	1.010–1.030
Optical rotation (°) (20 °C)	1·96′–0.40′	Slightly laevorotatory
Refractive index (20 °C)	1.529–1.537	1.573–1.591
Aldehyde content	4 %	65–76 %
Eugenol content	77.3–90.5 %	4–10 %
Solubility characteristics	Soluble in 1.5 volumes of 70 % alcohol	Soluble in 2.0–3.0 volumes of 70 % alcohol

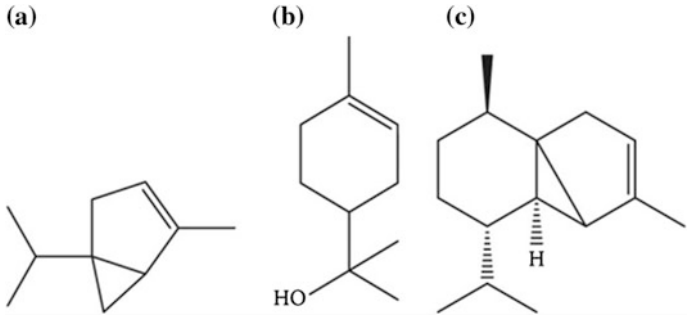

Fig. 1 Endocyclic double bond-containing compounds

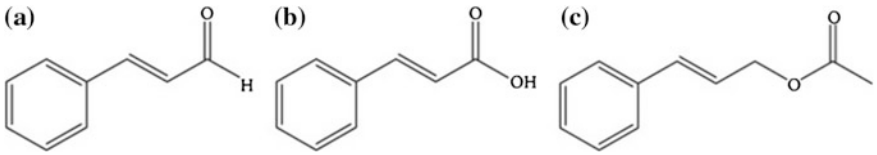

Fig. 2 Cinnamyl group-containing compounds

terpineol, terpinolene, and -thujene, has been reported. The chemical structures of some important constituents of cinnamon are shown in Figs. 1 and 2.

3 Modulation of Cell Signaling Pathways by Cinnamon

New evidence recently demonstrated that a mixture of polyphenols from an aqueous extract of cinnamon possessed anticancer properties by blocking cell cycle progression of leukemic cell lines at the G2/M phase [15]. They indicated treatment of asynchronously growing cells with cinnamon caused an enhancement of cell percentage in G2/M that is because of an increase in activated p38 MAPK by phosphorylation of p38 MAPK in cinnamon-treated cells compared with the non-treated control cells.

Cinnamon has been said to have an insulin-mimetic and insulin-sensitizing action [16]. *Cinnamon cassia* plays a significant role in phosphorylation of signaling proteins and enhancement of expression of insulin-sensitive glucose transporters, which results in mitigation of the insulin resistance [16, 17]. Eugenol component in cinnamon oil can inhibit peroxynitrite-induced nitration and lipid peroxidation in in vitro models [18].

A recent study reported that 2′-hydroxycinnamaldehyde isolated from *C. cassia* bark exhibited an inhibitory effect on the production of nitric oxide by inhibiting the activation of the nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB), indicating that this substance can potentially be used as an

anti-inflammatory agent [19]. The ethanolic extract of *C. cassia* showed significant anti-inflammatory effects by reducing the activation of Src/spleen tyrosine-kinase (Src/Syk)-mediated NF-κB [20, 21]. Various compounds contained in *Cinnamomum ramulus* showed anti-inflammatory effects by suppressing the expression of inducible nitric oxide synthesis (iNOS), cyclooxygenase-2 (COX-2), and nitric oxide (NO) production in the central nervous system (CNS). Cinnamophilin is a novel thromboxane A2 receptor antagonist isolated from *Capillaria philippinensis* [22]. A study reported that cinnamophilin confers protection against ischemic damage in rat brains when administered at 80 mg/kg at different time intervals (2, 4, and 6 h) after insult. The effects were found to have a considerable effect (by 34–43 %) on abridged brain infarction [23] and further enhance neurobehavioral outcomes. Cinnamophilin also dramatically condenses the oxygen glucose deprivation-induced neuronal damage in organotypic hippocampal slices in experimental rats. A substance called procyanidin type A trimer (trimer 1) isolated from cinnamon's water-soluble extract showed that trimer 1 may reduce cell swelling by controlling the movement of intracellular calcium [Ca^{2+}] [24]. Trimer 1 also considerably alleviates the oxygen glucose deprivation-induced diminishing effects on glutamate uptake. The protective effects of trimer 1 in attenuating the diminution in glutamate uptake are possibly arbitrated via their effects on the mitochondria.

4 Role of Cinnamon in Chronic Diseases

4.1 Cinnamon Used to Reduce Blood Sugar in Diabetics

C. zeylanicum [true cinnamon] is a popular kitchen spice widely investigated for insulin potentiating effects. Researchers in India investigated water-soluble polyphenols (oligomeric procyanidins) to evaluate their effect on insulin and blood sugar [25]. The polyphenol-enhanced extracts were shown to be safe, while offering good antioxidant potential. The diabetic rats that were treated with the polyphenol-enhanced extracts experienced reduced blood sugar during the 30-day experiment [3]. The same benefit was obtained by a group of 15 human volunteers with chronically elevated fasting blood sugar levels who were not using medication to control blood sugar [26].

A review of studies conducted by California researchers examined cinnamon's effect on blood sugar and lipid (blood fat) levels in diabetic patients. Ten random control trials with a total of 543 patients were examined. Cinnamon doses of 120 mg per day to 6 g per day were given for a period of 4–18 weeks. (6 g is slightly more than 2 teaspoons.) Among the findings was an average reduction in fasting blood sugar levels of 24.59 mg/dL. The reductions ranged from 40.52 to 8.67 mg/dL depending on the study. The studies did not affect hemoglobin A1c levels [27].

A group of researchers from England investigated the blood glucose lowering effect of cinnamon on HbA1c, blood pressure, and lipid profiles in poorly controlled type 2 diabetic patients. Fifty-eight type 2 diabetic patients aged 45–65 years of age, who were being treated only with hypoglycemic agents and who had HbA1c test results of more than 7 % were randomly assigned to receive either 2 g of cinnamon or placebo per day for 12 weeks. At the end of the study, the cinnamon group had an 8.22 % average reduction in HbA1c. Average blood pressures were also significantly reduced [28]. Systolic blood pressure fell from 132.6 to 129.2 mmHg, and the diastolic pressure fell from 85.2 to 80.2 mmHg.

A significant reduction in fasting plasma glucose, waist circumference, and body mass index was observed at week 12 compared with the values at the beginning of the study for the cinnamon group. However, these changes were not significant when compared to the placebo group. The researchers concluded that intake of 2 g (slightly less than a teaspoon) of cinnamon for 12 weeks significantly reduces the HbA1c and blood pressure for poorly controlled type 2 diabetes patients. Cinnamon supplementation could be considered as an additional dietary supplement option to regulate blood glucose and blood pressure levels along with conventional medications to treat type 2 diabetes mellitus [29].

In a study conducted by Chinese researchers, the effects of giving cinnamon polyphenols to diabetic mice were investigated. The mice were fed a high-sugar, high-fat diet. Their results were similar with other studies, which produced reductions in blood sugar, blood insulin levels, and markers of oxidative stress. What was even more interesting was that damage to the pancreatic beta cells in the islets of the pancreas was ameliorated. These benefits may have actually resulted from the repair of pancreatic beta cells and from improvements in their antioxidative capacity, which came from the use of cinnamon polyphenols [30].

Studies which employed the largest doses of cinnamon relative to carbohydrate in the test meal (carbohydrate/cinnamon ratio of 15 or lower [31, 32]) appear to have had the most potent effects on reducing postprandial glycemia [33]. Recent data indicate that the addition of 3 g cinnamon to a low-fat rice pudding test meal had no significant effect on postprandial glycemia in healthy individuals [34]. However, cinnamon did significantly lower serum insulin levels and increase glucagon-like peptide-1 (GLP-1) concentrations, a gastric inhibitory (GI) peptide, which has been shown to increase glucose-dependent secretion of insulin, delay gastric emptying (GE) and reduce glucose absorption and postprandial glycemia [35, 36].

Scientists from Spain also conducted research on polyphenols. They noted that polyphenols have been reported to prevent chronic diseases such as cardiovascular disease, cancer, diabetes, and neurodegenerative diseases [37]. In one study, rats were fed a high-fat and high-sugar diet and were given various polyphenolic plant extracts. They tested extracts from almond, apple, cinnamon, orange blossom, hamamelis, lime blossom, grape vine, and birch. Rats were treated for 56–64 days. Their results showed that only apple and cinnamon extracts were finally considered as potentially important anti-obesity extracts due to their ability to reduce body fat.