Biomedical Effects of Cinnamon

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Cinnamon, appreciated for centuries for its peculiar flavor and aroma, is the dried brown colored inner bark of an evergreen tree of the laurel family. Cinnamon is used by people all over the world for cooking (spice and flavoring agent), in perfumes industry , and in medicinal products.

Phytonutrients Phytochemicals Cinnamon Lipinski's rule of 5 Veber's rules Ghose filter Anticancer Antioxidant Antimicrobial Anti-inflammatory Immunomodulatory

1. Botanical Description

The *Cinnamomum* genus, which the cinnamons are part of, belongs to the laurel family (*Lauraceae*), and it includes about 250 evergreen aromatic trees and shrubs [1]. The Cinnamomum verum, commonly called "true" cinnamon or Ceylon cinnamon, is native of Sri Lanka and India. However, most of the spice sold as cinnamon in the United States comes from another cinnamon species, *Cinnamonum cassia*, also called Chinese cinnamon, because of its geographical origin in the mountains of China [2]. The botanical features of *C. verum* are summarized as trees (up to 50 ft) with long lance-shaped leaves, small yellow flowers organized in a cluster, and ovoid-shaped fruits. The botanical features of *C. cassia* are summarized as trees (up to 65 ft) with thin lance-shaped leaves, white flowers, axial inflorescences, and globose drupe fruits [3].

2. Phytochemicals

Qualitative phytochemical screening of a methanolic extract from the bark of *C. verum* showed the presence of all four categories of secondary metabolites. It has also been shown that the phytoprofiles of the cinnamon extracts depend on the botanical part of the tree used for extraction. At the same time, essential oils from the *C. verum* bark mainly contain cinnamaldehyde and linalool, the flower and fruit extracts are enriched in (E)-cinnamyl acetate, and eugenol is the main compound of leaf extracts [4][5]. The bark of the cinnamon tree has also been reported to contain coumarin, a benzenoid lactone. *C. cassia* that is particularly rich in coumarin (3462.0 mg/kg in *C. cassia* vs. 12.3 to 143.0 mg/kg for *C. verum*) [6]. The solvent and temperature should also be carefully selected according to the molecule one wishes to extract; for example, water is a better solvent for extracting the phenols from *C. verum* than polar organic solvents at 200 °C [7]. For Klejdus et al., however, the factor for efficient extraction mainly depends on the state of the destruction of the cinnamon cell structures during the extraction protocol [8].

3. Biomedical effects

3.1. Anticancer

In vitro and in vivo studies by Yang et al. showed that the essential oil of cinnamon extracted from the bark of *C. cassia* significantly inhibits the growth of head and neck cancer cells and tumors in mice. The antitumor activity was believed to be mediated by the trans-cinnamaldehyde acting as a competitive inhibitor of the epidermal growth factor receptor (EGFR). This kinase is often mutated and overexpressed in many tumors and regulates key cancer metabolic pathways, such as proliferation, apoptosis, angiogenesis, and tumor invasiveness [9]. Similarly, Koppikar et al. reported that aqueous bark extract from *C. cassia* inhibits the growth of cervical carcinoma *cells* in a dose-dependent manner (IC_{50} = 80 µg/mL) by apoptosis and loss of mitochondrial membrane potential. The treated cells exhibited reduced migration potential by the downregulation matrix metallopeptidase 2 (MMP-2) and the EGFR [10]. Furthermore, Perng et al. demonstrated that *C. verum* component 2-methoxy-cinnamaldehyde had an antiproliferative effect on human hepatic adenocarcinoma both in vitro (IC_{50} = 25.72 µM for 48 h) and in vivo (10–20 mg/kg/d administration of 2-methoxy-cinnamaldehyde). The targeted metabolisms determined by this group were similar to the previous studies (i.e., mitochondrial apoptotic pathway) due to the activation of caspase-3 and -9, a sub-G1 phase cell-cycle arrest, and the downregulation of nuclear factor- Kβ (NF-Kβ) [11].

3.2. Antioxidant

A study on the peripheral blood mononuclear cells of rheumatoid arthritis patients showed that cinnamaldehyde and eugenol significantly reduced the levels of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6. Additionally, these patients showed enhanced activity of superoxide dismutase, glutathione peroxidase, and catalase enzymes, suggesting an antioxidant effect [12]. In the same way, Davaatseren et al. demonstrated that trans-cinnamaldehyde diminishes the production of nitric oxide and reactive oxygen species in macrophages [13]. Furthermore, cinnamon capsules were orally administered for 12 weeks in a small controlled clinical trial to women with polycystic ovary syndrome. This study demonstrated that cinnamon improved the antioxidant status and lipid profile of these patients by decreasing serum levels of malondialdehyde (derived from lipid peroxidation), total cholesterol, triacylglycerol, and increasing high-density lipoproteins [14].

3.3. Antimicrobial

3.3.1. Antiviral

In vitro studies concluded that essential oil extracts from the leaves of *C. verum* extract had an antiviral effect in cells infected with influenza type A (*H1N1*) [15]. Similarly, a study by Moshaverinia and colleagues suggests that a hydroalcoholic extract of *C. verum* at 1 mg/mL significantly reduces the viral titer of the human herpes simplex virus type 1 -infected cells [16]. Furthermore, in silico studies by Kulkarni et al. suggest that cinnamaldehyde possesses a strong affinity to the S1 receptor binding domain of the spike (S) glycoprotein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Cinnamaldehyde could therefore be an efficient pharmacological agent to inhibit the entry of the virus into the host cells [17].

3.3.2. Antibacterial

Ahmed et al. showed that aqueous, methanolic, and acetone extracts from *C. verum* bark exerted significant antibacterial effects on *S. aureus*, *P. aeruginosa*, and *E. coli.* The inhibitory effect of the extracts was believed to be mediated by cinnamaldehyde [18]. Furthermore, in an in vivo study conducted on aquatic pathogens in zebrafish, Faikoh et al. concluded significant antimicrobial effects of liposome-encapsulated cinnamaldehyde in fish infected by *A. hydrophilia*, *V. vulnificus*, S. *agalactiae*, *V. parahaemolyticus*, and *V. alginolyticus.* The antimicrobial activity of cinnamaldehyde was associated with a decrease in the expression of pro-inflammatory interleukins, i.e., -1β, -6, -15, and an increase in anti-inflammatory interleukin-10 [19].

3.3.3. Antifungal

In a 2019 study, Kowalska et al. demonstrated the antifungal properties of 1% (*v*/*w*) aqueous *C. verum* bark after a 6-day treatment against *Botrytis cinerea*, the mycelium responsible for the grey mold disease in tomato plants [20]. Furthermore, cinnamon seems to inhibit the growth of the microorganisms of the *Candida* family, which are responsible for most of the fungal diseases in humans. In a clinical trial study, Wang et al. showed that an oil extract from *C. verum* significantly inhibited the growth of three species of *C. albicans* (minimum inhibitory concentration (MIC) = 0.064 mg/mL), *C. tropicalis* (MIC = 0.129 mg/mL), and *C. krusei* (MIC = 0.129 mg/mL) [21]. Additionally, a study conducted on guinea pigs suggests that topical treatments with methanolic extracts of *C. verum* inhibit the growth of *M. canis* and *T. mentagrophytes*, two fungi involved in skin infections in animals and humans [22].

3.4. Anti-Inflammatory

A study conducted in an in vitro human skin model for chronic inflammation and fibrosis suggests that a cinnamon concentration of 0.0012% (v:v) significantly inhibits the expression of genes involved in the inflammation and immune DNA damage responses [23]. The authors attributed the effect to cinnamaldehyde and cinnamyl acetate, the two main chemical compounds present in the extract. Likewise, Gunawardena et al. have demonstrated that *C. verum* and *C. cassia* extracts inhibited the release of pro-inflammatory nitric oxide molecule and tumor necrosis factor protein in activated macrophages. From these results, the ethanolic extract from *C. verum* showed more activity than the aqueous extract (IC_{50} = 36.4 and 122 µg/mL, respectively). The phytochemicals with more potent anti-inflammatory effects were E-cinnamaldehyde and o-methoxycinnamaldehyde [24]. Furthermore, in an in vivo study, 4.5 mL/kg of the ethanolic cinnamon extract was orally administered to a mouse model for colitis. The treated mice exhibited significantly enhanced resorption of their colon fibrotic tissues and reduction in the fibrotic score associated with a decrease in the expression of extracellular matrix proteinases [25].

3.5. Immunomodulatory

As previously described, cinnamon has antioxidant, antimicrobial, and anti-inflammatory properties leading to improved immune response. Several studies have concluded that the phytochemicals present in cinnamon extracts inhibit the immune response associated with allergies. Mast cells, key effectors in allergic diseases, are considered

promising therapeutic targets. Hagenlocher et al. have shown that cinnamon extracts decrease the release and expression of pro-inflammatory mast cell mediators such as β-hexosaminidase; cytokines CXCL8; and chemokine ligand 2, 3, and 4. From this study, the anti-allergic properties are believed to be mediated by cinnamaldehyde [26]. Similar results have been found in human and murine models for allergic inflammation. Cinnamon extracts significantly inhibited the allergen-specific T-cell proliferation as well as TH1 and TH2 cytokine production [27]. Recent studies have also shown the possibility of cinnamon application in COVID-19 symptoms reduction and as preventive treatment through immune system strengthening [28]. However, further research should focus on the safety and route of cinnamon administration to maximize the therapeutic effects.

3.6. Predicted gastrointestinal (GI) absorption

The physicochemical properties for the main five most bioactive phytochemicals in cinnamon ((E)-trans-cinnamaldehyde, (E)-cinnamyl acetate, eugenol, cuminaldehyde, protocatechuic Acid) were calculated based on the combination of Lipinski's, Ghose's, and Veber's rules (L-Ro5, GF, VR), summarized as follow: molecular weight (160-500 Da); hydrogen bond donors ≤5; hydrogen bond acceptors ≤10; molar refractivity (40-130); lipophilicity (-0.4–5.6); rotatable bonds ≤ 10: polar surface area <140; total number of atoms (20-70) [29],[30],[31],[32]. These are described as an approximation for the pharmacokinetics of a molecule in the body. From cinnamon's phytochemicals, 40% ((E)-cinnamyl acetate and eugenol) comply with all of the "drug-likeness" rules. The 60% ((E)-trans-cinnamaldehyde, cuminaldehyde, protocatechuic acid) just violate the GF of MW = 160 – 480 Da. Both, (E)-trans-cinnamaldehyde and protocatechuic acid violate TNA and only the latest violates the molar refractivity. Accordingly, protocatechuic acid is predicted to have the lowest probability of absorption in the GI, followed by ((E)-trans-cinnamaldehyde, and then, cuminaldehyde.

4. Contraindications

While cinnamon possesses a large spectrum of medicinal properties, its regular consumption can also lead to adverse health effects. Due to its cellulose fiber composition, which does not dissolve or biodegrade in the lungs, cinnamon inhalation or its dry consumption can trigger a hypersensitive airway and irritate mucous membranes in the lungs [33]. Due to the apoptotic effect of the cinnamon component cinnamaldehyde on B- and T-cells, the consumption of cinnamon is contraindicated in patients under an immunotherapy treatment [34]. The consumption of cinnamon supplements should be avoided during pregnancy since cinnamon can lead to uterine contractions, miscarriage, or premature labor [35]. Importantly, studies conducted both in vitro and in vivo suggest that the toxic compound coumarin, found abundantly in *C. cassia*, and less in *ceylon* cinnamon (~250 times less), is a potential carcinogen to individuals with mutations of the cytochrome P450 2A6 [36].

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