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Review Article

Antioxidant and anti-inflammatory effects of *Cinnamomum* species and their bioactive compounds: An updated review of the molecular mechanisms

Farzaneh Davoudi [1], Elham Ramazani [2]

1. Department of Cell and Molecular Biology, Kosar University of Bojnord, Bojnord, Iran
2. Department of Biology, Faculty of Science, Yazd University, Yazd, Iran

ABSTRACT

Introduction: The genus *Cinnamomum* (cinnamon) is one of the well-known aromatic spices throughout the world with numerous medicinal applications. Several beneficial pharmacological properties of cinnamon have been evaluated, including antioxidant, anti-inflammatory, anti-diabetic, anticancer, cardiovascular-disease-lowering, and neurological disorder-improving effects. This review critically evaluates studies regarding the molecular mechanisms underlying the antioxidant and anti-inflammatory properties of cinnamon species.

Methods: Using three online literature databases (PubMed, Scopus, Science Direct), we identified studies describing the antioxidant and anti-inflammatory properties of cinnamon species. A literature search was carried out using a combination of keywords such as ("*Cinnamomum*,") AND ("antioxidant" OR "anti-inflammatory") or other related words. In this review, we evaluated new findings regarding the molecular mechanisms of antioxidant and anti-inflammatory effects of *Cinnamomum* species published from 2005 until December 2022. A total of 38 papers were selected to describe the antioxidant and anti-inflammatory properties of cinnamon species.

Results: Cinnamon species possess antioxidant effects by reducing ROS, MDA, and NO levels, and depleting GSH, decreasing MPO activity, and enhancing the growth of SOD and CAT. Additionally, the suppression of caspase-3 and caspase-9 activity and the upregulation of bcl-2 expression determine the anti-apoptotic effects of cinnamon. Their anti-inflammatory effects are mainly related to the reduction of TNF-α, IL-1β, IL-6, IL-18, IL-10, iNOS, MCP-1, and COX-2, and the inhibition of NF-κB, ERK1/2, p38, and JNK activation.

Conclusion: This review highlighted the antioxidant and anti-inflammatory effects of genus cinnamon and can provide a suitable basis for further pharmacologic surveys and efficient clinical research on cinnamon to obtain new evidence on its benefits for human health.

Keywords:
Cinnamon
Antioxidant
Anti-inflammatory

* Corresponding author: Elham Ramazani, el.ramazani@um.ac.ir
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Introduction

The genus *Cinnamomum* (cinnamon), as a member of the Lauraceae family, comprises about 250 species distributed mostly in Asia and some areas in South and Central America, as well as Australia (Dassanayake and Larsen, 1996; Ramazani et al., 2021; Ramazani rt al., 2020). Cinnamon is one of the most economically important spices worldwide and has been used as a traditional herbal medicine for thousands of years (Mahmoodnia et al., 2017). Mostly, cinnamon can be categorized into two main types including true or Ceylon cinnamon (*Cinnamomum verum and C. zeylanicum*) and cassia cinnamon (*C. aromaticum and C. burmannii*) (Shalaby and Saifan, 2014; Ramazani rt al., 2020). Cinnamon is considered an essential spice due to its significant amounts of manganese, iron, calcium, and fiber (Chan et al., 2014; Tulunay et al., 2015). The most common method for extracting cinnamon essential oil is water vapor distillation (Wong et al., 2014). Cinnamon essential oil is a rich source of bioactive compounds including eugenol (10.5%), α-phellandrene (7.41%), cinnamyl acetate (7.13%), terpinolene (4.49%), safrole (5.69%), cinnamaldehyde (4.25%), α-terpineol (3.21%), Linalol (2.96%) and β-pinene (2.51%), which are listed in Table 1 (Mahmoodnia et al., 2017; Jayaprakasha et al., 2006; Plata-Rueda et al., 2018). Cinnamon bark contains phenolic compounds such as tannin, flavonoid, volatiles, and phenolics, which significantly contribute to its antioxidant activity (Peng et al., 2008; Ervina et al., 2016). Additionally, cinnamon leaf essential oil contains β-cadinene (12.45%), chavicol (6.46%), α-muurolene (8.79%), cis-β-ocimene (5.17%), citral (5.33%), bornyl acetate (4.15%), γ-muurolene (4.34%), linalool (3.31%), α-copaene (3.78%), 3-allyl-6-methoxyphenol (3.17%) methyl cinnamate (3.28%), and geraniol (3.31%), that show anti-inflammatory properties via suppressing the release of inflammatory mediators (Hao et al., 2019). Numerous studies have been reported a wide range of pharmacological activities for cinnamon, including antioxidant, anti-inflammatory, antimicrobial, antifungal, antitumor, ant-diabetic, anti-cholesterol, amelioration of unpleasant menopausal symptoms, gastrointestinal healing, and neuroprotection (Wang, et al., 2005; Jindarat et al., 2006; Elshafie et al., 2012; Csikós et al., 2020; Ramazani et al., 2021; Ramazani et al., 2020). Recently, the ability of cinnamon and its compounds to slow the SARS-CoV-2 progression has been examined (Yakhchali et al., 2021). It should be mentioned that, According to the Food and Drug Administration (FDA), the use of different types of cinnamon in typical amounts in food is generally considered safe (Anderson, 2008). Taken together, the present study is designed to review the biomedical applications of cinnamon as potential pharmacological agents based on the latest research findings.

Pharmacological effects

Among the numerous pharmacological properties of cinnamon, substantial evidence highlights its antioxidant and anti-inflammatory effects. Several *in vivo* and *in vitro* experiments have documented these impacts. Table 2 and Figure 1 summarize the main features of published studies focusing on these pharmacological properties of cinnamon.

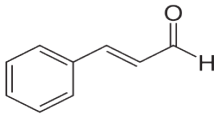
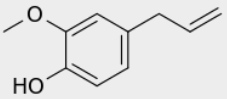
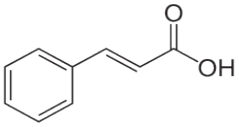
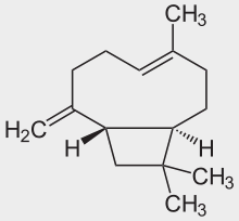
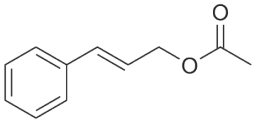
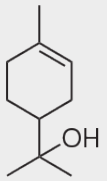
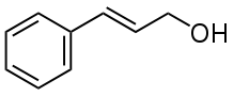
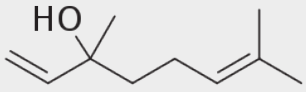
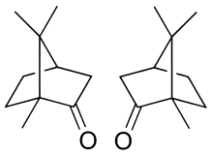
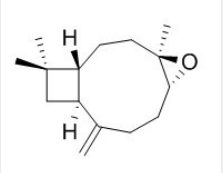
Antioxidant effects of cinnamon

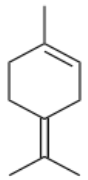
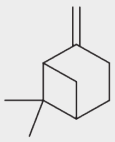
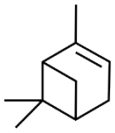
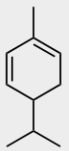
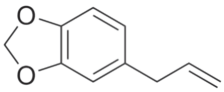
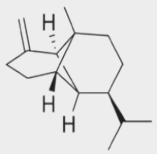
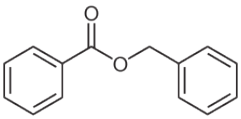
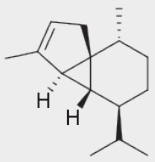
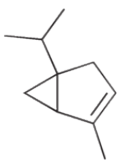
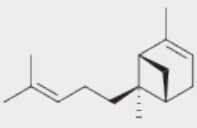
ROS encompass free radicals such as the hydroxyl radical (•OH) and superoxide anion (O2•−), as well as non-radical molecules like hydrogen peroxide (H2O2) and singlet oxygen (1O2). The accumulation of ROS concentrations, induced by various environmental stresses, poses significant harm to organisms, leading to oxidative damage to lipids, proteins, and DNA. This oxidative damage can result in alterations to intrinsic membrane properties, including fluidity and ion transport, as well as the loss of enzyme activity, protein crosslinking, inhibition of protein synthesis, DNA damage, and ultimately, cell death (Sharma et al., 2012). Internal and external antioxidants can reduce both ROS levels and cellular oxidation (Gilgun-sherki et al., 2001).

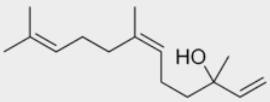
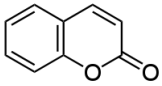
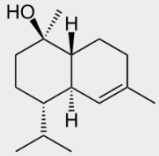
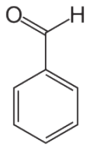
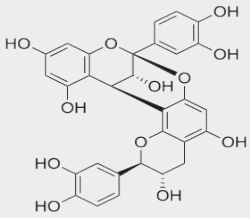
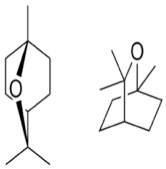
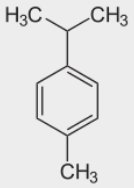
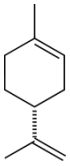
Clinical studies

Few Clinical studies have shown the antioxidant effects of cinnamon supplementation. In a study (25 type 2 diabetic patients for 12-weeks) showed that 1000 mg of cinnamon significantly increased the level of serum superoxide dismutase (SOD) and decreased malondialdehyde (MDA) level (Sahib, 2016). In addition, Borzoei et al. (2018) reported that 500 mg of cinnamon for 8 weeks in obese polycystic ovary syndrome (PCOS) patients exhibited antioxidant activity via reducing the level of MDA and serum total antioxidant capacity (TAC) (Borzoei et al., 2018). Also, in a double-blind study, the administration of 250 mg of cinnamon extract for 12 weeks demonstrated a considerable reduction in plasma

TABLE 1: Some of the main chemical constituents of *Cinnamomum* species and their bioactive compounds.

NO.	Name	Formula	Structure
1	Cinnamaldehyde	C_9H_8O	
2	Eugenol 2-Methoxy-4-(prop-2-en-1-yl) phenol	$C_{10}H_{12}O_2$	
3	Cinnamic acid (2*E*)-3-Phenylprop-2-enoic acid	$C_9H_8O_2$	
4	(−)-β-caryophyllene	$C_{15}H_{24}$	
5	Cinnamyl acetate	$C_{11}H_{12}O_2$	
6	Terpineol	$C_{10}H_{18}O$	
7	Cinnamyl alcohol (2*E*)-3-Phenylprop-2-en-1-ol	$C_9H_{10}O$	
8	Linalool	$C_{10}H_{18}O$	
9	Camphore	$C_{10}H_{16}O$	
10	Caryophyllene oxide	$C_{15}H_{24}O$	

NO.	Name	Formula	Structure
11	terpinolene δ-Terpinene	$C_{10}H_{16}$	
12	beta-Pinene	$C_{10}H_{16}$	
13	α-pinene	$C_{10}H_{16}$	
14	α-Phellandrene	$C_{10}H_{16}$	
15	Safrole	$C_{10}H_{10}O_2$	
16	Copaene	$C_{15}H_{24}$	
17	Benzyl benzoate Ascabin	$C_{14}H_{12}O_2$	
18	α-Cubebene	$C_{15}H_{24}$	
19	α-Thujene	$C_{10}H_{16}$	
20	α-*trans*-bergamotene	$C_{15}H_{24}$	

NO.	Name	Formula	Structure
21	Borneol	$C_{10}H_{18}O$	
22	Nerolidol	$C_{15}H_{26}O$	
23	Coumarin	$C_9H_6O_2$	
24	α-Cadinol	$C_{15}H_{26}O$	
25	Benzaldehyde	C_7H_6O	
26	Procyanidin A1	$C_{30}H_{24}O_{12}$	
27	1,8-Cineole	$C_{10}H_{18}O$	
28	p-Cymene	$C_{10}H_{14}$	
29	Limonene	$C_{10}H_{16}$	

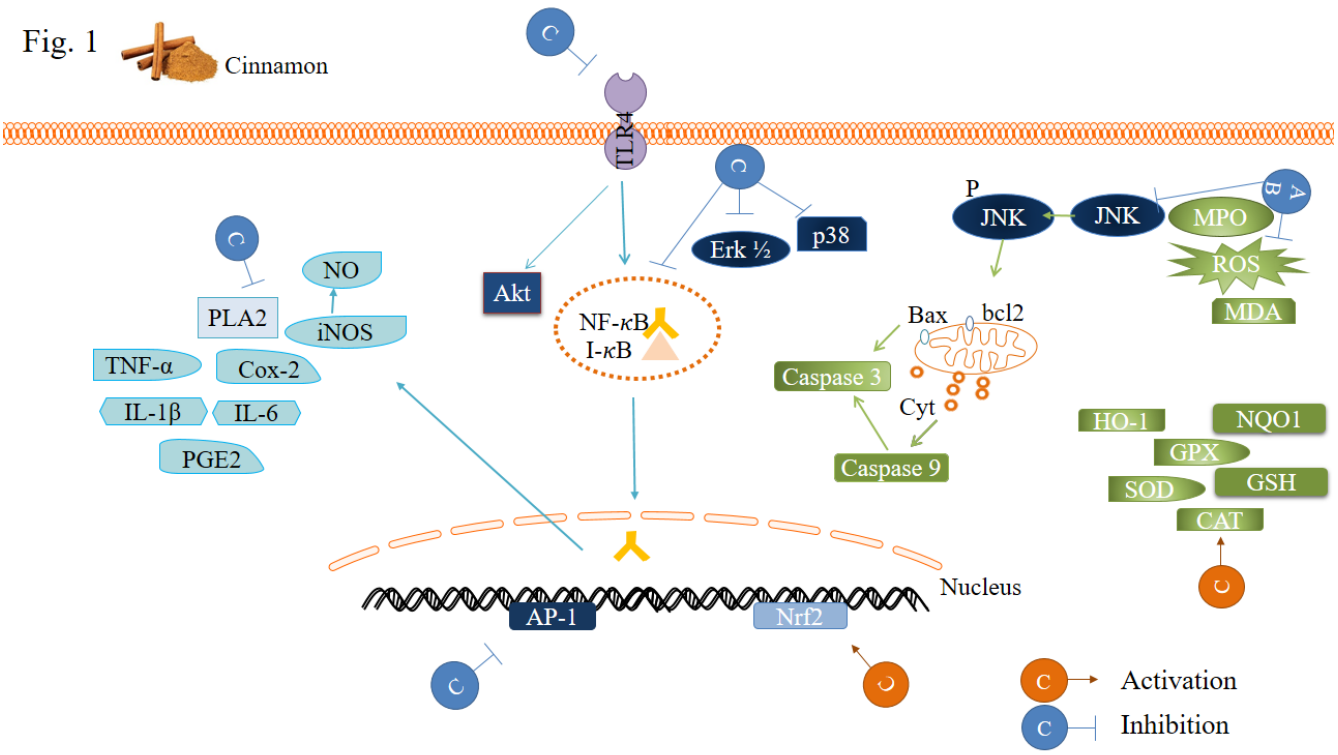


FIGURE 1. Intracellular signaling pathway through antioxidant (green), anti-inflammatory (blue), activity of *Cinnamomum* species and their bioactive compounds. Akt1, Protein kinase B1; AP-1, Activator protein 1; Bax, Bcl-2 associated X; Bcl-2, B-cell lymphoma 2; CAT, Catalase; COX-2, Cyclooxygenase-2; Erk1/2, Extracellular signal–regulated kinases ½; GSH-Px, Glutathione peroxidase; IL-6, Interleukin 6; IL1-β, interleukin 1-b; iNOS, Inducible nitric oxide synthase; JNK, c-Jun N-terminal kinases; MDA, Malondialdehyde; NF-κB, Nuclear factor kappa B; NO, Nitric oxide; NQO1, NADPH-dehydrogenase-quinone-1; Nrf2, Nuclear factor erythroid 2-related factor 2; PL, Phospholipase; PG, Prostaglandin; PGE2, Prostaglandin E2; PLA2, Phospholipase A2; ROS, Reactive oxygen species; SOD, Superoxide dismutase; TNF-α, Tumour necrosis factor-α; TLR, Toll-like receptor.

MDA and an increase in plasma sulfhydryl (SH) groups of plasma which all prove the antioxidant potential of this tropical herb in overweight or obese people (Roussel et al., 2009).

In vivo and in vitro studies

Mathew and Abraham confirmed that the antioxidant activity of cinnamon is dose-dependent. In their study, they used the methanolic extract of *C. Verum* leaf (12.5-50 µM) and found that higher concentrations of the methanolic leaf extracts were directly related to reduced free radicals. They demonstrated that the methanolic extract of *C. Verum* leaf showed antioxidant activity through scavenging free radicals such as hydroxyl radicals and superoxide anions, and also inhibited lipid peroxidation against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and 2,2′-azinobis-3- ethylbenzothiazoline-6-sulfonic acid (ABTS) radicals (Mathew and Abraham, 2006). Similar results were reported by Udayaprakash et al. They found that internal methanolic extract of cinnamon leaves exhibited higher antioxidant capacity than butylated hydroxyanisole (BHA) (Udayaprakash et al., 2015). Similar to these results, the essential oil extracted from *C. glaucescens* showed a higher free radical-scavenging activity than butylated hydroxytoluene (BHT) (Prakash et al., 2013). Numerous pharmacological studies confirmed the antioxidant activities of cinnamon on human health. Tuzcu et al. observed that cinnamon polyphenol extract (100 mg/kg b.wt.) for 12 weeks had antioxidant effects through modulation of transcription factors including nuclear factor kappa B (NF-κB), and nuclear factor erythroid 2-related factor 2 (Nrf2) in high fat diet (HFD) rat liver. In another *in vivo* study by Noori et al. (2012), oral consumption of 10 mg/kg cinnamon aqueous extract for 13 consecutive days, significantly increased the level of glutathione (GSH) in rats (Noori et al., 2012). Likewise, Seyed Ahmadi et al. (2019) indicated that topical administration of cinnamon oil on infected wounds significantly reduced the high content of MDA along with increasing the antioxidant capacity

TABLE 2: The potential pharmacological effects of *Cinnamomum* species and their bioactive compounds.

Subject	Dose (Duration)	Mechanism	Ref.
Cinnamon and Oxidative stress			
Type 2 diabetes patients	1000 mg (12-weeks)	Increased serum SOD levels and decreased MDA levels	(Sahib, 2016)
Obese polycystic ovary Syndrome (PCOS) patients	500 mg/day (8weeks)	Increased antioxidant activity, reduced MDA and TAC levels	(Borzoei et al., 2018)
Diabetic subjects	250 g/day (12 weeks)	Decreased plasma MDA and increase in plasma thiol (SH) groups of plasma, increased antioxidant activity	(Roussel et al., 2009)
HFD-induced rats (liver)	100 mg/kg b.wt (12 weeks)	Modulated NF-κB and Nrf2, reduced NF-κB p65 expression levels, induced expression of HO-1	(Tuzcu et al., 2017)
Human colon cancer cells (HCT116, HT29) and non-immortalized primary fetal colon cells (FHC)	1.25-40 µM (4 h)	Increased Nrf2 protein levels and HO-1	(Wondrak et al., 2010)
Glucose-treated mice	10 µM	Inhibited ROS generation and NO level, up-regulated Nrf2 expression, HO-1, NQO1, Catalase and Gpx1	(Wang et al., 2015)
In vitro study	12.5-150 µg	Antioxidant activity by free radical scavenging including superoxide anions and hydroxyl radicals, inhibited lipid peroxidation against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals and ABTS radicals action	(Mathew and Abraham, 2006)
Rats	10 mg/kg (13 days)	Increased GSH	Noori et al.,) (2012
Wound model (mice)	2 and 4% (2 and 4 g of C verum essential oil was added into 98 and 96 g of soft yellow paraffin)	Moderated MDA levels, increased the antioxidant capacity in wound tissue	(Seyed Ahmadi et al., 2019)
Mice induced by APAP	200 mg/kg/day	Induced total antioxidant capacity and and total oxidant status.	(Hussain et al., 2019)
APAP-induced rats	100 and 200 mg/kg (14 days)	Decreased MDA levels, increased GSH levels and antioxidant enzymes (CAT, SOD, GR and GPx) activities	(Hussain et al., 2020)
Rats	200 mg/kg (14 days before gamma irradiation)	Restricted the TNF-α and NO as well as induced SOD	(Azab et al., 2011)
Nephropathic mice	200 and 400 mg/kg (14 days)	Decreased TNF-α, IL- 1β, and IL-6, increased SOD, GSH, and catalase	(Atsamo et al., 2021)
HeLa and Raji cells	0.125 to 4 µg/mL 12 to 0.375 µg/mL	Increased antioxidant activity	(Kallel et al., 2019)
Human colon cancer cells	75 µM	Increased antioxidant activity	(Petrocelli et al., 2021)

Subject	Dose (Duration)	Mechanism	Ref.
Obese diabetic rats	200, 400 mg/kg (6 weeks)	Increased antioxidant activity	(Shalaby and Saifan, 2014)
BV2 microglial cells	100, 150, 200 µg/ mL	Reduced NO and inflammatory cytokines IL-6, IL-18, IL-1β	(Chen, Tang et al., 2020)
LPS-induced mice	50 mg/kg (7 days)	Inhibited IL-1β, MDA, and caspase-3 stimulated Nrf2 pathway	(El-ezz et al., 2018)
PC12 cells	20 µg/ml (*C. verum* and *C. cassia)* 5 and 10 µM (cinnamaldehyde) (24 h)	ROS scavenging	(Ramazani et al., 2020)
	Cinnamon and Inflammation		
Type 2 diabetes patients	3g/day (8weeks)	Reduced NF-kB level (Restricted inflammatory factors).	(Davari et al., 2020)
Caco-2 and RAW264.7	25, 50, and 100 µg/ml	PGE2, IL-6, IL-8¸TNF-α and suppressed the phosphorylation NF-κB pathways factors.	(Kim and Kim, 2019)
Acrylamide-intoxicated rats	250 and 500 mg/kg/day (28 days)	Induced TAC levels in the liver, lowered serum MDA and inflammatory cytokines (TNF-α, hs-CRP)	(Haidari et al., 2020)
RAW264.7 cells	100 µg/ml	Decreased the IL-1β ،IL-6, TNF-α, inhibited PGE2 and NO	(Lee et al., 2006)
LPS-induced mice	20, 100 and 500 mg/kg b.we. (6 days)	Reduced TNF-α and IL-6 levels, suppressed IκBα degradation and the activation of JNK, p٣٨, and ERK.	(Hong et al., 2012)
LPS-stimulated RAW 264.7 cells	25 g/ml and 10 g/ml	Inhibited production of NO and PGE2	(Tung et al., 2008)
Raw cells	1 to 5l g/ml	Reduced NO production	(Lee et al., 2002)
RAW 264.7 and J774A.1 macrophages	0.5-1.25 mg/ml	Induced NO and TNF-α exhibited anti-inflammatory activity	(Gunawardena et al., 2015)
LPS-activated RAW264.7 cells and peritoneal macrophages	100 µg/mL	Inhibited the activation of NF-κB, suppressed iNOS expression and NO production, lowered (COX)-2, TNF-α and PGE2 levels	(Yu et al., 2012)
Rats	8 mg/kg (12 to 21 days)	Enhanced serum CRP levels	(Vetal et al., 2013)
Colonic homogenate of colitis animals	150 mg/kg/day (10 days)	Decreased activity of MPO and the levels of NO, TNF-α, IL-1β, IL-6, and COX-2	(Salamatian et al., 2019)

Subject	Dose (Duration)	Mechanism	Ref.
HDF3CGF, a human skin disease model	0.0012% v/v	Decreased monocyte chemoattractant protein-1, interferon gamma-induced protein 10, interferon-inducible T-cell alpha, and MIG	(Han and Parker, 2017)
Raw induced by LPS	20, 50 mM	Reduced NF-κB, prevented transcription of COX-2 and IFNβ	(Youn et al., 2008)
APAP-induced rats	50, 100 and 200 mg/kg (14 days)	Reduced IL-1β, IL-6, active caspase-3 and -9	(Hussain et al., 2020)
Pneumonitis mice	6.55 µL/L	Restrained inflammatory activity	(Csikós et al., 2020)
THP-1 monocytes	25 µg/ml	Inhibited phosphorylation of Akt, IκBα, suppressed TLR۴ and TLR۲	(Schink et al., 2018)
Atherosclerotic mice	5, 10, 20 mg/kg (8 weeks)	Repressed IκBα and p۶۵ NF-κB phosphorylation, decreased TNF-α, IL-6, ROS, and MCP-1	(Li et al., 2019)
LPS-induced human OA chondrocytes cells	(10, 20, and 50 mM) for 24h	Suppressed expression of IL-1β, IL-6, and TNF-α.	(Chen, Ruan et al., 2020)

of the tissue (Seyed Ahmadi et al., 2019).

Also, it was found that cinnamon polyphenol decreased NF-κB expression levels, thereby suppressing the expression of pro-*inflammatory cytokines*, and increased the expression of genes encoding antioxidant proteins, resulting in upregulation of Nrf2 expression (Tuzcu et al., 2017). ROS are signal transduction pathways, and it has been found that one of the critical intracellular signaling pathways leading to NF-κB activation is the ROS (Ghosh and Karin, 2002). Similarly, cinnamaldehyde treatment showed antioxidant effects in the endothelium of mouse aortas by inhibiting ROS generation, protecting NO levels, and up-regulating Nrf2 expression, which led to increased downstream target proteins such as NADPH-dehydrogenase-quinone-1 (NQO1), heme oxygenase 1 (HO-1), glutathione peroxidase 1 (Gpx1), and catalase (CAT) under high glucose condition (Wang et al., 2015). It has been revealed that cinnamon bark aqueous extract at 200 mg/kg/day, for 14 days induced total antioxidant capacity by elevating serum TAC and total oxidant status (TOS) in mice and ameliorated the intensity of tissue damage induced by acetaminophen (APAP, 200 mg/kg) (Hussain et al., 2019). Similarly, in another study, cinnamon oil at 100 and 200 mg/kg b.w. for 14 days showed antioxidant activities via diminishing MDA levels, increasing GSH levels, and enhancing antioxidant enzymes (CAT, SOD, glutathione reductase (GR), and GPx) activities (Hussain et al., 2020). Also, treatment with 200 mg/kg cinnamon aqueous extract for 14 days before gamma irradiation led to antioxidant effects and limited levels of tumor necrosis factor-alpha (TNF-α) and liver NO, as well as inducing SOD activity in rats (weighing 100–120 g) (Azab et al., 2011). According to Atsamo et al. (2021), 200 mg/kg and 400 mg/kg of aqueous extract of *C. zeylanicum* for 14 consecutive days considerably reduced oxidative stress in nephropathic mice. The proposed antioxidant mechanism for the aqueous extract of *C. zeylanicum* is the reduction of oxidative stress markers including TNF-α, interleukin (IL)-6, and IL- 1β, and enhancement of antioxidant parameters such as SOD, GSH, and CAT (Atsamo et al., 2021). Cinnamaldehyde significantly affects cancer signaling pathways. In an *in vivo* experiment, human colon cancer cells were treated with 75µM of cinnamaldehyde showed antioxidant effects (Petrocelli et al., 2021). Similarly, Shalaby and coworkers claimed that the treatment of animals with an aqueous extract of cinnamon (200, 400 mg/kg for 6 weeks) enhanced antioxidant activity in obese diabetic rats (Shalaby and Saifan, 2014). In another study, cinnamon administration (50 mg/kg for 7 days) stimulated the Nrf2 pathway, leading to induced levels of antioxidant

enzymes. It should be mentioned that cinnamon significantly suppressed the expression of MDA, IL-1β, and caspase-3 in lipopolysaccharide (LPS)-induced mice with neuroinflammation (El-ezz et al., 2018). Also, we found that hydro-alcohol extract and essential oil of *C. verum* and *C. cassia* along with its main bioactive component cinnamaldehyde, exhibited antioxidant activity via ROS scavenging in 6-OHDA-exposed PC12 cells, which serve as an in vitro model of Parkinson's disease (Ramazani et al., 2020).

Nrf2, a transcription factor, plays a crucial role in defending cells and tissues against oxidative stress by regulating the expression of antioxidant genes, including heme oxygenase 1 (HO-1) (Bendavit et al., 2016). Evaluation of the ethanolic extract and trans-cinnamic aldehyde (cinnamaldehyde) prepared from C. cassia bark on HCT116 and HT29 (human colon cancer cells) and FHC (non-immortalized primary fetal colon cells) demonstrated upregulated cellular Nrf2 protein levels, leading to increased HO-1 expression as part of the antioxidant response element (Wondrak et al., 2010).

A recent study has pointed out that cinnamon essential oil displayed significant antioxidant properties on human cell lines HeLa (0.125-4 μg/mL) and Raji (12-0.375 μg/mL) when compared with synthetic antioxidant BHT (butylated hydroxytoluene) and ascorbic acid (vitamin C) (Kallel et al., 2019). In addition, cinnamon essential oil showed cytotoxic activity toward PC-3, A549, and MCF-7 human tumor cell lines with concentrations of (0.012, 0.017, 0.076 v/v) (Zu et al., 2010). Pretreatment of BV2 microglial cells with essential oil from *C. camphora* (Linn.) for 48 h at different concentrations (100, 150, 200 μg/ mL) caused a reduction of NO as well as to measure of cytokines including IL-1β, IL-6، and IL-18, induced by LPS (Chen, Tang et al., 2020). Overall, it seems that cinnamon chemical compositions reveal their antioxidant effects through lessening ROS levels, increasing SOD, GSH-Px, CAT, HO-1and NQO1 activity, decreasing the MDA and TAC level. Additionally, the antioxidant effect of cinnamon leads to diminution in caspase-3, caspase-9, TNF-α, and NF-κB levels and enhancement of Erk1/2, Akt1, and JNK levels.

Anti-inflammatory effects of cinnamon

Inflammation is a vital defense mechanism that protects injured or infected cells *via* eliminating injurious factors and promoting the healing of damaged tissues. Pro-inflammatory mediators, including cytokines such as TNF-α, IL-1, IL-6, IL-10, and type 1 interferons (IFNs), induce a cellular inflammatory process (Lawrence, 2009). IL-1 stimulates mRNA expression and protein synthesis of inducible nitric oxide synthase (iNOS), cyclooxygenase (COX-2), and phospholipase A2 (PLA2), which promote the formation of NO, platelet-activating factor, and prostaglandin E2 (PGE2) (Kany et al., 2019). NF-kB is an important regulator of inflammatory responses, activated by IL-1β and TNF-α (Somade et al., 2019). The NF-κB represents a family of transcription factors involved in regulating the expression of hundreds of genes, especially those related to inflammatory and immune responses. In unstimulated cells, NF-κB dimers exist in the cytoplasm in an inactive form bound to inhibitor of nuclear factor kappa B (I-κB). Upon degradation of IκB, NF-κB translocates into the nucleus, where it binds to DNA consensus sequences on gene promoters (Giuliani et al., 2018). Due to the increasing prevalence of diseases associated with inflammation, scientists are increasingly investing in bioactive compounds with potential biological activities found in traditional herbal medicine.

Clinical studies

Based on the results, 3 g/day cinnamon supplementation for 8 weeks did not significantly reduce NF-κB, IL-6, and TNF-α levels in patients with type 2 diabetes. However, it did show a significant reduction in NF-κB levels between groups (Davari et al., 2020).

In vivo and in vitro studies

Interestingly, administration of cinnamon extract at both 250 and 500 mg/kg/day for 28 days to acrylamide-intoxicated rats markedly augmented serum and liver TAC levels and lowered liver and serum MDA levels. It also ameliorated inflammatory responses *via* a reduction in the leptin serum levels (one of the major adipocytokines) and TNF-α (Haidari et al., 2020). It has been documented that oral administration of 20, 100, and 500 mg/kg of cinnamon water extract exhibited anti-inflammatory activities *in vivo* and *in vitro* LPS-induced models. After 6 days of oral administration, the serum levels of IL-6 and TNF-α significantly decreased in mice. Moreover, cinnamon water extract significantly reduced mRNA expression of TNF-α, suppressed IκBα degradation, and inhibited the activation

of extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun N-terminal kinases (JNK), and p38 in peritoneal macrophages from glycollate-injected mice (Hong et al., 2012). In 2019, Vallianou and collaborators reported that *C. Zeylanicum* supplementation enhanced serum C-reactive protein levels (Vallianou et al., 2019). C-reactive protein is an acute-phase inflammatory protein, and its increased levels are observed during the early stages of several chronic conditions including type 2 diabetes mellitus, pre-diabetes, obesity, coronary artery disease, rheumatoid arthritis, and nonalcoholic fatty liver disease (Taghizadeh et al., 2019). In a study by Vetal et al. the anti-inflammatory of TAPP of the bark of C. zeylanicum in rats was reported. Based on the result, administration 8 mg/kg, p.o., of TAPP daily (day-12 to day-21) significantly showed anti-inflammatory and anti-arthritic activities in adjuvant induced established arthritis (AIA) model. (Vetal et al., 2013). Besides, it was shown that *C. zeylanicum* extract (150 mg/kg/day for 10 days) treatment had antioxidant and anti-inflammatory effects in colonic homogenate of colitis animals. It decreased the activity of myeloperoxidase (MPO) and the levels of nitric oxide (NO), and significantly reduced the expression of various cytokines (TNF-α, IL-1β, IL-6) and inflammatory enzymes (COX-2) (Salamatian et al., 2019). Acetaminophen (APAP) can stimulate inflammatory cytokines such as IL-1β and IL-6, as well as activate caspase-3 and -9, thereby increasing liver injury (Das et al., 2010; Woolbright and Jaeschke, 2018; Wu et al., 2019). cinnamon oil at doses of 50, 100, and 200 mg/kg b.w. for 14 days exerted anti-inflammatory effects by decreasing IL-1β, IL-6 levels, and caspase-3 and -9 expressions in APAP-induced rats (170−220 g), suggesting it could be an alternative treatment for liver damage (Hussain et al., 2020). Recent research reported that inhalation of cinnamon oil (6.55 μL/L) restrained inflammatory airway hyperresponsiveness and reduced some of the cellular inflammatory markers in pneumonitis mice (Csikós et al., 2020). Furthermore, Li et al. reported the treatment of atherosclerotic mice with5 , 10, 20 mg/kg of cinnamaldehyde for 8 weeks reduced the phosphorylation level of IκBα and NF-κB, and significantly decreased inflammatory cytokines (TNF-α, IL-6, ROS, and monocyte chemoattractant protein-1 (MCP-1)) (Li et al., 2019). Given the influence of NF-κB activation on inflammation and ROS, it has been suggested that the anti-inflammatory process is sometimes concomitant with antioxidant activities (Flohé et al., 1997). Wondrak and colleagues revealed that cinnamon acts as an Nrf2 activator in cultured human colon cells, reducing the risk of colon cancer (Wondrak et al., 2010).

Kim et al. evaluated the effects of *C. japonicum Sieb*. subcritical water extract on anti-inflammation in the RAW264.7 and Caco-2 co-culture model of cellular intestinal inflammation. The results displayed that cinnamon subcritical water extract (CSWE) significantly reduced nitrite, PGE2, IL-6, IL-8, TNF-α levels, and NF-κB activity. They concluded that cinnamaldehyde (the major components of *C. japonicum*) and cinnamic acid suppressed the phosphorylation of factors in the NF-κB pathway (Kim and Kim, 2019). The evaluation of *C. camphora* extracts effects on RAW264.7 cells demonstrated the anti-inflammatory properties of methanol (MeOH), hexane, and ethyl acetate (EtOAc) extracts (100 μg/ml) through suppressing the production of interleukins IL-1β, IL-6, and TNF-α. Additionally, treatment with hexane and EtOAc extracts (100 μg/ml) induced inhibitory effects on NO production, while EtOAc and n-butanol (BuOH) extracts strongly inhibited PGE2 production in LPS/ IFN-γ-activated macrophages. EtOAc and BuOH extracts also have antiplatelet effects when tested by the DPPH and xanthine oxide assays (Lee et al., 2006). The anti-inflammation activities of essential oil and its constituents from indigenous *C. osmophloeum* twigs in LPS-stimulated RAW 264.7 cells were evaluated by Tung et al. The results showed the inhibitory effect of *C. osmophloeum* twig essential oil on NO and PGE2 production at concentrations of 25 μg/ml and 10 μg/ml, respectively (Tung et al., 2008). Similar to these results, Lee et al. reported that *C. cassia* extract significantly reduced NO production with an IC_{50} value between 0.1-10 μg/μL (Lee et al., 2002). *Cinnamomum zeylanicum and C. cassia* extracts exhibited anti-inflammatory effects *via* decreasing LPS+IFN-γ induced NO and TNF-α production in RAW 264.7 and J774A.1 macrophages (Gunawardena et al., 2015). Yu et al. confirmed that *C. cassia* ethanol extract (100 μg/mL) suppressed NF-κB activation, which resulted in the suppression of iNOS, COX-2, and TNF-α mRNA expression in LPS-activated RAW264.7 cells and peritoneal macrophages. Also, they observed lowered levels of NO, TNF-α, and PGE2 production (Yu et al., 2012). In addition, following treatment with the fruit essential oil of *C. insularimontanum*, inhibitory

effects on the protein expression of IκB kinase, iNOS, and nuclear NF-κB reduction were documented (Lin et al., 2008). Similarly, TAPP isolated from *C. zeylanicum* bark can exhibit anti-inflammatory effects *via* inhibiting COX enzyme activity, and reducing the production of pro-inflammatory cytokines such as IL-1β and TNF-α (Ping et al., 2010; Miguel, 2010). Anti-inflammatory activities of cinnamaldehyde, eugenol, and terpene in cinnamon have been shown in various studies (Hsueh and Law, 1998; Lee et al., 2002; Penckofer, et al., 2002). New findings revealed that cinnamaldehyde can exert anti-inflammatory properties by activating peroxisome proliferator-activated receptors (PPARs), which results in attenuating NF-κB functioning (Miguel, 2010; Huang et al., 2011). Following treatment of a dermal fibroblast cell system, HDF3CGF, which serves as a human skin disease model, with 0.0012% *v/v* of *C. zeylanicum* bark essential oil, several inflammatory protein biomarkers like IFN-γ-induced protein 10, monocyte chemoattractant protein-1, interferon-inducible T-cell alpha chemoattractant, and monokine induced by gamma interferon (MIG) were significantly diminished (Han and Parker, 2017). Pre-treating Raw cells with cinnamaldehyde (20 and 50 mM) for 1 hour disrupts the toll-like receptor 4 (TLR4) oligomerization process induced by LPS. Based on the results, cinnamaldehyde significantly reduces NF-κB induced by pro-inflammatory stimuli and prevents downstream gene transcription such as COX-2 and IFNβ (Youn et al., 2008). In 2018, Schink and colleagues found that cinnamon extract exerts anti-inflammatory effects (25 μg/ml) against toll-like receptors (TLR4, TLR2) and mitigates the phosphorylation of Akt and IκBα in an *in vitro* model of THP-1 monocytes stimulated with LPS (Schink et al., 2018). Chen and colleagues had evaluated the effects of cinnamic aldehyde on IκB protein phosphorylation in NF-κB signaling pathway in the LPS-induced human osteoarthritis chondrocytes cells. The authors reported that different concentrations of cinnamic aldehyde (10, 20, and 50 μM) for 24 h significantly downregulated the IL-1β, IL-6, TNF-α expression (Chen, Ruan et al., 2020). Overall, cinnamon chemical compositions can display anti-inflammatory properties via reducing TNF-α, IL-1β, IL-1, IL-2, IL-6, IL-8, COX-2, and PGE2 levels, and decreasing the IκBα phosphorylation and NO production through NF-κB activity disruption.

Covid-19 and cinnamon

In recent years, the world has experienced outbreaks of coronavirus with a high mortality rate causing viral pneumonia (Ramazani et al., 2021). COVID-19 is caused by the SARS-CoV-2 family of coronaviruses with singular stranded RNA. Its shape is round or elliptic enveloped by special spike proteins required for attachment, and its diameter is about 60-140 nm (Weiss and Navas-Martin, 2005; Aspland et al., 2021). It has been reported that COVID-19 infection releases a considerable amount of inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, TNF-α, leading to long-term neurological disturbances, kidney, and myocardial disorders, as well as chronic fatigue (Berlin et al., 2020; Heneka et al., 2020; Mitrani et al., 2020; Pelaia et al., 2020). In several cases, SARS-CoV-2 has been shown to cause a reduction in NO expression which leads to diffuse pneumonia and organs failure (Taneja, 2020). Few studies have been published on the immune system performance against COVID-19.

Cinnamon has shown inhibitory effects on covid-19 infection by interrupting TLR2 and TLR4, reducing pro-inflammatory cytokines, and preventing NF-κB/ activator protein 1 (AP-1) signaling (Yakhchali et al., 2021). It has been demonstrated that cinnamon plant extract, which contains hydroxyl group, can deactivate the active components of the virus, specifically proteins and RNA, through an esterification process involving amino (-NH2) and carboxyl (-COOH) groups (Taneja, 2020). *in vitro* experiments have shown that cinnamon extract exhibits dose-dependent exhibits dose-dependent antiviral activity against wild-type SARS-CoV-2, likely by disrupting viral endocytic pathways and viral replication (Zhuang et al., 2009). Altogether, these studies suggest potential roles for cinnamon against SARS-CoV-2 infection.

Other Uses

Based on the numerous studies, Cinnamon exhibited various beneficial pharmacological and therapeutic properties for centuries (Ekor, 2014). This plant, which belongs to the Lauraceae family, has about 250 species spread across Australia, India, and China (Jayaprakasha et al., 2003). *Cinnamomum verum* essential Oil was used to treat neurological diseases, sinusitis, and colds (Jayaprakasha et al., 2003). Cinnamon bark is commonly used as spices and in tea to prevent the common cold

and cardiovascular diseases (Ranasinghe et al., 2013). Traditionally, it has been applied to relieve muscular pain, typhoid fever, and gastrointestinal diseases (Jazet Dongmo et al., 2007). Several studies have reported the use of cinnamon bark and its oil for treating toothaches and dental issues (Aneja et al., 2009; Gupta et al., 2011). Moreover, cinnamon has been mentioned in various sources as a remedy for blood circulation disorders, inflammatory disturbances, and digestive problems (Tanaka et al., 1989; Yu et al., 2007; Csikós et al., 2020).

Strengths and limitations

Numerous studies have evaluated the pharmacological and therapeutic effects of cinnamon, providing new insights into its molecular mechanisms and biological activities, such as antioxidant, anti-inflammatory, anti-diabetic, and antibacterial properties.

The potential therapeutic impacts of cinnamon on human health have been reported in a few articles. However, the effects of cinnamon on coronavirus infection and inflammation is not clear yet. Further research is needed to elucidate the biological molecular mechanisms and pharmacological activities of cinnamon comprehensively.

Conclusion

In recent decades, extensive research has explored the phototherapeutic properties of cinnamon and its compounds, uncovering explicit and implicit anti-inflammatory and antioxidant effects. This study reviews cinnamon's molecular mechanisms in relation to coronavirus infections, highlighting its advantageous therapeutic potential for advancing clinical trials.

Cinnamon exerts antioxidant effects by reducing ROS through the induction of CAT, GSH-Px, HO-1 and NQO1 activities, while decreasing MDA and TAC levels. It also suppresses TNF-α and NF-κB gene expression, and enhances SOD as well as CAT mRNA levels. Additionally, cinnamon's antioxidant effect results in decreased levels of caspase-3 and caspase-9, while enhancing Erk1/2, Akt1, and JNK levels.

Furthermore, cinnamon's complex chemical composition demonstrates anti-inflammatory properties by reducing pro-inflammatory cytokines TNF-α, IL-1β, IL-1, IL-2, IL-6, IL-8, COX-2, and PGE2, and by suppressing IκBα phosphorylation and nitric oxide (NO) production through disruption of NF-κB activity. Cinnamon's ability to inactivate the NF-κB pathway via interruption of TLR4 and TLR2 underscores its pharmacological potential for therapeutic research against viral infections.

Experimental studies have indicated effective doses of cinnamon ranging from 110-500 mg/kg in animals and 10-100 mM in cell-based tests. However, while clinical studies have shown some efficacy, larger-scale investigations are needed to confirm these effects.

Conflict of interest

The authors declare that there are no conflicts of interest.

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