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REVIEW ARTICLE

A PROMISING ROLE OF CINNAMON TOWARDS RHEUMATOID ARTHRITIS

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Summary

Rheumatoid arthritis (RA) is a chronic disorder manifested by joint damage due to inflammation and autoimmunity which in turn has significant impacts on a patient's lifestyle. During disease, inflammation occurs due to activation of different immune cells, including macrophages and lymphocytes. Currently, the mainstay of treatment for RA is drug therapy. However, drug options are limited due to their negative effects and the possibility of reducing therapeutic benefits over time. Therefore, an effective and tolerable alternative therapy is needed. Several natural products have been found to have anti-inflammatory and anti-oxidant effects by affecting multiple molecular targets such as transcription factors and cytokines. Cinnamon, an aromatic plant, is a popular spice used for cooking and in traditional medicine all over the world. Cinnamon is composed mostly of essential oils and various components, such as cinnamaldehyde and eugenol. This review demonstrates the anti-inflammatory activity of cinnamon components in various preclinical and clinical studies illustrating their potential role in the treatment of RA.

Key words: Cinnamaldehyde; Cinnamon; Cytokines; Inflammation; Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA), a systemic and chronic disease, is marked by autoimmune response and inflammation of the synovium in different joints in the body, such as the hand and knee joints, resulting in pain, swelling, and morning rigidity (1, 2). It affects almost 1% of the overall population worldwide, particularly women (1, 3). RA is responsible for bone and cartilage degradation (Figure 1) and poor quality of life due to reduced mobility and pain (4). The pathogenesis of RA has been thoroughly studied and it is well demonstrated that various factors, genetic and environmental, are implicated in disease progression (5, 6). RA is caused by an impaired immune response including activation of T-cells and synthesis of various proinflammatory cytokines such as prostaglandins, nitric oxide (NO), cyclooxygenase tumour necrosis factor-α (TNF-α) and interleukins (ILs) including (IL-1, IL-3, and IL-6), which result in synovial tissue inflammation and joint damage (7-10). Moreover, macrophages have a key role in disease development by generating a range of pro-inflammatory mediators including TNF-α and Interleukin1β (IL-1β), and by causing cartilage and bone destruction (11-13). Various therapeutic options,

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such as glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying antirheumatic drugs (DMARDs), are available nowadays for RA treatment by reducing inflammation and pain in the joints (7). However, use of these medicines is restricted by toxicity and adverse effects, which in turn reduce patients' compliance. NSAIDs can cause renal complications and gastrointestinal problems such as perforations, ulcers, and bleeding if used for a long time (14, 15), whereas chronic use of a high dose of glucocorticoids can lead to metabolic effects, cardiovascular morbidity, infections, cataract, glaucoma, and osteoporosis (16). Furthermore, long-term use of DMARDs and biological agents has been linked to immunosuppression and severe infection (17). Accordingly, there has been an increasing interest in finding alternatives to RA management. In the last few years, the utilization of medicinal plants has garnered a lot of attention (18-20). Various studies have demonstrated that cinnamon has pleiotropic beneficial health effects on different conditions, including infection, cardiovascular disease, diabetes, and colonic cancer (21-23). In addition, cinnamon and its components have shown anti-inflammatory activity in various animal and human studies (24-29), suggesting that cinnamon may have a potential and promising role in RA treatment.

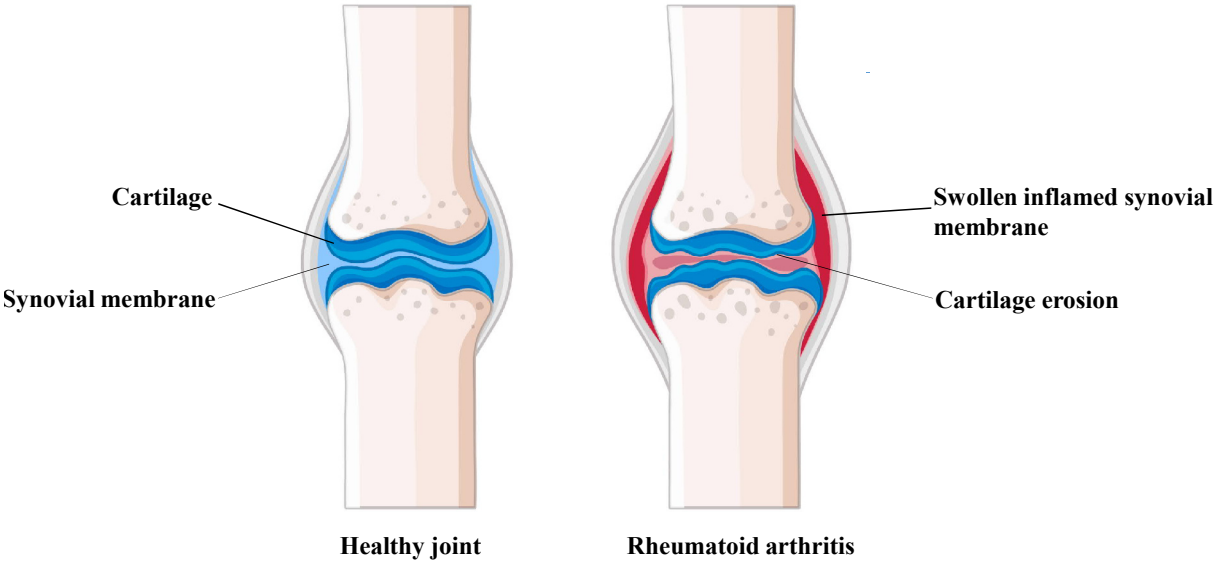

Figure 1. Rheumatoid arthritis. Designed by brgfx / Freepik

Chemical composition, pharmacological activity and toxicity of cinnamon

There are over 250 evergreen trees of the genus cinnamon distributed primarily in Asia and Australia (30). The most common types of cinnamon include: true or Ceylon cinnamon (Cinnamon zeylanicum) and Cassia or Chinese cinnamon (Cinnamomum aromaticum) (31). Other types of cinnamon include Indonesian cinnamon (Cinnamon burmannii) and Vietnamese cinnamon (Cinnamon loureiroi) (32). Extraction of various parts of cinnamon such as leaves, bark and roots has resulted in essential oil and extracts that contain different compounds, including cinnamaldehyde, eugenol, phenol, and linalool (Figure 2). Cinnamaldehyde is highly concentrated in the essential oil from bark, whereas eugenol is mainly concentrated in leaf oil (33-35).

Peeled and dried cinnamon bark has been used in Chinese medicine for treatment of dysmenorrhea, chest and abdominal pain. Cinnamon oil produced from Ceylon and Chinese cinnamon has a role in aromatherapy (36-38). In addition, aqueous and alcoholic cinnamon extracts of various types, may have a role in the treatment of oxidative stress-related diseases due to their antioxidant activity (39, 40). Moreover, cinnamaldehyde showed antioxidant, hypoglycaemic, anti-inflammatory, and vascular protectiv effects (41-43), whereas eugenol, the main component of cinnamon zeylanicum leaves, revealed remarkable effectiveness against lipid peroxidation by inhibiting peroxynitrite (33, 41, 44).

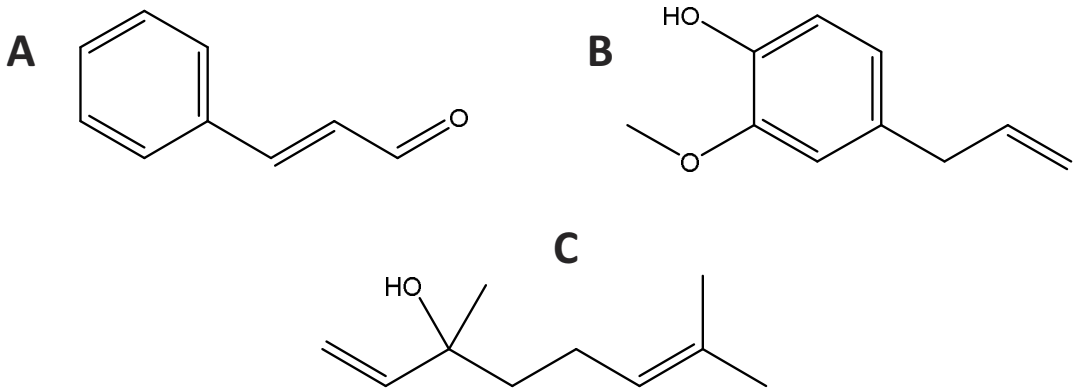

Figure 2. Chemical structure of A) Cinnamaldehyde, B) Eugenol and C) Linalool.

Cinnamon can be used as a seasoning and/or flavouring ingredient due to its low toxicity and side effects (45). A study conducted on healthy individuals showed that cinnamon zeylanicum water extracts at different doses (85, 250 and 500 mg/d) did not produce serious adverse effects within 3 months of treatment or 3 months after the treatment period (46). Moreover, an *in vitro* study revealed that cinnamon osmophloeum twig extracts (100 mg/mL) did not cause toxicity to 3T3-L1 cells (47). However, other studies have found that cinnamon can lead to some adverse effects including gastrointestinal disturbances and allergic reactions (48-50).

Anti-inflammatory effect of Cinnamon in arthritis

Cinnamon is one of the most popular herbal medicines used in the world to cure certain inflammatory diseases (51). Cinnamon's anti-inflammatory properties may be related to its principal phytochemical components, including cinnamaldehyde (Figure 3) and eugenol (24, 42). TNF-α, a proinflammatory cytokine, is a key contributor to many chronic inflammatory conditions such as RA (26). It has a critical role in the development of osteoclasts, which eventually cause bone and cartilage damage (52). In addition, pro-inflammatory mediators such as IL-1β and IL-6 have an essential role in the progression of RA (17), by promoting inflammatory cell infiltration and activation of osteoclasts, resulting in cartilage damage in inflamed joints and bone resorption (53, 54). Hence, lowering of these cytokines might have a positive impact on this disease through reduction of inflammation (17, 55). Many studies have revealed that cinnamon and its main components have a significant effect on various inflammatory mediators. An aqueous extract of cinnamon caused a reduction in the serum level of TNF-α in collagen and lipopolysaccharide-induced arthritis mice (29, 56). Previous studies have shown an association between oxidative stress and various diseases including diabetes, endothelial dysfunction, and RA (57, 58). Free radicals are essential secondary mediators in inflammation and can aggravate joint damage. In particular, free radicals potentiate inflammation by causing lipid peroxidation and damage to DNA, collagen, and protein. Both malondialdehyde (MDA) and glutathione (GSH) have an impact on the degree of oxidative stress. Lipid peroxidation is the main cause of MDA formation, while GSH is essential in scavenging ROS (reactive oxygen species) and preventing oxidative stress (59, 60). Liao *et al*. and Sharma *et al.* revealed that Cinnamomum cassia bark extract has an anti-inflammatory role by reducing MDA levels and increasing GSH levels (29, 61). Moreover, Sharma *et al*. showed that the same extract has anti-arthritic activity in rats with formaldehyde- or complete Freund's adjuvant (CFA)-induced arthritis by reducing joint swelling and levels of IL-1β and TNF-α . It has been shown that IL-1β and TNF-α cytokines activate signal transducer and activator of transcription 3 (STAT3), which in turn boosts joint damage and osteoclastogenesis. Therefore, Cinnamomum cassia bark extract can prevent persistent inflammation and joint destruction (62, 63). It has been found that elevated levels of vascular endothelial growth factor (VEGF) in RA patients lead to joint damage and pannus development. Kim *et al*. showed that cinnamon cassia water extract has anti-inflammatory activity by inhibiting VEGF (64, 65). Another study by Lee and Lim demonstrated that C. cassia twigs extract has activity against acute and chronic arthritis and inflammation by decreasing the volume of edema in the paws of rats with chronic arthritis (66). Qadir *et al*. showed that Cinnamomum verum extract has anti-inflammatory and antioxidant activity in arthritic mice. Additionally, they have demonstrated that cinnamaldehyde,

the main component of the extract, inhibits essential proteins including TNF-α , carbonic anhydrase II, NFATc3 (Nuclear Factor of Activated T Cells 3) and m-Calpain that are involved in the development and exacerbation of rheumatoid arthritis (67). Due to the increase in the generation of H^+ ions, prior research has linked carbonic anhydrase II expression to joint damage (68). Moreover, inflammatory reactions at the joint are amplified by carbonic anhydrase II (67). Overexpression of m-Calpain, a homocystiene proteinase, is associated with joint damage (67, 69), while NFATc3 stimulates inflammation by increasing the production of proinflammatory cytokines, such as IL2, and causes articular damage due to auto-antibodies formation (70, 71). In humans, a randomized clinical trial involving 36 women with RA found that 8 weeks of receiving cinnamon (2000 mg/d) resulted in a substantial reduction in inflammatory biomarkers such as TNF-α and a marked improvement in clinical symptoms including inflammation (26).

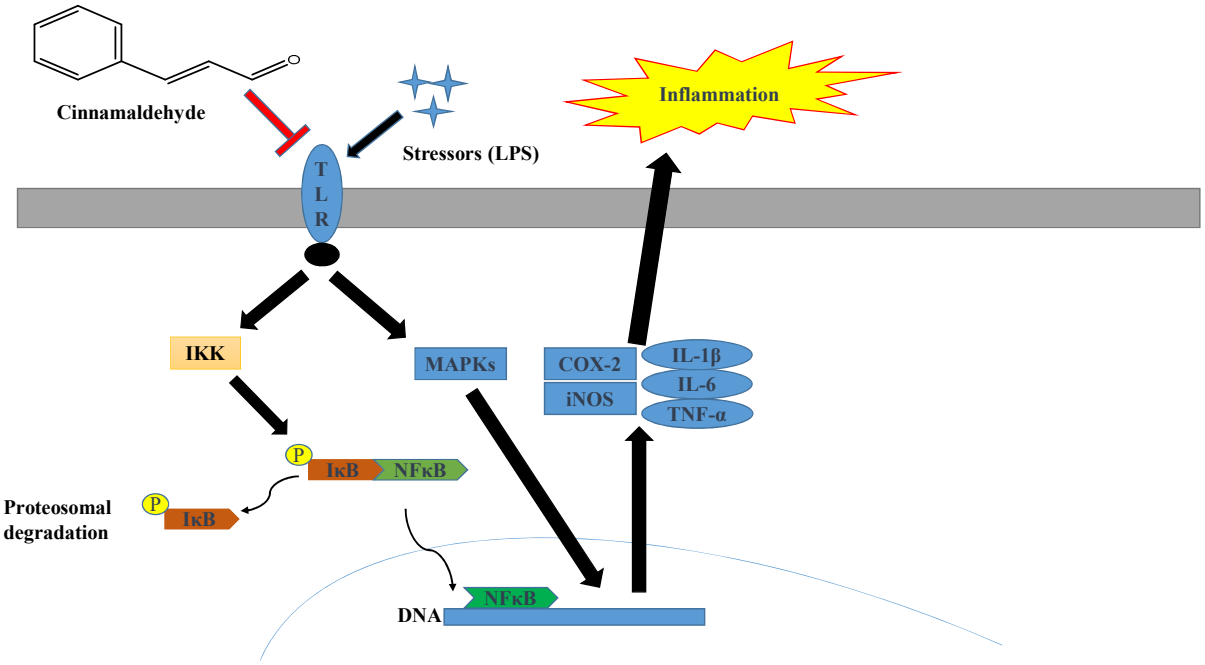

Figure 3. Anti-inflammatory effects of cinnamaldehyde. iNOS: Inducible nitric oxide synthase; TLRs: toll-like receptors; IKK: kappa B kinase; IL-1β: Interleukin 1β; IL-6: Interleukin 6; MAPKs: mitogen-activated protein kinases; IκB: inhibitor of kappa B; NFκB: nuclear factor kappa B; COX-2 cyclooxygenase 2; TNF-α: tumour necrosis factor alpha; LPS: lipopolysaccharide.

Regarding the components of cinnamon, Liao *et al*. showed that administration of cinnamaldehyde results in a decrease in TNF-α in a rat with arthritis (29). In addition, cinnamaldehyde decreased prostaglandin E2 (PGE2) generation and cyclooxygenase-2 (COX-2) activity by reducing IL-1β in rats and mice (72, 73). Furthermore, Kim *et al*. revealed that cinnamaldehyde suppresses inflammation by lowering TNF-α, IL-1β and IL-6 levels in murine macrophage cell lines (74), whereas Mateen *et al*. demonstrated a significant decrease in the levels of IL-6 and TNF-α by cinnamaldehyde and eugenol in RA patients (42). In addition, cinnamaldehyde and eugenol showed anti-arthritic activity by reducing arthritis score, swelling, proinflammatory cytokines and free radicals (28). Li and Yue demonstrated that cinnamaldehyde has promising therapeutic effects against RA by blocking the phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signaling pathway, which in turn inhibits the metastasis and proliferation of fibroblast-like synoviocytes (FLSs) (75). FLSs, the synovial joint's predominant cells, play an essential role in the pathogenesis of RA by causing autoimmunity, cartilage damage and inflammation (76).

Since inflammation can be stimulated by induction of nuclear factor kappa B (NF-κB), a pro-inflammatory transcription factor, by ROS (77), it is essential for the drug to have anti-inflammatory activity by decreasing NF-κB activation (78). Kwon *et al*. revealed that Cinnamomum cassia has direct and indirect effects against NF-κB resulting in a decrease in pro-inflammatory cytokine expression (63, 79). Moreover, a study of 2′-hydroxycinnamaldehyde

isolated from cinnamon cassia showed significant inhibition of NO formation and NF-κB activation indicating its potential anti-inflammatory role due its antioxidant effect (77). In addition, Kim *et al*. revealed that the antioxidant effect of cinnamaldehyde results in modification of NF-κB activation by the redox sensitive IκB kinases (IkappaB kinase or IKK) and mitogen-activated protein kinase (MAPK) pathways, resulting in inhibition of upregulation of COX-2, NF-κB targeting genes and inducible nitric oxide synthase (iNOS) (80). On the other hand, cinnamon's anti-inflammatory effect may be related to the polyphenolic components such as procyanidins and tannins, which deactivate NF-κB by lowering reactive oxygen species production, leading to prevention of pro-inflammatory cytokine formation (81-83).

Anti-inflammatory effect of Cinnamon in other diseases

Hyperglycemia has been linked to increased proinflammatory mediators incuding IL-1β and TNF-α in diabetic patients (84). It has been found that inflammation can lead to β-cell impairment and the development of diabetes (85). Numerous studies revealed that cinnamon products have anti-inflammatory effect (86). A study conducted by Peana *et al*. showed that linalool, cinnamon's major constituent, inhibits production of COX-2, NO and prostaglandin E2 by macrophages (87). In addition, Deepa and Venkatraman Anuradha showed that linalool results in lowered cytokine levels in STZ-induced diabetic rats (88). Other studies revealed that cinnamaldehyde has anti-inflammatory activity by reducing NO , IL-1β and TNF-α, levels (86, 89, 90).

In heart diseases, cinnamon prevents inflammation by blocking the effects of arachidonic acid, an inflammatory fatty acid, and thromboxane A2, an inflammatory mediator, in the blood (91). Several studies have revealed promising anti-atherosclerotic effects of cinnamon and its active ingredients due to various effects including anti-inflammatory activity (92-95).

Neuroinflammation due to uncontrolled activation of microglia with substances such as lipopolysaccharides, b-amyloid, arachidonate and glutamate can result in Alzheimer's disease (96, 97). Many studies showed that cinnamon has a role in neurodegenerative diseases due to its antineuroinflammatory effects. In allergic diseases, the anti-inflammatory properties of cinnamon have been shown to be attributed to its role in inhibiting the production of histamine from fatty substances (98).

Conclusion

Despite research supporting its potential advantages, cinnamon is not utilized as a routine therapeutic choice for RA. Several studies have revealed that cinnamon and its components, notably cinnamaldehyde, have an anti-inflammatory action through reducing generation of many pro-inflammatory mediators, TNF-α, IL-1β and IL-6, and suppressing activation of NF-κB. As a result, cinnamon and cinnamaldehyde have the potential to help RA patients.

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Conflict of interest

There are no conflicts of interest.

Adherence to ethical standards

Not applicable

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