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CINNAMALDEHYDE ANALOGUES: A NOVEL THERAPEUTIC AGENT FOR RHEUMATOID ARTHRITIS

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ABSTRACT

Cinnamaldehyde analogues are a class of chemical substances originated from derivatives of cinnamaldehyde, and are structurally characterized by the presence of cinnamoyl moiety. Cinnamaldehyde is obtained from cinnamon which consists of dried inner bark of the shoots of coppiced trees of cinnamomum zeylanicum of the family Lauraceae. They have diverse range of biological property such as flavourant, agrichemical, anti-microbial agent, anticancer agent, mild astringent, fungicide, anti- inflammatory etc. Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation of joints which also cause inflammation of tissues around the joints as well as in the other organs in the body, which is responsible for the deformity and disability. Due to the presence of highly reactive α, α-unsaturated carbonyl pharmacophore in their structure, these molecules are apt to react with some enzymes and receptors as electrophiles. The naturally occurring molecules of this group such as transcinnamaldehyde and all have attracted lots of interest for their bioactivities especially for anti-inflammatory properties. This review summarises the progress of cinnamaldehyde analogue on anti-arthritic patients, illustrate its potent bioactivity, and discuss their potential as therapeutic agents.

KEYWORDS: Cinnamaldehyde, Schiffs base, Phenylpropanoids, Anti-inflammatory, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid Arthritis is an autoimmune disease that causes chronic inflammation of joints. It also can cause inflammation of tissues around the joins, as well as other organs in the body. The cause of rheumatoid arthritis is unknown. Even though infectious agents such as viruses, bacteria, and fungi have long been suspected, none has been proven as the cause. The symptoms of rheumatoid arthritis come and go, depending on the degree of tissue inflammation. When the disease is active, symptoms can indulge fatigue, loss of energy, lack of appetite, low grade fever, muscle and joint aches, and stiffness. In the diagnosis of rheumatoid arthritis, certain blood and X-ray tests are often obtained and it mostly based on the pattern of symptoms, the distribution of the inflamed joints and the blood and X-rays findings. The goal of treatment is to reduce the joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Two class of medications are used in treating rheumatoid arthritis, fast acting first line drugs and slow acting second line drugs(DMARDs, BRMs, Adjuvant drugs).[1]

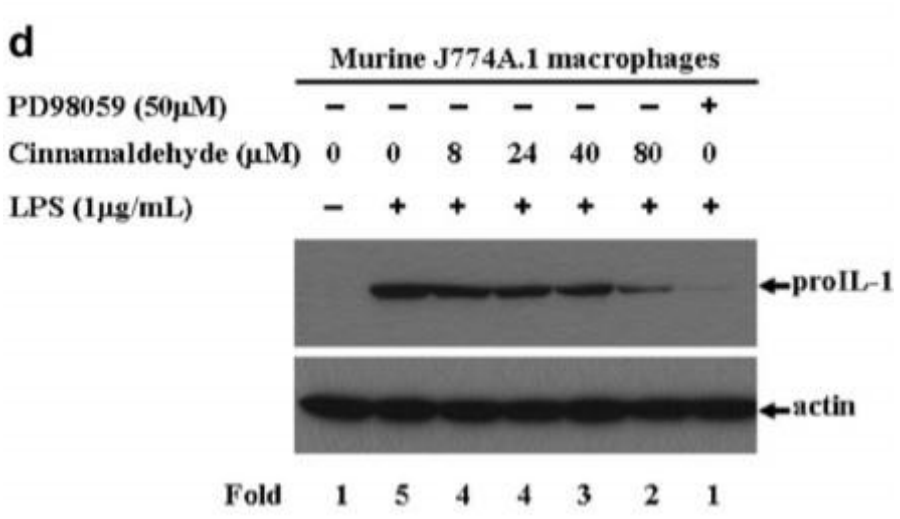
Cinnamaldehyde is obtained from cinnamon which consists of the dried inner bark of the shoots of coppiced trees of Cinnamomum zeylanicum belongs to the family Lauraceae. Cinnamaldehyde is the organic compound that gives cinnamon its flavour and odour. Several methods of laboratory synthesis exist, but cinnamaldehyde is most economically obtained from the steam distillation of the oil of cinnamon bark. The compound can be prepared from related compounds like cinnamoyl alcohol, but the first synthesis from unrelated compound was the aldol condensation of benzaldehyde and acetaldehyde. It has several applications as a flavourant agrichemical, antimicrobial, anti cancer agent etc.[2]

Azomethine group (-C=N-) containing compounds typically known as Schiff bases have been synthesised by condensation primary amines with active carbonyls. Schiff bases have several biological applications that include antibacterial, antifungal antitumor activity. Schiff base complexes play a vital role in designing metal complexes related to synthetic and natural oxygen carriers. Metal complexes make these compounds effective as stereo specific catalysts towards the oxidation, reduction, hydrolysis, biological activity and other transformations of organic and inorganic chemistry. In organic compounds, the presence of –C=N- along with the other functional groups from more stable complexes compared to compounds with only –C=N- coordinating moiety.

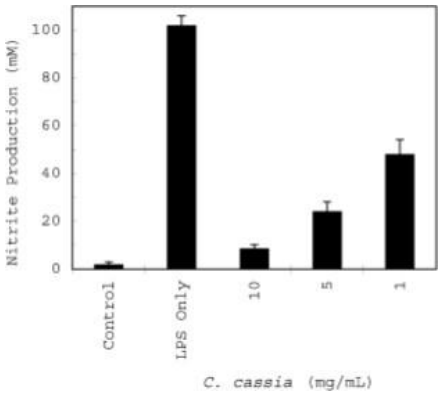
In this review we are aiming to evaluate the anti-arthritic activity of novel Schiff bases of cinnamaldehyde analogues and also to discuss the future attempt to study the anti-rheumatic activity using these.[3]

RESULTS AND DISCUSSION

Cinnamaldehyde inhibits pro-inflammatory cytokines secretion from monocytes/macrophages through suppression of intracellular signalling. The low concentration of cinnamaldehyde inhibited the secretion of interleukin-1beta and tumour necrosis factor alpha within lipopolysaccharides (LPS) or lipoteichoic acid (LTA) stimulated murin J774A. 1 macrophages. Cinnamaldehyde also suppressed the production of these cytokines from LPS. Stimulated human blood monocytes. It also inhibited the production of prointerleukin-1beta within LPS or LTS stimulated human THP-1 monocytes.[4]



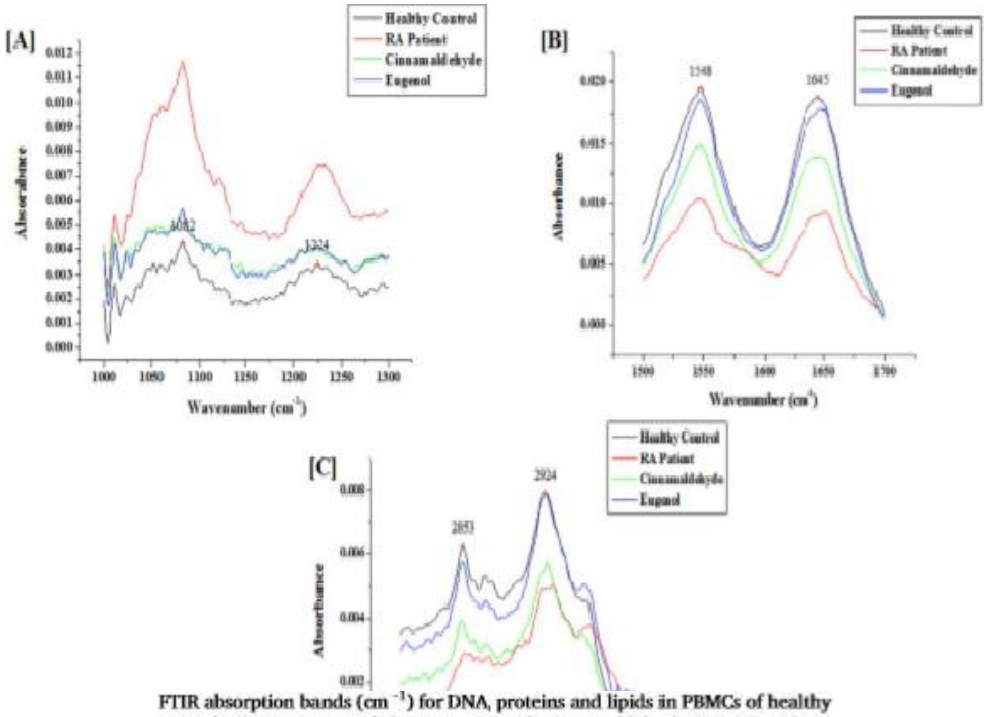
The inhibitory effects of Cinnamomum cassia bark derived material on nitric oxide, the biologically active constituents of C.cassia extract were characterised as trans- cinnamaldehyde by spectral analysis. Potent inhibitory effects of cinnamaldehyde against NO production were 81.5%, 71.7 at 1.0 and 0.5 μg/μl respectively and a 41.2% inhibitory effect was revealed at 0.1 μg/μl as a naturally occurring therapeutic agent, trans-cinnamaldehyde could be useful for developing new types of NO inhibitors.[5]



3D QSAR studies on cinnamaldehyde analogue as farnesyl protein tansferase inhibitors showed the three-Dimensional quantitative structural activity relationship (3D-QSAR) studies on 55 cinnamaldehyde analogues as Farnesyl protein transferase (FPTase) inhibitors investigated using comparative molecular field analysis (CoMFA) with the PLS region-focusing method. 49 training set inhibitors were used for CoMFA with two different grid spacings, 2A and 1A. 10 compound, which were not used in model generation, were used to validate the CoMFA models. After the PLS analysis, the best predictive CoMFA model showed that the cross-validated value (r2cv) n and the non-cross validated conventional value (r2ncv) are 0.557 and 0.950, respectively. From the CoMFA contour maps, the steric and electrostatic properties of cinnamaldehyde analogues can be identified and verified.[6]

The MTT assay examine the effect of cinnamaldehyde and eugenol on RA induced alteration in the macromolecules of FTIR is an effective and non-destructive technique for studying the cellular alterations in various diseases. The region between 1000 and 1300cm-1 corresponds to DNA. The band at 1082 and 1224cm-1 corresponds to symmetric and asymmetric phosphate group stretching in DNA. There occurred a shift in the band position in the PBMCs of RA patients. However, cells coincubated with cinnamaldehyde/ eugenol ameliorated this shift in the band position. The region between 1600 and 1700cm-1 and 1500–1600cm-1 corresponds to amide I and amide II band of proteins respectively. Amide I band corresponds to stretching vibrations of CO, CN bonds and bending of NH bond of peptide linkages. The amide II band originates mainly from NH bending and CN stretching vibrations. The amide I and amide II band of healthy controls appeared at 1645cm-1 and 1548cm-1. The amide I and amide II band position of PBMCs of RA patients and those treated with cinnamaldehyde and eugenol has been given. The

amide II peak remains unaltered in RA patients, however change in the intensity of both amide I and amide II has been found. Absorption between 2800 and 3000cm-1 occurs mainly due to stretching of CH2 and CH3 groups present in the lipid acyl chains. The band at 2853 and 2924cm-1 corresponds to asymmetric stretching of CH2 group of lipids. The change in band position of various groups has been given in Table.[7]



FTIR absorption bands (cm $^{-1}$) for DNA, proteins and lipids in PBMCs of healthy controls, RA patients and those treated with cinnamaldehyde (40 µM) and eugenol (40 µM).

	Controls	RA Patients	Cinnamaldehyde	Eugenol
DNA (cm $^{-1}$)	1082	1082	1082	1082
	1224	1231	1226	1223
Amide I (cm $^{-1}$)	1645	1652	1648	1647
Amide II (cm $^{-1}$)	1548	1548	1548	1547
Lipids (cm $^{-1}$)	2853	2853	2853	2852
	2924	2931	2926	2926

Cinnamaldehyde and eugenol were effective in suppressing the secretion of pro- inflammatory cytokines from the cultured PBMCs of RA patients. These compounds have also reduced the neutralizing reactive oxygen/nitrogen species formation which in turn has ameliorated biomolecular oxidation and antioxidant defence response in the PBMC culture of RA patients. Thus these compounds have potential to be used as an adjunct in the management of RA by virtue of their free radical scavenging and anti-inflammatory effects.

The effect of TAPP in CPE model, subplanter injection of carrageenan produced significant amount of edema in all the groups of animals. The increase in the paw volume was observed within an hour and sustained upto 6 hr. the standard NSAID dicofenac sodium caused significant reduction in the edema compared with vehicles treated rats at 1hr of treatment until 6hr. TAPP did not show anti-inflammatory effect. The onset of effect of TAPP was at 3 hr, 3 and 1 h for dose levels of 4,8 and 25mg/kg respectively. The absence of the analgesic and the ulcerogenicity potential with reduction in serum CPR levels in AIA rats qualifies TAPP as a disease-modifying anti-rheumatic drug(DMARD). DMARDs suppress the rheumatoid process and bring about a remission, but do not have nonspecific anti-inflammatory or analgesic action. TAPP offer added advantage of moderate anti-inflammatory effects at daily dose of 8mg/kg, p.o. in arthritic rats. The DMARD effect shown by TAPP can also be substantiated by earlier reports on cinnamon bark extracts. For example, cinnamon bark was shown to inhibit gastric secretions and eradicate H.pylori, TAPP is also expected to protective on the cardiovascular system as cinnamon polyphenols especially TAPP by virtue of its anti-oxidant activity. TAPP, type-A procyanidine polyphenols isolated from the bark of cinnamomum zeylanicum showed anti- inflammatory and anti-arthritic effects in animal models without ulcerogenicity potential. Lack of analgesic activity in present study and reports of immune modulatory potential suggested TAPP as potential DMARD. Further studies are required to explain the mechanism of action of TAPP towards autoimmune and inflammatory disease processes.[8]

Here it has been shown that NF-κB is activated by various stimuli, such as oxidative stress, and in addition to activating pro-inflammatory genes through various kinases, it also then modulates the cellular signalling mechanisms that is involved in inflammation induced by oxidative stress during aging. In a study by Kim et al. male Fischer fed 344 rats with a diet containing 2 or 6mg/kg cinnamaldehyde for very few days. The results showed that cinnamaldehyde inhibited age-related oxidative stress and suppressed age-related NF-κB activation that over-regulated the target genes of NF-κB, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). In addition to the NIK / IKK pathway, the kinase pathways regulated by extracellular signal transduction (ERK) and MAPK p38 pathways are also involved in the inhibition of NF-κB; however, during aging, increased degradation of the NF cellular inhibitory protein. The transcription factor -κB known as IκB by IKK leads to increased NF-κB binding activity. On the other hand, cinnamaldehyde inhibited this activity by inactivating IKK, resulting in the positive regulation of the nuclear factor of the kappa light polypeptide gene enhancer in the B cell inhibitor, B cell inhibitor, alpha (IκBα) and IκBβ. In addition, cinnamaldehyde suppressed NF-κB activation by inhibiting ERK and p38 MAPK pathways, suggesting that the antioxidant effect and the restoration of redox balance were related to the anti-inflammatory activity exhibited by this compound.[9]

Chao et al. also showed the in vitro anti-inflammatory activity of cinnamaldehyde (24–80 μM) obtained from the essential oil of C. osmophloeum leaves. The following effects have been observed: inhibition of the production of IL-1β and TNF-α in murine J774A-1 macrophages stimulated by LPS or lipoteichoic acid (LTA) and in primary macrophages derived from human blood monocytes stimulated by LPS and THP-1 monocytes; suppression of pro-IL-1β production in human THP-1 monocytes stimulated by LPS or LTA; reduced release of reactive oxygen species (ROS) from J774A-1 macrophages stimulated by LPS; and inhibition of LPS-induced ERK 1/2 and N-terminal kinase 1/2 (JNK 1/2) c-jun phosphorylation. As these MAPK subtypes have been implicated in the regulation of cytokine gene expression, such as TNF and IL-1, as evidenced in human and murine macrophage culture, it is believed that the inhibitory action of cinnamaldehyde in cytokine synthesis related to the reduction of ERK 1/2 and JNK 1/2 activation in L77-stimulated J774A-1 macrophages. In this case, these findings provide further evidence of the anti-inflammatory activity performed by cinnamaldehyde, involving the participation of MAPKs and their regulatory role in immune responses, suggesting its potential pharmaceutical use as an immunomodulatory agent.[10]

Cinnamomum cassia (Nees & T.Nees) J.Presl (Lauraceae), popularly known as cinnamon, is a spice used in traditional medicine in the treatment of gastritis and also has pharmacological properties such as anti-inflammatory and anti-tumor activity.[11,12] The effect of C. cassia on atherogenesis has been assessed, providing further evidence of the anti-inflammatory action of this species. the anti- inflammatory effects of cinnamaldehyde were exhibited by interrupting the degradation of IκBα, while in long-term treatment, the anti-inflammatory effects of cinnamaldehyde were caused by the induction of Nrf2-related genes, such as heme oxygenase-1 (HO -1), known to be associated with the inhibition of TNF-α-induced ICAM-1 expression.[13] In addition, nuclear extensions of Nrf2 with positive regulation of cinnamaldehyde, increased the activity of gluciferase of the antioxidant response element (ARE) and increased the regulation of another gene related to Nrf2, thioredoxin reductase-1. These findings indicate that cinnamaldehyde has two distinct mechanisms, activated by different treatment periods, to suppress TNF- induced signalling pathways.[14]

Other studies have discussed the inhibition of the NF-κB pathway by cinnamaldehyde and its interrelation with TLRs. As previously mentioned, TLR4 activation is associated with an increased inflammatory response, as it leads to the activation of proinflammatory elements, such as cytokines, COX-2, NOS, NF-κB, a regulatory factor of interferon 3 (IRF3), a component which plays an important role in the response of the innate immune system to viral infection[15], and in the expression of inflammatory mediators that may involve My88 and TRIF-dependent signalling pathways .In vitro assays using RAW 264.7 macrophages showed that LPS-induced activation of NF-κB and IRF3 (TLR4 agonist) was inhibited by cinnamaldehyde, resulting in reduced expression of target genes such as COX-2 and IFN-β. Although cinnamaldehyde fails to suppress NF-κB or IRF3 activation induced by MyD88 and TRIF-dependent pathways, LPS-induced TLR4 oligomerization was inhibited by cinnamaldehyde, leading to down regulation of NF-κB activation16. In addition, cinnamaldehyde inhibited constitutively active TRL4 or ligand-induced NF-κB activation or wild-type TRL4. These findings suggest a different mechanism for cinnamaldehyde's anti-inflammatory activity, aimed at oligomerization of TLR4 and not downstream signaling molecules, indicating that TRL4 and signalling components may become interesting therapeutic targets for chronic diseases related to inflammation.[16] The in vitro investigation of O. quixos essential oil and two of its main constituents, trans-cinnamaldehyde and methyl cinnamate showed that O. quixos essential oil and trans-cinnamaldehyde (1 to 10 μg / mL) reduced significantly the LPS-induced release of NO from J774 macrophages, while methyl cinnamate was unable to inhibit NO production to the highest concentration (10 μg / mL). In addition, oil and trans-cinnamaldehyde suppressed LPS-induced COX-2 expression and increased forskolin-induced cAMP production. In vivo, both essential oil (30–100 mg / kg) and trans-cinnamaldehyde (10 mg / kg) exhibited an anti- inflammatory action, reducing rat paw edema induced by carrageenan. On the other hand,

methyl cinnamate (30 mg / kg) did not suppress the anti-inflammatory effects induced by carrageenan. In addition, all animals treated with indomethacin (10 mg / kg - positive control) exhibited ulcerated gastric mucosa, while rats treated with essential oil of O. quixes and trans-cinnamaldehyde did not present gastric lesion. In fact, the administration of essential oil of O. quixes (100 mg / kg) and trans- cinnamaldehyde (10 mg / kg), but not of methyl cinnamate (30 mg / kg), prevented lesions in the gastric mucosa after oral administration of 90% ethanol for rats. These findings indicate that trans-cinnamaldehyde has an anti-inflammatory effect with a gastro protective property.[17]

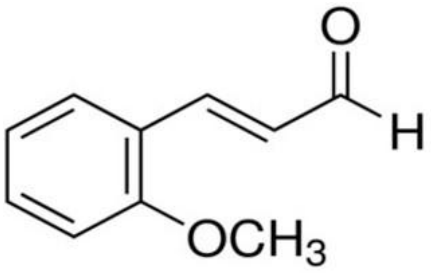
In addition to trans-cinnamaldehyde, cinnamic acid is another phenylpropanoid found in the essential oil of plants such as Panax ginseng C.A. Meyer (Apiaceae), known in China and Korea as a respected herbal medicine, used to maintain physical vitality.[18] An in vitro study showed that cinnamic acid significantly inhibited NO production induced by LPS in RAW 264.7 macrophages and effectively suppressed oxidative damage in human neuroblastoma SH-SY5Y cells, suggesting that this compound contributes to the neuroprotective and anti-inflammatory actions of P. ginseng. In another study, the anti-inflammatory action of safrole, dillapiole and its anhydrous dihydrodilapiole was evidenced in the model of rat paw edema induced by carrageenan. These compounds were isolated from the essential oil extracted from Piper aduncum L. (Piperaceae), a species known to exert a protective action against phytopathogens (for example, bacteria and fungi) and for having an analgesic effect. Dillapiole and dihydrodillapiole significantly suppressed paw edema, while safrole showed less inhibitory action than indomethacin (positive control), indicating a possible use of dillapiole and dihydrodillapiole as compounds exhibiting anti- inflammatory action.[19]

Myristicin is a phenylpropanoid found in carrots, basil, cinnamon, sparingly and nutmeg (seed of Myristicafragrans Houtt., Myristicaceae). In traditional medicine, it is used to treat diarrhea, stomach pain and anxiety. It is also known to exhibit anticholinergic, antibacterial and hepatoprotective properties. An in vitro evaluation of the anti-inflammatory action of myristicin (10, 25 and 50 μM) on macrophages of RAW 264.7 mice stimulated by double-stranded RNA showed that the production of calcium, NO, IL-6, IL-10, interferon protein inducible-10, monocyte chemotactic protein (MCP) -1, MCP-3, granulocyte and macrophage colony stimulating factor (GM-CSF), macrophage inflammatory protein (MIP) -1α, MIP-1β and leukemia inhibiting factor (LIF, a member of the IL-6 family) was significantly suppressed by this compound. These results indicate that myristicin exhibits anti-inflammatory activity inhibiting several participants in the inflammatory response and suggests the involvement of the calcium pathway in this process. Pathogenic oxidative stress with infection results in increased intracellular calcium concentration, leading to stimulation of calcium-dependent kinases and pro-inflammatory activation. Since myristicin has decreased intracellular calcium levels, it is believed that the production of inflammatory mediator in macrophages is being under-regulated by myristicin via the calcium pathway.[20] The latter, although known as anti-inflammatory cytokine, participates in the pathobiological mechanism of autoimmune diseases, such as lupus and encephalomyelitis. In addition, myristicin can alleviate inflammatory lung diseases (for example, bronchial pneumonia and chronic asthma caused by viral infection), as it significantly inhibited the synthesis of MCP-1, MCP-3, GM-CSF, MIR-1α and MIP - 1β, which are implicated in the inflammatory response of many lung diseases. In addition, it can have an anti-inflammatory action against pathogenic infections caused by bacteria and viruses, since it inhibits the production of NO, which is believed to be an important pro-inflammatory mediator in these infections.[20]

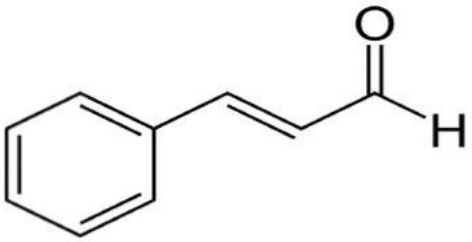
Asarone is a phenylpropanoid found in related herbs. The anti-inflammatory action of asarone has been demonstrated in assays that inhibit the enzyme cyclooxygenase (COX). The investigation of Daucuscarota seed extracts resulted in the isolation and characterization of this compound, which showed 46.15% inhibiting activity of prostaglandin H synthase I (COX-I) and 64.39% of endoperoxide inhibiting activity of endotoxide synthase-II (COX-II) prostaglandin H, both with 100 mg · mL – 1.[21]

Anethole is a natural constituent of the essential oils of many plants, such as star anise (Illiciumverum Hook. F., Illiciacea) and is known to have antioxidant, antifungal, antibacterial, anesthetic and anti-inflammatory properties. Two models of inflammatory pain - acute inflammation induced by carrageenan and persistent inflammation induced by Freund's complement - showed that oral treatment with anethole (125, 250 and 500 mg / kg) in mice suppressed paw edema, myeloperoxidase activity (MLP) and decreased the levels of TNF-α, IL-1β and IL-17, indicating that anethole exerts anti-inflammatory activity in acute and persistent inflammatory models.[22]

E-cinnamaldehyde and o-methoxycinnamaldehyde are responsible for most of the inflammatory activity of cinnamon. If therapeutic concentrations (for example, using advanced methods of administration, such as microencapsulation) can be achieved in target tissues without toxicity, cinnamon and its components can be useful as a treatment for improving age-related inflammatory conditions.



Ortho methoxy cinnamaldehyde



E-cinnamaldehyde

It was also an attempt to isolate the essential oils of three species of Cinnamomum, visibly, C. zeylanicum, C. camphora and C. tamala. LC-MS analysis showed that only C. zeylanicum oil contains cinnamaldehyde. The different oils showed the presence of a number of monoterpenes, diterpenes, etc. A sincere attempt is made to prepare cinnamaldehyde derivatives with available substituted amines using the Schiff base formation scheme.[23]

Cinnamaldehyde and eugenol were effective in suppressing the secretion of proinflammatory cytokines from the cultured PBMCs of RA patients. These compounds have also reduced the neutralizing reactive oxygen/nitrogen species formation which in turn has ameliorated bio molecular oxidation and antioxidant defence response in the PBMC culture of RA patients. Thus these compounds have potential to be used as an adjunct in the management of RA by virtue of their free radical scavenging and anti-inflammatory effects.[24]

Cinnamaldehyde derivative Cinnan 2 showed significant activity at various concentrations and its effect was compared with the standard drug Diclofenac sodium. The maximum percentage inhibition of protein denaturation was observed in 93.84% and 85.61% at 2000 µg / ml, respectively, as shown in Table 1. When compared to standard Diclofenac, sodium was considered Cinnan 2 with activity similar to of Diclofenac sodium.[25]

CONCLUSION

Considerable attention is being paid to the discovery of new drugs capable of combating inflammation, particularly those of plant origin. Essential oils and their active constituents, such as phenylpropanoids, are a promising source of anti- inflammatory substances and the date presented in this review show the possible roles that phenylpropanoids and other cinnmaldehyde derivatives can play in this field. The information available in the scientific literature indicates the participation of phenylpropanoids and cinnamaldehyde analogues in different mechanism of action related to immunomodulation and suppressive action in the inflammatory response, as disclosed in experimental protocols in vitro and in vivo. Cinnamaldehyde and Eugenol showed the progression of arthritis in rats, reducing the formation of reactive species and improving antioxidant status. It also decreased the levels of pro-inflammatory mediators. It is expected that further studies involving clinical trials will be carried out to ensure the safe use of these substances as a therapeutic agent against inflammatory diseases. The results may contribute to clinical application in the management and treatment of rheumatoid arthritis. However, further studies are needed to gain an in-depth view of the action of cinnamaldehyde analogues on rheumatoid arthritis.

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