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Synergizing Nature and Medicine: The Anti-Inflammatory and Analgesic Potential of Essential Oils in Adjunctive Rheumatoid Arthritis Treatment

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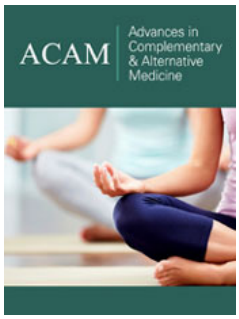

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Abstract

Essential Oils (EO) have been used in traditional medicine for centuries due to their aromatic and medicinal properties. Extracted from aromatic plants through methods like water distillation and supercritical extraction, EO consists of volatile terpenes and hydrocarbons, which are responsible for their biological activities. In traditional medicine, these oils have been used for the treatment of various ailments. As holistic practices have gained popularity in modern medicine, there has been research into the mechanisms of action of the active ingredients of EO, revealing significant anti-inflammatory, antioxidant, and analgesic effects. Although EO show potential in modulating inflammation, studies exploring their use in RA treatment remain limited. This paper reviews the current literature on the anti-inflammatory and analgesic properties of eucalyptus, cinnamon, citronella, and pine essential oils, and evaluates their potential as complementary treatments for rheumatoid arthritis. By bridging traditional practices with evidence-based medicine, we aim to explore new possibilities for managing this debilitating condition.

Keywords: Essential oils; Anti-inflammatory; Analgesic; *Eucalyptus*; Cinnamon; Citronella; Pine; Medicinal effects

Abbreviations: EO: Essential Oils; RA: Rheumatoid Arthritis; TNF-α: Tumor Necrosis Factor-Alpha; IL-1: Interleukin-1; IL-6: Interleukin-6; NSAIDs: Nonsteroidal Anti-Inflammatory Drugs; DMARDs: Disease-Modifying Antirheumatic Drugs; COPD: Chronic Obstructive Pulmonary Disease; MAPK: Mitogen-Activated Protein Kinase; NF-kB: Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; IL-17: Interleukin-17; IL-1B: Interleukin-1B; 5-LOX: 5-Lipoxygenase; COX: Cyclooxygenase; IL-4: Interleukin-4; IL-10: Interleukin-10; KC: Keratinocyte-Derived Cytokine; TLR-4: Toll-Like Receptor 4; MMP-9: Matrix-Metalloproteinase-9; Egr-1: Early Growth Response Factor 1; TRP: Transient Receptor Potential; P2X: Purine 2X; DPPH: 2,2-Diphenyl-1-Picrylhydrazyl; ABTS: 2,2'-Azino-Bis(3-Ethylbenzothiazoline-6-Sulfonic Acid); iNOS: Inducible Nitric Oxide Synthesis; NO: Nitric Oxide; PGE2: Prostaglandin E2; MDA: Malondialdehyde; MPO: Myeloperoxidase: LPS: Lipopolysaccharide; TGF-B: Transforming Growth Factor-Beta; ERK: Extracellular Signal-Regulated Kinase; JNK: Jun N-Terminal Kinase; NLRP3: Nucleotide-Binding Domain Leucine-Rich-Containing Family, Pyrin Domain-Containing-3; cGMP: Cyclic Guanosine Monophosphate; ACPA: Anti-Cyclic Citrullinated Peptide Antibodies: IFN-γ: Interferon-Gamma.

Introduction

Essential Oils (EO) have been a central component of traditional medicine for centuries, valued not only for their aromatic properties but also for their therapeutic benefits [1]. EO are naturally occurring volatile organic compounds extracted from plants through methods like water or steam distillation, solvent extraction, and supercritical extraction [1]. These processes yield concentrated oils rich in bioactive compounds like terpenes and hydrocarbons, which have been the subject of extensive preclinical research [1]. In cell and animal models, EO has demonstrated a wide range of biological activities, including significant

anti-inflammatory, antioxidant, and analgesic effects [2-4]. These findings have sparked interest in the potential applications of EO in various medical conditions, including chronic inflammatory diseases [5]. Rheumatoid Arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation of the joints, leading to pain, swelling, and eventual joint destruction [6]. The pathogenesis of RA involves a complex interplay between genetic predisposition and environmental factors, triggering an abnormal immune response [6]. Key players in this process include pro-inflammatory cytokines such as tumor necrosis factor- alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which perpetuate the inflammatory cascade and damage synovial tissue [6]. Current treatment for RA focuses on both symptomatic relief and disease modification.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and corticosteroids are commonly prescribed to manage pain and inflammation, but their long-term use is associated with significant side effects, including gastrointestinal issues, cardiovascular risks, and osteoporosis. Disease-Modifying Antirheumatic Drugs (DMARDs), such as methotrexate, and biologics like TNF inhibitors aim to slow disease progression by targeting specific components of the immune system. However, these treatments can suppress the immune system, increasing the risk of infections and malignancies. Additionally, not all patients respond adequately to existing therapies, highlighting the need for alternative or complementary treatments [6]. Despite the potential of EO in modulating inflammation, there are limited studies exploring their use in RA treatment [7]. This paper aims to review existing literature on the anti-inflammatory and analgesic properties of eucalyptus, cinnamon, citronella, and pine essential oils, and to evaluate their potential as complementary treatments for rheumatoid arthritis. By integrating traditional knowledge with modern scientific research, we hope to uncover new avenues for the complementary treatment of RA.

Methods

The current review was conducted using a complete and organized search of the available literature until August 2024 on the key words: eucalyptus, cinnamon, citronella, pine, essential oils, anti-inflammatory effects, analgesic effects. The searches were performed using PubMed and Google Scholar.

Eucalyptus

The genus *Eucalyptus* belongs to the Myrtaceae family, which comprises 900 species and subspecies [8]. *Eucalyptus* is native to Australia and Tasmania and has since been introduced to Mediterranean and subtropical regions [8]. The leaves of *Eucalyptus* are an important source of *Eucalyptus* oil which is used in the pharmaceutical, agricultural, cosmetic, and food industries. Of the several *Eucalyptus* species, *E. globulus* is the most widely cultivated species and the world's leading source of *Eucalyptus* oil. The medicinal value of *Eucalyptus* oil largely depends on the monoterpene 1,8-cineole (eucalyptol), which constitutes more than 70% of the total oil. Other major chemical constituents of Eucalyptus oil include limonene and *a*- terpineol. The leaves and bark of *Eucalyptus* have been used for the treatment of various ailments in folk medicine since ancient times. *Eucalyptus* has been reported to possess antimicrobial, antiviral, mucolytic, antispasmodic, anti-diabetic, anti-cancer, antioxidant, anti-inflammatory, and analgesic properties [8]. The rich medicinal value of *Eucalyptus* EO has drawn the attention of several researchers to investigate the mechanisms by which it produces its multifaceted therapeutic effects.

Therapeutic applications of *Eucalyptus*: *Eucalyptus* EO, with its primary active component 1,8-cineole, has a broad range of therapeutic applications. *Eucalyptus* EO has been used for centuries to aid in wound healing. Recent research suggests that 1,8-cineole promotes wound healing through enhanced angiogenesis, collagen formation, granulation tissue development, epithelialization, and wound contraction [8]. The antibacterial properties of *Eucalyptus* EO make it useful for treating minor cuts and wounds and respiratory infections such as sinusitis and bronchitis. Research has demonstrated its antibacterial activity against oral pathogens, dental caries, and biofilm formation [8]. *Eucalyptus* has been used to treat infectious diseases for decades and has demonstrated antiviral activity against herpes simplex viruses as well as coronavirus [8].

Eucalyptus EO is used in various analgesic preparations to relieve pain, particularly in cases of sore muscles or joint pain. The antinociceptive effects of 1,8-cineole are thought to involve both peripheral and central pain systems [8]. 1,8-cineole has been used in the treatment of many respiratory disorders including influenza, rhinosinusitis, bronchitis, pneumonia, asthma, and Chronic Obstructive Pulmonary Disease (COPD) [8]. The therapeutic mechanisms of 1,8-cineole on respiratory disorders are largely due to its anti-inflammatory properties, smooth muscle relaxation, and inhibition of mucus hypersecretion, leading to amelioration of pathological features of chronic airway diseases [4]. 1,8-cineole has shown potential in cancer therapy by regulating various pathways that induce cancer cell apoptosis and senescence, including the tumor suppressor protein p53 signaling pathway, MAPK-mediated pathway, and phosphatidylinositol 3 kinase (PI3K)/AKt/mTOR signaling pathway [4]. The antispasmodic and antisecretory activities of 1,8-cineole make it useful in managing gastrointestinal issues such as diarrhea and peptic ulcer disease [4,8].

The antioxidant and anti-inflammatory properties of 1,8-cineole have therapeutic implications for cardiovascular diseases including hypertension, atherosclerosis, and stroke [4]. The anti-inflammatory effects of *Eucalyptus* have also been evaluated for use in Alzheimer's disease, where 1,8-cineole was shown to reduce neuroinflammation [8]. *Eucalyptus* has been used as a traditional medicine for the treatment of diabetes mellitus. 1,8-cineole has been shown to have promising antidiabetic activity by improving fasting blood glucose levels, insulin sensitivity, inhibiting fructose absorption, reducing proinflammatory cytokines, and blocking carbohydrate hydrolysis enzymes *a*-amylase and *a*-glucosidase [8]. *Eucalyptus* EO has anxiolytic properties due to its GABA agonistic activity [8]. These diverse medicinal attributes highlight the versatility of *Eucalyptus*, and its active component 1,8-cineole, in both traditional and modern medicine.

Anti-inflammatory effects of *Eucalyptus*: The anti-inflammatory properties of *Eucalyptus* EO are largely attributed to 1,8-cineole. On the molecular level, 1,8-cineole exhibits anti-inflammatory effects through attenuation of the NF-κB signaling pathway [4]. The NF-κB pathway is a family of transcription factors that play critical roles in inflammation, immunity, cell proliferation, and survival [9]. Important regulators of the NF-κB pathway include IκB*a*, p105, and A20 [9]. Activation of this pathway leads to the transcription of inflammatory genes including chemokines, cell adhesion molecules, factors of the complement cascade, and acute phase proteins [9]. The κB-dependent target genes include regulators of apoptosis (Bcl family members and inhibitors of apoptosis protein/IAPs) and proliferation (cyclins and growth factors) [9]. Given that NF-κB transcription regulates key cellular processes like cell survival, proliferation, and immunity, disruption of NF-κB pathways results in severe conditions such as arthritis, immunodeficiency, autoimmunity, and cancer [9].

1,8-cineole downregulates NF-κB and its downstream inflammatory genes including 5-LOX, COX-2, TNF-*a*, IL-1B, IL-6, IL-17 [10]. 1,8-cineole also increases expression of anti-inflammatory cytokines such as IL-4 and IL-10 [10]. Moreover, 1,8-cineole demonstrates antioxidant activity by increased superoxide dismutase, catalase, and glutathione levels [10]. One study found that 1,8-cineole significantly attenuated activity of NF-κB by increasing protein levels of IκB*a* and thereby restoring its interaction with NF-κB p65 in U373- and HeLa cells [11]. This interaction inhibited NF-κB p65 translocation to the nucleus, resulting in reduced expression of proinflammatory target genes. 1,8-cineole was also shown to attenuate NF-κB p65 subunit activation, decrease cytokine secretion (TNF-*a*, IL-1B, IL-6, and KC), myeloperoxidase, and oxidative stress in cigarette-induced lung inflammation in mice [12].

1,8-cineole was shown to increase the anti-inflammatory cytokine IL-10 while reducing expression of NF-κB p65, TLR-4, and myeloperoxidase in lung tissue [13]. Another study showed that 1,8-cineole attenuated inflammation-associated increases in cell numbers, matrix-metalloproteinase-9 (MMP-9) expression, and nitric oxide in bronchoalveolar lavage fluid from mice [14]. In human bronchial epithelial cells, 1,8-cineole inhibited phosphorylation of p38 Mitogen-Activated Protein Kinase (MAPK), Akt, and TLR-4 expression [15]. Another transcription factor important in the expression of pro-inflammatory cytokines is early growth response factor 1 (Egr-1) [15]. 1,8-cineole reduced the synthesis and nuclear internalization of Egr-1, thereby reducing the expression of proinflammatory genes [15]. Based on data that demonstrates 1,8- cineole downregulates NF-κB and its downstream pro-inflammatory products and upregulates anti- inflammatory mediators while reducing oxidative stress, it is reasonable to suggest that 1,8-cineole may be a potential therapeutic agent in rheumatoid arthritis.

Analgesic effects of *Eucalyptus*: *Eucalyptus* EO exhibits analgesic properties primarily through its relationship with Transient Receptor Potential (TRP) channels [8]. Following the onset of a painful stimulus, nociceptive neurons are activated and propagate action potentials to nerve terminals found in the dorsal horn of the spinal cord. These neurons release neurotransmitters such as glutamate, substance P, and Calcitonin Gene-Related Peptide (CGRP) to activate postsynaptic receptors, which transmit pain signals to the thalamus. TRP channels are the most important ion channel family that detects and transmits painful stimuli. TRP channels are nonselective integral membrane proteins that respond to various sensory stimuli, including pain, temperature, pH, and osmolarity [16].

1,8-cineole inhibits TRPA1, an excitatory ion channel targeted by cold nociception and inflammatory pain, and activates TRPM8, a thermosensitive receptor involved in pain relief [17]. One study found that 1,8-cineole attenuated edema and mechanical allodynia in mice with effects comparable to that of ibuprofen. Genetic deletion of TRPM8 reversed these effects, suggesting 1,8-cineole provides antinociceptive effects through TRPM8 agonism [18]. Another study showed that 1,8-cineole decreased face rubbing in mice after application of TRPA1 agonist, formalin, suggesting that 1,8-cineole is a TRPA1 receptor antagonist [19]. They also used capsaicin, a TRPV1 agonist, to investigate the mechanism involved in 1,8-cineole antinociception [19]. 1,8-cineole inhibited capsaicin-induced nociception, suggesting it may act as a TRPV1 antagonist [19]. 1,8-cineole effects on the μ-opioid receptor have also been studied. 1,8-cineole exhibited antinociceptive activity comparable to morphine in both tail-flick and hot-plate methods in mice [20]. 1,8- cineole also inhibited the licking response of mice in the early and late phases of the formalin test, comparable to morphine [21].

However, naloxone failed to reverse the antinociceptive effects of 1,8-cineole in both studies, indicating that it likely interacts with other pathways to produce analgesic effects [20,21]. In addition to peripheral pain, 1,8-cineole has been studied in alleviating neuropathic pain by through regulation of the transcription and translation of the purine 2X (P2X) receptor [22]. 1,8-cineole inhibited the transcription of P2X3 receptor mRNA and subsequent translation to P2X3 receptor protein, resulting in inhibition of neuropathic pain signals in rats [22]. Given the analgesic properties of 1,8-cineole, mainly through modulation of TRP channels, that are comparable with ibuprofen and morphine, it is plausible that *Eucalyptus* EO may be used as an adjunctive treatment in pain related to rheumatoid arthritis.

Side effects of *Eucalyptus*: While *Eucalyptus* EO is considered as safe and well-tolerated at normal therapeutic doses, excessive consumption can result in acute toxicity [23]. Common symptoms of acute toxicity include nausea, vomiting, diarrhea, bronchospasm, respiratory depression, drowsiness, slurred speech, ataxia, convulsions, and coma [23]. The recommended dose for adults is 0.05-0.2ml [24]. Fatalities have been reported with doses of 4-5ml. In children, 3-5ml is sufficient to cause fatal complications [24]. It is important to note that 1,8-cineole is metabolized in the liver by cytochrome P450 enzymes (CYP3A4/5) which may lead to enzyme induction, and thus may affect the metabolism of other drugs [25].

Cinnamon

Cinnamon is a common spice that has been used around the world for centuries [3]. Cinnamon is obtained from a tropical evergreen tree from the *Cinnamomum* genus [3]. *Cinnamomum* belongs to the *Lauraceae* family which has around 250 species [26]. The two main species are *Cinnamomum Zeylanicum* (CZ) and *Cinnamomum Cassia* (CC) [26]. CZ, also known as *Ceylon cinnamomum*, is native to Sri Lanka and other parts of southern India whereas CC is indigenous to China [26]. *Cinnamomum* essential oil contains cinnamaldehyde which is the main phytochemical responsible for its spicy taste and therapeutic potential [3]. *Cinnamomum* EO contains other chemical compounds such as eugenol, cinnamyl acetate, L-borneol, L-borneol acetate, B-caryophyllene, caryophyllene oxide, α-cubebene, α-terpinolene, linalool, benzaldehyde, procyanidins and coumarins [3,26]. Like other EO, *Cinnamomum* EO is obtained via distillation or organic solvent extraction [27]. In addition to its use in the food and perfume industries, *Cinnamomum* EO has been used in Ayurvedic medicine as a remedy for a wide array of diseases [28]. It has been used for its antimicrobial, antifungal, gastroprotective, neuroprotective, cardioprotective, antidiabetic, analgesic, antitumor, antioxidant, and anti-inflammatory effects [28]. The significant health benefits of *Cinnamomum* make it applicable in the treatment of various diseases.

Therapeutic applications of cinnamon: A review of 30 different studies evaluating the *in-vitro* antimicrobial properties of *Cinnamomum* found that it exhibits antimicrobial activity against a wide variety of bacteria including *Clostridium, Bacillus, Enterobacter, Enterococcus*, *Escherichia, Haemophilus, Helicobacter, Klebsiella, Listeria, Mycobacterium, Proteus, pseudomonas, Salmonella, Staphylococcus, Streptococcus*, and *Yersinia* species [3]. *Cinnamomum* also displayed antifungal activity against *Aspergillus, Candida, Cryptococcus, Histoplasma, Malassezia, Microsporum, and Trichophyton* species [3]. *Cinnamomum* has also been used in disorders of the gastrointestinal system including treatment of gastric ulcers and diarrhea [3]. *Cinnamomum* has effects on the gynecological system by increasing blood flow to the uterus, supporting tissue regeneration [28].

Cinnamomum was shown to offer ischemic protection by reducing glutamate uptake and cellular swelling in the setting of oxygen and glucose deprivation in rats [28]. *Cinnamomum* has also been studied for therapeutic use in Parkinson's and Alzheimer's disease. *Cinnamomum* increased neuroprotective proteins in Parkinson's disease in mice [28]. *Cinnamomum* reduced the formation of toxic B-amyloid oligomers, thereby reducing plaques and improving cognitive performance of transgenic mice [28]. Several studies have investigated the cardioprotective effects of *Cinnamomum* [28]. *Cinnamomum* protects against platelet aggregation and vascular smooth muscle cell proliferation via thromboxane receptor blocking activity which suggests it may aid in the prevention of vascular diseases and atherosclerosis [28]. *Cinnamomum* also has vasodilatory effects by impeding calcium influx and release [28]. *Cinnamomum* has positive effects on lipids, reducing total cholesterol and triglyceride levels in humans [28]. *Cinnamomum* has demonstrated numerous antidiabetic effects both *in-vitro* and *in- vivo* [28].

Cinnamomum reduced postprandial glucose absorption, increased glucose uptake by GLUT-4, increased glycogen synthesis, decreased gluconeogenesis and increased insulin activity [3]. The insulin-like activity of *Cinnamomum* is largely attributed to its polyphenols [28]. The analgesic potential of *Cinnamomum* has been studied in mice, which demonstrated analgesia through inhibition of prostaglandin synthesis [29]. *Cinnamomum* has been used as an aid in wound healing in traditional medicine [28]. *Cinnamomum* was shown to accelerate epithelialization and increase hydroxyproline content in the wounds of rats [3]. Research on the therapeutic application of *Cinnamomum* in cancer has demonstrated that its antioxidant properties were beneficial in colon cancer and melanoma in murine models [28]. In addition, *Cinnamomum* showed potential effects in restraining tumor cell growth and enhancing apoptosis through its effects on the NF-κB pathway [28].

Cinnamomum has been shown to effectively scavenge reactive oxygen species, including superoxide anions, hydroxyl radicals, and free radicals, and exert hydrogen donating ability capable of reducing DPPH radicals and ABTS radical cations [3]. Several studies have indicated the anti-inflammatory properties of *Cinnamomum* through its effects on the NF-κB pathway and suppression of inducible nitric oxide synthesis (iNOS), cyclooxygenase-2 (COX-2), and TNF-α [28]. In summary, *Cinnamomum* exhibits a broad spectrum of therapeutic potential, showing promise in treating various medical conditions. Its effects on disorders of multiple organ systems, alongside its antioxidant and anti-inflammatory properties, underscore its diverse utility in both traditional and modern medicine. Its multifaceted benefits, supported by a range of studies, highlight *Cinnamomum* as a valuable candidate for further research and therapeutic application.

Anti-inflammatory effects of cinnamon: Cinnamaldehyde is the primary chemical constituent responsible for the anti-inflammatory effects of *Cinnamomum*. It exerts its anti-inflammatory effects through multiple mechanisms. In LPS-stimulated RAW 264.7 macrophage and carrageenan-induced paw edema models, cinnamaldehyde demonstrated significant concentration-dependent inhibition of Nitric Oxide (NO), TNF-α, and prostaglandin E2 [30]. It also blocked expression of iNOS, COX-2, and NF-κB in these models [30]. Additionally, cinnamaldehyde enhanced activities of catalase, superoxide dismutase, and glutathione peroxidase, while decreasing Malondialdehyde (MDA) level and Myeloperoxidase (MPO) activity in the paw edema model [30].

Similarly, in IFN-Y activated RAW 264.7 macrophages, cinnamaldehyde decreased production of NO and TNF-α [31]. Cinnamaldehyde inhibited DNA binding of NF-κB and NF-κB transcriptional activity in LPS-induced RAW 264.7 macrophages [32]. Another study found that in cinnamaldehyde reduced expression of pro-inflammatory cytokines IL-1B, IL-6, and TNF-α in a dose-dependent manner in LPS-induced RAW 264.7 murine macrophages, and significantly decreased phosphorylation of

ERK, JNK, and p38 MAPK, suggesting that suppression of NO and pro- inflammatory cytokines occurs through these pathways [33]. Cinnamaldehyde also inhibited monocyte chemoattractant protein-1 and macrophage inflammatory protein-1α in LPS activated murine macrophages, while increasing levels of anti-inflammatory mediators including IL-10, TGF-B, and iron exporter ferroportin 1 [34]. Additionally, cinnamaldehyde suppressed activation of NF-κB and blocked degradation of IκB in H. pylori infected cells [35]., also exhibits anti-inflammatory and antioxidant properties.

In peripheral blood mononuclear cells of rheumatoid arthritis patients, cinnamaldehyde and eugenol significantly reduced levels of TNF-α and IL-6 and reactive oxygen species, ameliorating biomolecular oxidation [36]. Through reducing levels of TNF-α and reactive oxygen species, cinnamaldehyde and eugenol may suppress NF-κB activation to produce their anti-inflammatory effects [36]. Furthermore, eugenol inhibited NF-κB activation and decreased MPO activity in LPS-induced acute lung injury [37]. Eugenol also improved levels of catalase, superoxide dismutase, glutathione peroxidase, and glutathione-S-transferase in lung tissue after LPS treatment, demonstrating anti-inflammatory and antioxidant properties [37]. In summary, cinnamaldehyde inhibits the expression of proinflammatory mediators (NO, TNF-α, IL-6) and enzymes involved in inflammation such as iNOS and COX-2 while increasing expression of IL-10 and TGF-B. It also suppresses inflammatory pathways including NF-κB, ERK, JNK, and p38 MAPK. Additionally, eugenol inhibits inflammatory cytokine expression and NF-κB activation. Together, this preclinical data supports the potential use of *Cinnamomum* as a therapeutic agent for rheumatoid arthritis.

Analgesic effects of cinnamon: Cinnamaldehyde has peripheral analgesic properties but may produce central hyperalgesia. Research suggests that cinnamaldehyde exerts peripheral analgesic effects through inhibition of COX enzymes and reduction in prostaglandins. Cinnamaldehyde increased the pain threshold of mice in a dose dependent manner in an acetic acid induced writhing method. It also decreased the number and delayed the onset time of writhes compared to diclofenac sodium. When cinnamaldehyde was combined with diclofenac sodium, there was significantly better analgesic activity compared to diclofenac alone. Acetic acid in mice results in an acute inflammatory reaction that produces prostaglandins in the peritoneal fluid. Therefore, these results suggest that cinnamaldehyde may act through COX inhibition to decrease prostaglandin formation and alleviate pain, similar to non-steroidal anti-inflammatory drugs [29]. In contrast, cinnamaldehyde is a known agonist of TRPA1 and may also act on TRPV1 to produce acute pain and heat hyperalgesia [38].

Furthermore, a study evaluating the effect of cinnamaldehyde on central pain found that it had a dose-dependent hyperalgesia effect and decreased the effects of pentazocine [29]. Eugenol has peripheral and central analgesic effects [39]. Eugenol demonstrated a dose-dependent antinociceptive effect in the acetic-acid induced writhing test [39]. It also reduced the nociceptive response time for formalin, substance P, and glutamate injections [39]. When pretreated with yohimbine or naloxone, the antinociceptive effects of eugenol were diminished, suggesting it may also act on α2-adrenergic and opioid receptors [39]. In essence, *Cinnamomum* has analgesic effects from both cinnamaldehyde and eugenol. Cinnamaldehyde primarily reduces peripheral pain through inhibition of COX, whereas eugenol reduces peripheral and central pain through modulating multiple pathways.

Side effects of cinnamon: Cinnamon oil has relatively few adverse effects [40]. A systematic review found that the most frequent adverse events associated with cinnamon in humans were self-limiting gastrointestinal disorders and allergic reactions such as contact dermatitis [40]. A study on the toxicity of cinnamon in rats revealed that a dose of cinnamon aqueous extract below 0.5g/kg is low to moderate in toxicity with a high LD50 value [41]. Cinnamon contains small amounts (0.004-1.0%) of coumarins which have anticoagulant and hepatotoxic properties [3]. Therefore, cinnamon could increase risk of bleeding and liver damage in some patients.

Citronella

Cymbopogon, commonly known as lemongrass or citronella grass, is an aromatic plant belonging to the Poaceae family [42]. Originally native to West Malaysia, citronella grass is now cultivated worldwide, due to its adaptability to diverse climates [42]. The species *Cymbopogon nardus* and *Cymbopogon winterianus* are the primary sources of citronella EO, which is extracted from the grass using steam distillation, hydro-distillation, or supercritical fluid extraction [42]. Citronella EO is widely used in the soap, perfumery, cosmetic, insect repellent, and flavoring industries [42]. It is particularly rich in citronellal, geraniol, and citronellol, while also containing other constituents such as citronellyl acetate, L-limonene, elemol, and other sesquiterpene alcohols [42]. Traditionally, the therapeutic applications of citronella EO have focused on its antiparasitic, antifungal, and antibacterial properties [42]. However, recent research into its active components suggests that citronella EO may also possess anti-inflammatory and analgesic effects.

Therapeutic applications of citronella: Citronella EO is commonly used as a natural insect repellent due to its primary constituents, citronellal, citronellol, and geraniol, masking scents that attract insects thereby acting as food deterrents [43]. It also has antimicrobial properties through inhibition of biofilm formation [44]. Citronella EO has also been used as an anticonvulsant and anxiolytic, possibly by enhancing GABAA receptor activity and inhibiting the voltage-gated sodium channel receptor [45]. In traditional medicine, it has been used as a diuretic, antispasmodic, and in massage oil for joint and muscle pain [42]. Recently, its antioxidant, anti-inflammatory, and antiproliferative effects through induction of the cell cycle were demonstrated on prostate cancer cells [46]. More research is needed to fully evaluate the extent of the therapeutic effects of citronella, particularly in the treatment of inflammatory rheumatoid arthritis.

Anti-inflammatory effects of citronella: The primary active constituents of citronella EO are citronellal, geraniol, and citronellol. Research has shown that citronellol and geraniol

inhibit iNOS activity thereby suppressing NO production. These compounds also decrease LPS-induced COX-2 protein expression and prevent degradation of IκBα, reducing NF-κB nuclear translocation [47]. Additionally, geraniol has been shown to increase IL-10 production in human monocytes [48]. Citronellol has demonstrated anti-inflammatory effects in LPS-induced acute lung injury by attenuating the NF-κB pathway and reducing levels of TNF-α and COX-2 in a dose-dependent manner [5]. Citronellal, on the other hand, was shown to inhibit arachidonic acid-induced rat hind paw edema, suggesting that its anti- inflammatory activities are associated with inhibition of enzymes in the arachidonic acid pathway [49]. In a study on rats with urate-induced gouty arthritis, citronella EO was shown to reduce swelling and redness at joints, inhibit neutrophil infiltration and decrease proinflammatory mediator secretion [50]. They demonstrated that citronella EO exerts its anti-inflammatory effects by decreasing phosphorylation of the PI3k/AKT/mTOR signaling pathway and inhibiting activation of NLRP3 inflammation and production of inflammatory cytokines [50].

In a study on bleomycin-induced pulmonary fibrosis in mice, the major components of citronella EO-citronellal, geraniol, and citronellol-were found to significantly reduce inflammation in bronchoalveolar fluid, lower malondialdehyde levels, and increase superoxide dismutase activity. It also reduced expression of α-smooth muscle actin and TGF-B, likely because of reduced oxidative stress and inflammation [51]. Another study highlighted the anti-inflammatory and antioxidant properties of citronella EO, demonstrating its ability to inhibit neutrophil migration to the peritoneal cavity and scavenge free radicals in a DPPH assay conducted on mice [52]. Given its diverse anti-inflammatory properties, including the inhibition of key inflammatory pathways and reduction of oxidative stress, citronella essential oil shows promising potential as a therapeutic agent for the treatment of rheumatoid arthritis. Its ability to target multiple mechanisms of inflammation suggests it could be a valuable addition to the current range of treatments, offering a natural alternative for managing this condition.

Analgesic effects of citronella: Citronella exerts its analgesic effects likely through inhibition of both peripheral and central pain pathways [53]. Studies show that both citronellol and citronellal significantly reduced acetic acid induced writhing in mice which suggests their antinociceptive mechanism involves inhibition of prostaglandin synthesis through the arachidonic acid pathway and COX enzymes [53,54]. Both compounds increased the latency response on the hot-plate test in mice which indicates that they also have central analgesic effects [53,54]. In the mice treated with citronellal, the central analgesic activity was confirmed by blocking the effect with the opioid antagonist, naloxone [53]. The analgesic effect of citronellol was further evaluated using the formalin test. Citronellol inhibited the early and late phases of the test, indicating its effects on neurogenic and inflammatory pain [54]. Another study demonstrated that citronellal blocked the nociceptive response induced by treatment with TNF-α to a similar extent as observed with treatment with indomethacin [55]. Moreover, they showed that citronellal inhibited the nociceptive response induced by PGE2 and dopamine, highlighting its analgesic effects through attenuation of mechanical nociception through activation of the NO- cGMP-K+ ATP pathway [55].

Side effects of citronella: Citronella EO is recognized by the U.S. Food and Drug Administration as generally safe [56]. In animal studies, citronella EO showed little or no toxicity. The EO has been extensively used since 1948 without any reports of adverse effects other than mild skin irritation in some cases. Therefore, when used according to label instructions, citronella is not expected to pose significant health risks to people [57].

Pine

Pinus is the largest genus belonging to the Pinaceae family [58]. The Pinaceae family comprises 225 species with almost half considered as true pines. *Pinus* is commonly split into two subgenera, *Pinus* and Strobus, based on the number of fibrovascular bundles in the needle. Subgenus *Pinus* includes Middle European and mediterranean pines whereas *strobus* includes Asian and North American pines. Pines are tall resinous trees known for their distinct, needle-shaped evergreen leaves and are essential to temperate forests across the world. In addition to its use in the cosmetic industry for its fragrant odor, pine is an important source of timber, pulp, nuts, seeds, resin, and construction material. In traditional medicine, various preparations of pine have been used for the treatment of several ailments for years. Pine EO, obtained typically by hydrodistillation, is composed of important chemical compounds including monoterpenes (α-pinene, B-pinene, limonene, δ-3-carene, B-phellandrene) and sesquiterpenes (germacrene D, B-caryophyllene). Chemical analysis of pine EO has demonstrated that α-pinene is the principal compound of many *Pinus* species. Therefore, the therapeutic effects of pine EO are mainly attributed to α-pinene.

Therapeutic applications of pine: In traditional medicine, various preparations of pine have been used to aid in wound healing and for the treatment of dermatitis and respiratory tract infections [59]. Additionally, the turpentine extract of pine has been shown to have antioxidant, antiviral, analgesic, anti-inflammatory, and antimicrobial properties [58]. The EO of pine has demonstrated antibacterial, antiviral, and antifungal properties [58,60]. Recent research has investigated the anti-inflammatory and analgesic properties of pine EO. α-Pinene, a primary constituent of pine EO, is also found in many other plant EO and has demonstrated multiple promising therapeutic effects [61].

Anti-inflammatory effects of pine: There is limited research on the anti-inflammatory effects of pine EO. However, α-pinene, a primary constituent of many *Pinus* species and other plant EO, has been shown to have anti-inflammatory properties through attenuation of the NF-κB pathway and reducing proinflammatory molecules. Therefore, pine EO may demonstrate anti-inflammatory properties due to the presence of α-pinene. In human monocytes, α-pinene increased levels of IκBα and inhibited nuclear translocation of NF-κB p65 in a dose dependent

manner [62]. α-Pinene demonstrated anti-inflammatory activity through attenuation of MAPKs and the NF-κB pathways in murine macrophages [63]. It also inhibited LPS-induced secretion of IL-6, TNF-α, and NO, and expression of iNOS and COX-2 [63]. α-Pinene demonstrated protective effects in pancreatic and lung tissue by reducing histological damage and MPO activity. It also reduced TNF-α, IL-1B, and IL-6 in isolated cerulein treated pancreatic acinar cells [64].

Furthermore, α-pinene was shown to decrease lipid peroxidative markers, restore antioxidants, and attenuate expression of TNF-α, IL-6, and NF-κB in isoproterenol-treated cardiac tissue in rats [65]. Moreover, α-pinene improved antioxidant activity and neuroinflammation in hippocampal tissue in rats. It was shown to decrease MDA and NO levels, increase glutathione, and enhance catalase activity. It also reduced messenger RNA expression of IL-1B, TNF-α, IL-6, and N-methyl-D-aspartate receptor subunits 2A and 2B [66]. One study demonstrated that pine EO reduced secretion of proinflammatory cytokine IL-6 in LPS-stimulated RAW 264.7 macrophages [67]. Another group demonstrated that pine EO inhibited acetic acid-induced capillary permeability, suggesting it may also attenuate inflammation through the arachidonic acid pathway and inhibition of prostaglandin synthesis [68]. Additionally, it inhibited carrageenan-induced paw inflammation, indicating its potential action against release of early phase inflammatory mediators such as histamine, serotonin, and kinins, and later phase arachidonic acid metabolites and neutrophil degranulation [69].

Analgesic effects of pine: Research suggests that pine EO exhibits analgesic effects through multiple mechanisms. One study found that pine EO increased pain threshold in mice using the hot plate method [69]. Additionally, pine EO decreased abdominal writhing in the acetic acid induced model, suggesting it may inhibit products of the arachidonic acid pathway involved in inflammation and pain such as PGE2. Pine EO also suppressed pain behavior in the acute and chronic phase of the formalin test. The analgesic effect of pine EO was not reversed with administration of naloxone, ondansetron, or yohimbine, suggesting it does not act upon opioid, serotonin, or α2-adrenergic receptors [70]. Glibenclamide, an ATP-dependent K+-channel blocking agent, partially reversed the antinociceptive effect of pine EO, indicating its analgesic effects may partially involve the NO/cGMP/cGMP protein kinase pathway [70]. Pine EO has been shown to be effective in alleviating acute and chronic pain in various tests. Further research is needed to confirm its analgesic mechanism of action and its efficacy in humans.

Side effects of pine: There is limited information regarding the side effects and potential toxicity of pine EO. Case reports of patients who ingested pine oil cleaner reveal adverse effects including mucus membrane and gastrointestinal irritation, chemical pneumonitis, central nervous system depression, and rarely, coma [71]. Ingestion of pine oil was rarely life threatening; most cases required only gastrointestinal decontamination and supportive care [71]. α-Pinene has also demonstrated cytochrome P-450 inducing activity and anticoagulant properties in mice [61].

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic autoimmune disease characterized by inflammatory arthritis and extra-articular involvement [7]. The prevalence of RA in the United States is approximately 0.7% and affects women more commonly than men. Although the exact cause is unknown, it is believed to result from a combination of genetic predisposition, environmental factors, and immune dysregulation. The risk of developing RA has been associated with specific HLA-DRB1 alleles that contain the "Shared Epitope" (SE) gene, as well as polymorphisms in other genes. Interaction between environmental factors such as cigarette smoke and the HLA-DRB1 SE gene can activate the immune system and lead to the formation of autoantibodies such as Anti-Cyclic Citrullinated Peptide Antibodies (ACPA). The immune response in RA begins at extra-articular sites such as the lungs, gums, and gastrointestinal tract, where citrullination and formation of autoantibodies occur. Eventually, autoantibodies are produced by plasma cells in the synovium, leading to inflammation. Macrophages infiltrate the synovium, releasing proinflammatory molecules like TNF-α, IL-1, IL-6, and chemokines, while neutrophils egress from the blood and migrate to the synovial fluid and produce prostaglandins, proteases, and reactive oxygen species.

Altogether, this drives inflammation and causes cartilage destruction. Resident fibroblasts-like synoviocytes, chondrocytes, and osteoclasts are activated, resulting in cartilage damage and bone erosions. T cells and B cells also take up residence in the synovium. Their interaction leads to the production of Rheumatoid Factor (RF) and ACPA, which bind their respective antigens and form immune complexes that activate the complement system, promoting inflammation. Additionally, activated T cells in the synovium produce proinflammatory cytokines like IL-17 and IFN-γ which attract more inflammatory cells into the joint space. This overproduction of cytokines in the synovium propagates an intense, chronic inflammatory response resulting in cartilage loss and bone erosions [7]. RA is a progressive disease that without treatment is associated with increased disability and mortality. The current therapies for RA include Disease-Modifying Antirheumatic Drugs (DMARDs), Non-Steroidal Anti- Inflammatory Drugs (NSAIDS), and corticosteroids, with methotrexate being the initial drug of choice [7].

However, these therapies can be costly and associated with serious side effects. NSAIDs have the potential for gastrointestinal, renal, hematologic, and cardiovascular side effects, while long-term corticosteroid use carries the risk of weight gain, osteoporosis, and infection [7]. The most serious side effects are associated with DMARDs which are summarized in (Tables 1 & 2) [7,72-80]. Moreover, DMARDs are contraindicated or not well studied in certain populations such as pregnancy or those with heart failure or chronic obstructive pulmonary disease [7,72,76,77]. Given this information, the anti-inflammatory and analgesic compounds found in plant essential oils used in traditional medicine may hold significant therapeutic potential for the complementary treatment of rheumatoid arthritis. These natural remedies could offer a more

cost-effective and safer alternative with fewer adverse effects compared to conventional therapies, making them a promising option for managing RA, especially in populations where current treatments pose additional risks.

Table 1: Nonbiologic DMARDs.

Nonbiologic DMARDs	MOA	Side Effects
Methotrexate	Inhibits AICAR transformylase > adenosine accumulation suppresses activity of T cells and B cells	GI distress, rash, bone marrow suppression, hepatotoxicity, interstitial lung disease, folic acid deficiency
Leflunomide	Inhibits dihydro-orotate dehydrogenase > inhibits lymphocyte proliferation	GI distress, rash, bone marrow suppression, hepatotoxicity, hypertension, peripheral neuropathy, weight loss
Sulfasalazine	Exact mechanism unknown; may inhibit NF-kB pathway	GI distress, rash, bone marrow suppression, hepatotoxicity, DRESS syndrome
Hydroxychloroquine	Inhibits intracellular toll-like receptor TLR9	GI distress, rash, retinopathy/maculopathy

Table 2: Biologic DMARDs.

Nonbiologic DMARDs	MOA	Side Effects
TNF-alpha inhibitors	Inhibits TNF-alpha > blocks activation of NF-kB, caspases, and protein kinases (JNK, MAPK), > attenuates inflammation	Infection, reactivation of infection, malignancy, drug-induced lupus, demyelinating disorders, rash, avoid in CHF (NYHA Class II or IV), not studied in pregnancy or lactation.
Rituximab	Anti-CD20 monoclonal antibody > depletes B cells > attenuates inflammation	Infusion reactions, infection, reactivation of infection, pancytopenia, rash, renal, respiratory, cardiovascular, GI, and neuropsychiatric effects, not recommended in pregnancy, live vaccines contraindicated
Abatacept	Binds to CD80 and CD86 > inhibits T cell activation > attenuates inflammation	Infection, reactivation of infection, hypersensitivity reactions, malignancy, caution in COPD, not studied in pregnancy or lactation
Tocilizumab	Monoclonal antibody that inhibits IL-6 receptor > attenuates inflammation and prevents activation of synovial fibroblasts	Hyperlipidemia, hepatotoxicity, infusion reactions, hypertension, GI distress, leukopenia, neutropenia, thrombocytopenia, infection
Tocilizumab	Inhibits JAK enzymes > attenuates intracellular growth factor and cytokine-mediated signals by the JAK-STAT pathways	Infection, reactivation of infection, malignancy, hyperlipidemia, anemia, leukopenia, GI distress, rash, hypertension

Discussion

Essential oils have been used in traditional medicine for centuries to treat a wide variety of diseases [1]. The literature has documented many therapeutic applications of EO, including antimicrobial, antiviral, antidiabetic, antitumor, antioxidant, analgesic, anti-inflammatory, cardioprotective, and neuroprotective effects [3,4,47,69]. Despite their common use in traditional medicine for muscle and joint pain, and their demonstrated anti-inflammatory and analgesic effects, there are relatively few studies specifically evaluating the use of EO for the treatment of Rheumatoid Arthritis (RA) [2]. This paper reviewed the current research on the EO of *Eucalyptus*, cinnamon, citronella, and pine, focusing on their active components to assess their potential use in treating RA. Among the EO reviewed, *Eucalyptus* and cinnamon have the most substantial and well-researched anti-inflammatory effects. The primary active component of *Eucalyptus* EO, 1,8-cineole, has been shown to inhibit the NF-κB signaling pathway and reduce the secretion of pro-inflammatory cytokines [4,11-13].

Additionally, 1,8-cineole exhibits analgesic effects by modulating TRP channels [8]. Cinnamaldehyde, a major constituent of cinnamon EO, demonstrates anti-inflammatory effects by potentially suppressing multiple pathways, including NF-κB, ERK, JNK, and p38 MAPK [30-34]. It also inhibits several inflammatory mediators, such as TNF-α, COX-2, PGE2, IL-6, IL-1β, and NO [30-34]. Another active component of cinnamon EO, eugenol, also inhibits NF-κB and suppresses pro-inflammatory cytokines [36,37]. Both cinnamaldehyde and eugenol reduce pain primarily through the inhibition of COX and the subsequent reduction of prostaglandins [29,39]. Although there are fewer studies on citronella EO, the existing literature suggests that it inhibits NF-κB and the PI3K/AKT/mTOR pathways and reduces pro-inflammatory mediators like TNF-α and COX-2 [5,47-50]. Citronella EO appears to alleviate peripheral and central pain through multiple mechanisms, including the inhibition of the arachidonic acid pathway and COX, opioid receptor antagonism, and activation of the NO-cGMP-K+ ATP pathway [5,47-50]. The anti-inflammatory potential of pine EO is not well-documented, but the available studies suggest that it inhibits early-phase inflammatory mediators and later-phase arachidonic acid metabolites [68,69].

More research has been conducted on α- pinene, a major component of pine EO, which has been shown to inhibit NF-κB and reduce the secretion of pro-inflammatory molecules [62,63]. Pine EO is thought to reduce pain by inhibiting the arachidonic acid pathway and COX, with additional analgesic effects possibly mediated through partial action on the NO/cGMP/cGMP protein kinase pathway [70]. The combined anti-inflammatory and analgesic properties of these EO suggest that they are promising candidates for complementary treatment of RA. Although the exact etiology of RA is unknown, the overproduction of pro-inflammatory molecules results in chronic inflammation, cartilage damage, and bone loss [7]. Thus, EO that inhibit NF-κB and other inflammatory pathways may alleviate RA symptoms by reducing secretion of pro-inflammatory molecules. Their ability to reduce both inflammation

and pain could complement current RA treatments, potentially improving symptoms and reducing disability, while offering fewer side effects and being cost-effective.

Conclusion

In conclusion, the essential oils of *Eucalyptus*, cinnamon, citronella, and pine show promising potential as complementary treatments for rheumatoid arthritis due to their anti-inflammatory and analgesic properties (Figure 1 & 2). The inhibition of key inflammatory pathways, such as NF-κB, and reduction of pro-inflammatory cytokines by active compounds like 1,8-cineole, cinnamaldehyde, eugenol, citronellol, geraniol and α-pinene, positions these EO as effective agents in managing the chronic inflammation and pain associated with RA. While current research highlights the benefits of these EO, further studies are necessary to fully understand their mechanisms of action, optimal usage, and long-term efficacy in RA treatment. Integrating these EO into existing therapeutic strategies could potentially enhance patient outcomes by reducing symptoms, improving quality of life, and offering a cost-effective and natural adjunct to conventional RA therapy (Figure 3 & 4).

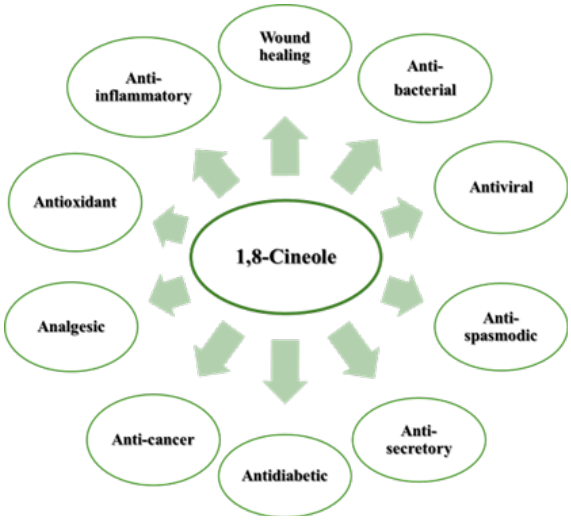

Figure 1: Therapeutic effects of 1,8-cineole.

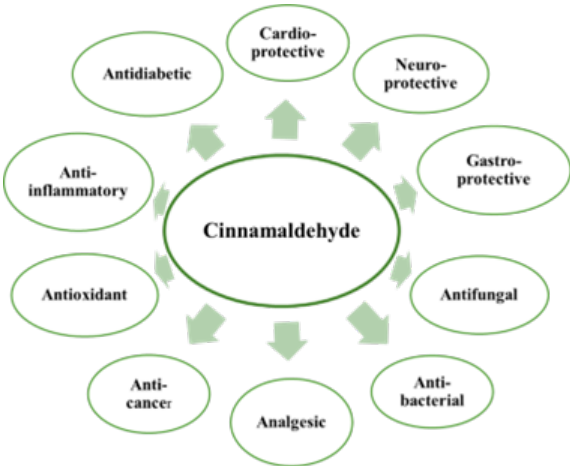

Figure 2: Therapeutic effects of cinnamaldehyde.

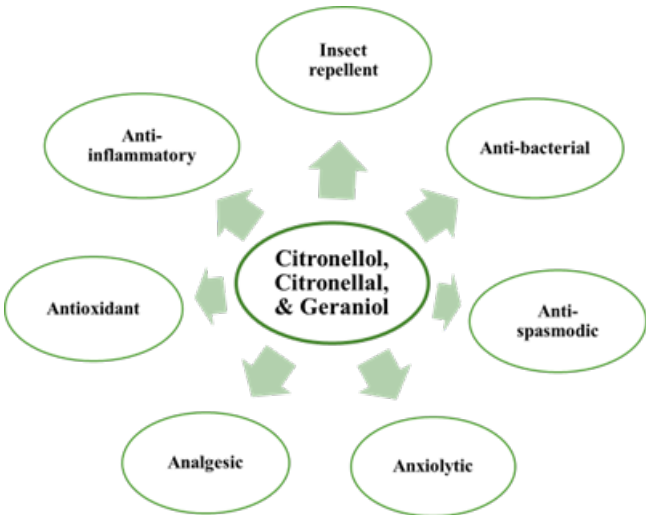

Figure 3: Therapeutic effects of Citronellol, Citronellal, and Geraniol.

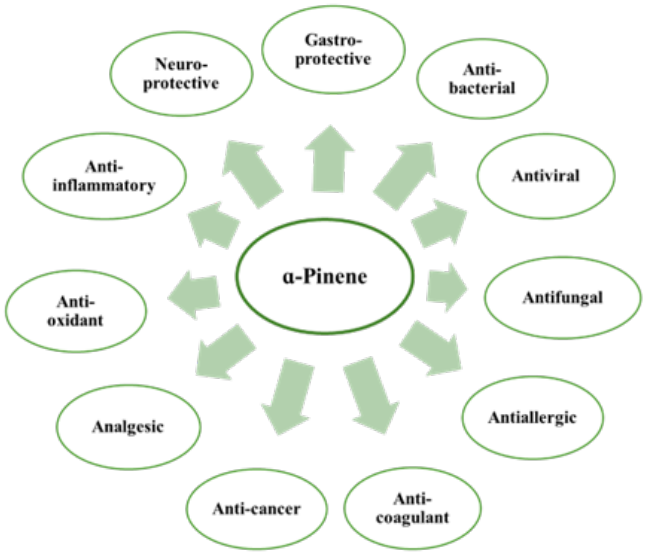

Figure 4: Therapeutic effects of α-Pinene.

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Conflicts of Interest

The authors declare no conflicts of interest.

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