

# 1,8-cineole: An Underappreciated Anti-inflammatory Therapeutic

Sarah K Brown, William S Garver and Robert A Orlando\*

Department of Biochemistry and Molecular Biology, University of New Mexico, Albuquerque, USA

## Abstract

The inflammatory response is typically initiated by infection or cellular injury, and provides host protection aimed at clearing the initial triggering event, as well as providing long-term protective immunity. When properly functioning, the inflammatory process is a mediator of acute injury to restore tissue health and is characteristically self-limiting once tissue repair and homeostasis have been restored. If tissue health is not restored, such as if the tissue harbors a continuous low grade inflammatory stimulant, then the inflammatory process becomes a chronic response that continuously damages the surrounding tissue in its attempt to provide repair. Left unchecked, long-term inflammation can result in diseases of chronic inflammation, such as autoimmunity or age-related diseases. Choice of current anti-inflammatory therapies is often limited by patient risk-benefit considerations. Traditional approaches to manage chronic inflammation include non-steroidal anti-inflammatory drugs or corticosteroids which provide short-term benefits, but are often plagued with significant side effects that preclude their use for long-term therapy. The newest classes of anti-inflammatory therapeutics, biologics, are engineered monoclonal antibodies that bind pro-inflammatory mediators and neutralize their effects by preventing pro-inflammatory signaling.

Unfortunately, biologic therapies are often prohibitively expensive and have serious, sometimes life-threatening side effects. In lieu of biologics or chemically synthesized small molecules, natural products have provided a rich source of small molecule effectors. One particular natural product, 1,8-cineole, also called eucalyptol, is reported to have anti-inflammatory, anti-microbial, and anti-oxidant activity. Several clinical trials have established potent anti-inflammatory activity for 1,8-cineole, which may suggest its use as a primary treatment, or at the very least, an adjunct therapy for current anti-inflammatory agents. We argue that use of 1,8-cineole as an anti-inflammatory agent needs greater study in other diseases with a chronic inflammatory component, including atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and arthritic complications.

**Keywords:** 1,8-cineole; Eucalyptol; Inflammation

## Introduction

The inflammatory response is a vital physiologic function that is initiated by infection or cellular injury, autoimmune activation, or age-related mechanisms [1]. Age-related mechanisms include atherosclerotic cardiovascular disease, type 2 diabetes, and most forms of neurodegenerative diseases. In the case of infection or cellular injury, inflammation provides host protection aimed at clearing the initial triggering event, as well as providing long-term protective immunity. The primary trigger for this type of inflammation involves activation of the innate immune system and is mediated by macrophages, mast cells, and dendritic cells, as well as circulating leukocytes, including monocytes and neutrophils [2]. Activation of innate immunity is a first-line response to pathogen invasion or cell damage through antigen recognition using pattern recognition receptors, such as scavenger and Toll-like receptors [3]. Once these pattern recognition receptors are engaged, signaling cascades through Nuclear Factor-kappa B (NF-κB) and Mitogen Dependent Protein Kinase (MAPKs) pathways are activated that trigger the release of chemo attractive factors that accelerate recruitment of leukocytes to the region [4]. Cells of the innate immune system respond to antigen presentation in a less specific manner than the adaptive immune system [5]. The innate response is not designed to provide long-lasting immunity to the host, this being the function of the adaptive system. The innate immune system provides rapid and immediate defense against infection and cell injury and is typically self-limiting once tissue repair and homeostasis have been restored.

Unlike infection and cellular injury, inflammatory responses due to autoimmune and age-related, non-autoimmune processes are largely non-resolvable and often result in chronic disease states. Characterizing non-autoimmune inflammation presents unique challenges since the initiating signals are sometimes obscure; as in the case of obesity-dependent type 2 diabetes, or often simply an excess of natural occurring factors, such as saturated fatty acids in the case of atherosclerosis [6,7] or deposits of protein aggregates in the case of

neurodegeneration [8]. Regardless of the initiating stimulus, the chronic inflammatory component in these diseases establishes the necessary conditions for developing a non-resolvable immune response. For example, developing insulin resistance in type 2 diabetes is often linked with obesity as a result of activation of the innate immune response within obese adipose tissue [9]. In obese adipose tissue, infiltration and activation of M1 macrophages serves to initiate and sustain chronic expression of pro-inflammatory cytokines in both adipocyte and macrophage populations through an NF-κB-dependent mechanism [10]. Once chronic systemic levels of inflammation are achieved from this expression, insulin receptor signaling activity becomes increasingly impaired [11]. In developing atherosclerosis, resident arterial macrophages provide cellular clearance of Oxidized Low-density Lipoprotein (oxLDL) particles, which over time and excess, severely impairs their phagocytic function because of intracellular cholesterol accumulation and defective HDL-mediated efflux. These events lead to macrophage-to-foam cell transition that significantly increases immune cell residence time within arterial lesions resulting in a sustained innate immune response and progressive tissue damage. This persistent pro-inflammatory phenotype has recently been termed “trained innate immunity” and is likely responsible for the chronic inflammatory process in atherosclerotic disease [1]. There is no question that inflammation is essential for maintaining organismic health and survival. The inflammatory process properly functions as a

\*Corresponding author: Robert A Orlando, Department of Biochemistry and Molecular Biology, University of New Mexico, Albuquerque, USA, Tel: 505-272-5593; Fax: 505-272-5593; E-mail: [rorlando@salud.unm.edu](mailto:rorlando@salud.unm.edu)

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mediator of acute injury to restore tissue health. If tissue health is not restored or if the tissue harbors a continuous low grade inflammatory stimulant, then the inflammatory process becomes a chronic response that continuously damages the surrounding tissue in its attempt to provide repair. Left unchecked, long-term inflammation can result in diseases of chronic inflammation, manifested by both autoimmune and non-autoimmune mechanisms. Collectively, these and other discoveries have provided focused research opportunities to begin developing anti-inflammatory therapies that target multiple diseases.

### Treatment Modalities for Chronic Systemic Inflammation

When selecting an anti-inflammatory therapy, one of the most important considerations is patient risk-benefit profile. Traditional approaches to manage chronic inflammation, which include Non-steroidal Anti-inflammatory Drugs (NSAIDs), provide short-term benefits, but are often plagued with significant secondary side effects that preclude their use for long-term therapy [12]. NSAIDs such as ibuprofen and naproxen provide temporary relief from inflammatory events; however their extended use also results in serious gastrointestinal complications due to non-specific targeting of both cyclooxygenase 1 and 2 enzymes.

Cyclooxygenase 2-specific inhibitors circumvent gastrointestinal complications, yet negatively alter platelet activity leading to thrombotic disease and stroke [13]. These more classical approaches to management of inflammation are still in practice, largely due to poor or costly alternatives. Because of serious side effects, patients on these therapeutics must be closely monitored and terminate the therapy when complications begin to surface, only to continue suffering from the consequences of chronic inflammation.

Methotrexate is classified as a Disease-modifying Anti-rheumatic Drug (DMARD). Weekly administration of methotrexate is accepted as a first-line therapy for patients with Rheumatoid Arthritis (RA) [14,15]. The precise mechanism-of-action of methotrexate is still subject to considerable debate [16]. Originally, methotrexate was identified as an anti-folate therapy as it is a potent inhibitor of dihydrofolate reductase. As such, high doses demonstrate anti-proliferative effects by inhibiting nucleotide biosynthesis. Low-dose methotrexate treatment has presented a more complicated mechanistic picture, which includes antagonism of folate metabolism, stimulation of adenosine signaling, inhibition of methyl-donor substrates, generation of reactive oxygen species, down regulation of adhesion-molecule expression, modification of cytokine profiles and down regulation of eicosanoids and matrix metalloproteinase [15,17]. Common side effects associated with low-dose methotrexate use include gastrointestinal adverse effects (>10%; nausea, diarrhea) and central nervous system toxicity (~20%; fatigue, malaise, dizziness, impaired cognition) [14,18]. Corticosteroids, such as prednisone, mimic the effects of hormones produced in the adrenal gland. The primary anti-inflammatory function of corticosteroids is to inactivate multiple inflammatory genes, including those encoding cytokines, chemokines, adhesion molecules, inflammatory enzymes, and cell surface receptors, that have been activated during the chronic inflammatory process. Corticosteroids readily diffuse across the plasma membrane and bind to cytosolic glucocorticoid receptors. This binding induces translocation of the steroid: Receptor complex into the nucleus and association with co-repressors. This association activates histone deacetylase enzymes to induce chromosomal condensation and inactivate inflammatory gene expression (trans-repression) [19]. Higher concentrations of corticosteroids also have additional effects of activating anti-inflammatory gene expression. Under these conditions, steroid: receptor complexes associate with co-activators followed

by binding glucocorticoid response elements in steroid-responsive anti-inflammatory genes to enhance gene expression (cis-activation). Additionally, steroid: Receptor complexes are also capable of activating histone acetyltransferases to induce chromosomal de-condensation, thereby permitting active gene expression (trans-activation). Of course, the well-known, serious side effects for long-term use of corticosteroids includes immunosuppression with increased risk of infection [20], cataracts and glaucoma [21], cardiovascular disease [22], osteoporosis [23], and adrenal insufficiency [24]. Patients on long-term therapy with corticosteroids must be closely monitored for clinical side effects [25] and slowly tapered off the drug to regain proper adrenal function [24]. A new class of anti-inflammatory therapeutics has emerged over the past decade and is generally termed biologics. These agents are typically engineered monoclonal antibodies that specifically react with pro-inflammatory mediators, such as tumor necrosis factor-alpha (TNF- $\alpha$ ; e.g. infliximab, adalimumab) and interleukin-1 $\beta$  (IL-1 $\beta$ ; e.g. canakinumab). The biologics work by directly binding and neutralizing soluble inflammatory mediators by inhibiting their interactions with specific receptors, thus abrogating inflammatory signal activation. Infliximab has shown significant success in clinical trials for arthritic conditions [26], as well as adalimumab for reducing cardiovascular events [27]. However, biologic therapies are often prohibitively expensive due to costly manufacturing and patient delivery, and generally pose serious, sometimes life-threatening side effects; some of which include, development of fungal, bacterial, or viral infections, reactivation of hepatitis B virus, hepatobiliary disorders, allergic/infusion-related reactions, and malignancies [28]. Long-term use can also be compromised by autoantibody formation, e.g., lupus-like condition, or simply autoantibodies generated against the biologic thus rendering it ineffective.

Based on traditional (non-biologics) and newer designs (biologics) for anti-inflammatory reagents, searches continue for novel therapeutics with improved efficacy and reduced levels of undesirable and unacceptable side effects. In lieu of biologics or chemically synthesized small molecules, such as those found in combinatorial libraries, natural products have provided a rich source of small molecule effectors due to their diverse biological activities and medicinal potentials handed down through the ages [29]. Many natural products have been identified as potent anti-inflammatory agents, both from plant and non-plant sources [30,31].

One particular natural product, 1,8-cineole, is reported to have anti-inflammatory, anti-microbial, and anti-oxidant activity, which may be beneficial as an adjuvant therapy with pharmaceuticals or as a primary treatment in inflammatory based diseases [32]. Bioactivities of 1,8-cineole have been effective in the treatment of asthma, Chronic Obstructive Pulmonary Disease (COPD), bronchitis, and sinusitis [32]. However, in spite of its promising therapeutic potential, 1,8-cineole remains an under-investigated natural product with the majority of published reports limited to respiratory complications. Because of its potent effects documented in these clinical trials, greater investigation is warranted to examine the potential of 1,8-cineole as a treatment for other diseases of chronic inflammation.

### Chemical Properties of 1,8-cineole

1,8-cineole (1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane), also known as eucalyptol, is a bicyclic monoterpene [32] and has been isolated from essential oils prepared from eucalyptus, daphne, cardamom, rosemary, sage, bay leaves, and other plants. 1,8-cineole often represents the major secondary metabolite in these preparations; for example, in bay leaf (*Laurus nobilis*), 1,8-cineole represents 59% of

the total oil volume and 90% of the total oil in eucalyptus leaf [33,34]. Pure 1,8-cineole is a clear liquid at room temperature with a melting point of 1.5°C and flash point of 49°C [35]. A logP value of 2.74 provides a good balance between solubility and permeability, suggesting good bioavailability following oral administration [36].

All members of the terpene family are synthesized using multiple isoprene units (molecular formula of  $C_5H_8$ ) [37]. Isoprene units are first activated for oligomerization by phosphate addition into Isopentenyl Pyrophosphate (IPP) and Dimethylallyl Pyrophosphate (DMAPP) (Figure 1). These two substrates are then linked in repetition to form monoterpenes (2 isoprene units; C<sub>10</sub>), sesquiterpenes (3 isoprene units; C<sub>15</sub>), diterpenes (4 isoprene units; C<sub>20</sub>),

etc. For monoterpenes, the geranyl phosphate intermediate (C<sub>10</sub>) may remain acyclic or modified into mono- and bi-cyclic ring structures (Figure 2).

Limited pharmacokinetic studies have been reported using both *in vivo* and *in vitro* analyses. Oral administration of 200 mg/kg 1,8-cineole to rabbits resulted in a peak plasma concentration by 1 h, confirming good intestinal absorption. In a rodent model, 1,8-cineole undergoes oxidative modifications to produce 2-hydroxy-1,8-cineole and 3-hydroxy-1,8-cineole [38,39]. Both of these metabolites were found within 2 h post-oral administration. Prior to excretion, the metabolites are further conjugated to form glucuronide products. Similar findings were reported using isolated rat and human liver microsomes [40,41]. More extensive safety measurements are necessary to evaluate 1,8-cineole, however, subacute hepato- and nephro-toxicity was reported with only high doses (500-1000 mg/kg body weight) [42,43]. LD50 value in rats is 2.5 g oral dose/kg body weight [44], which is considerably higher than the reported effective therapeutic dosing (see below) suggesting that 1,8-cineole is likely to be safe as a therapeutic modality.

### Human Trials Conducted with 1,8-cineole

The most widely reported human clinical trials examining the effects of 1,8-cineole as an anti-inflammatory therapeutic have come from respiratory studies. In a bronchial asthma trial, 1,8-cineole was administered as an adjunct therapy with prednisolone. Due to the

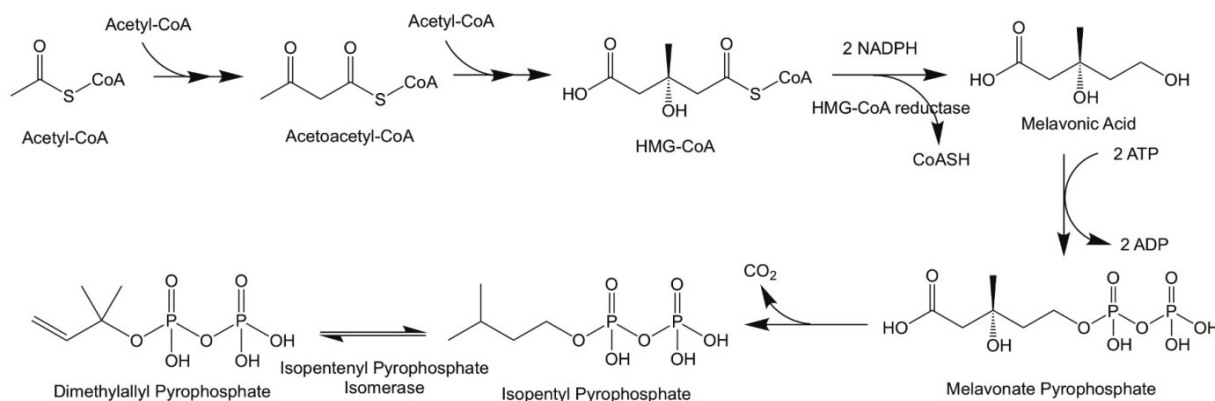
consequences of long-term steroid use, this study assessed if patients could decrease prednisolone use while maintaining effective clinical management. Patients received 200 mg 1,8-cineole or placebo orally, three times per day, and showed marked improvement in respiratory volume and on a follow-up asthma quality of life questionnaire [45]. Improvement was maintained even when prednisolone dosage was decreased by 36% [45,46]. 1,8-cineole demonstrated a positive clinical effect in controlling airway inflammation at an equivalent of 3 mg prednisolone.

In a study examining the effect of adjunct 1,8-cineole therapy in patients with chronic obstructive pulmonary disease (COPD), 1,8-cineole was shown to reduce the severity, duration, and frequency of COPD exacerbations when compared to the placebo group. Patients received 200 mg 1,8-cineole or placebo orally, three times per day, as a concomitant therapy for 6 months and reported significant reductions in labored breathing, coughing, and dyspnea, and reported significant improvements in quality of life [46]. As in the bronchial asthma study, few side effects were reported and treatment compliance was considered good in all patients.

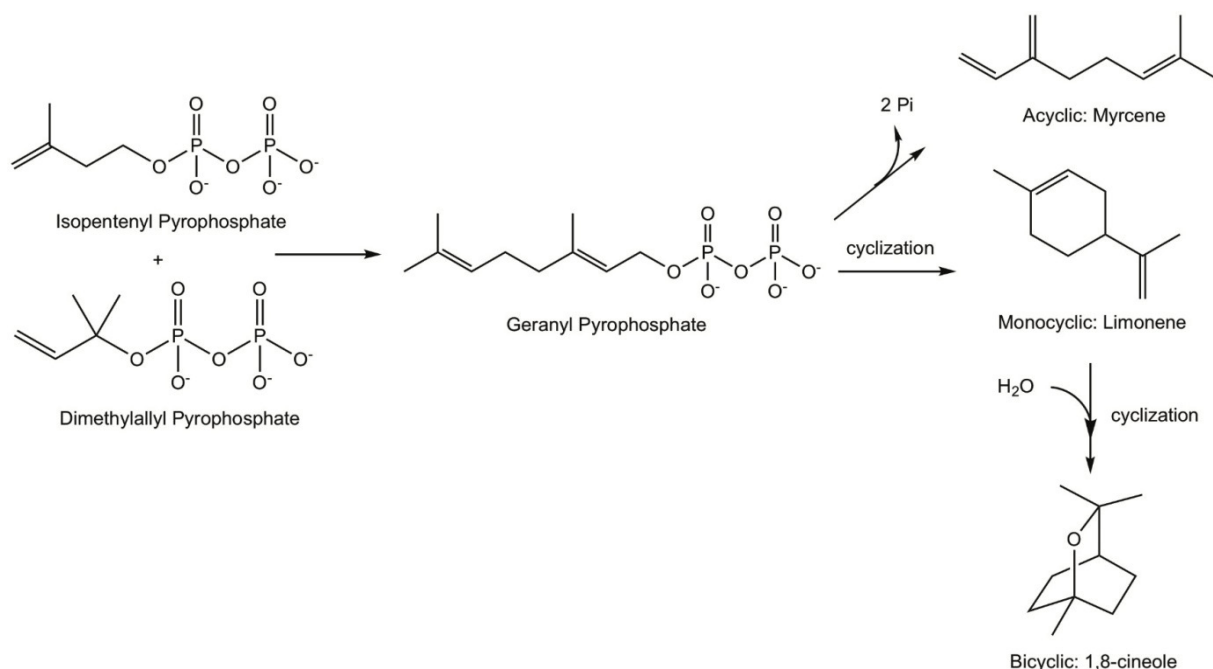
Acute nonpurulent nasal congestion often advances to bacterial sinusitis requiring antibiotic therapy. To prevent this advancement and reduce antibiotic use, treatment of nonpurulent rhinosinusitis with 1,8-cineole was examined in 76 patients with a 7-day administration of 200 mg, three times per day orally [47]. At 4 and 7-day assessment, 1,8-cineole treated patients showed a significant improvement in frontal headache, nasal obstruction, and rhinological secretions when compared with placebo.

### Animal Models

Anti-inflammatory properties of 1,8-cineole have also been investigated in animal models of acute lung injury, acute respiratory distress syndrome, asthma, and colonic inflammation. Lipopolysaccharide was administered to mice intratracheally to induce acute lung injury and related acute respiratory distress syndrome commonly associated with sepsis, shock, pneumonia, trauma and pancreatitis in humans [48]. Intragastric administration of 100 mg/kg 1,8-cineole decreased the number of neutrophils and macrophages by 40-50% as compared with the control group in bronchoalveolar lavage



**Figure 1:** Pathway of isoprenoid precursor biosynthesis. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate are intermediates in the cholesterol biosynthesis pathway, generated primarily through the mevalonate pathway in higher eukaryotes. This pathway begins with acetyl-CoA being transferred from the mitochondrial matrix into the cytoplasm using citrate as a carrier. Two cytosolic acetyl-CoA units then condense to form acetoacetyl-CoA, which then condenses with a third acetyl-CoA to form 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA). HMG-CoA undergoes an irreversible, committed step into cholesterol biosynthesis becoming mevalonate by the highly regulated enzyme HMG-CoA reductase. Mevalonate is charged with the addition of two phosphates (from ATP hydrolysis) to form mevalonate pyrophosphate. A final decarboxylation reaction converts mevalonate pyrophosphate into isopentenyl pyrophosphate. Formation of dimethylallyl pyrophosphate requires a simple isomerization of isopentenyl-5-pyrophosphate.



**Figure 2:** Pathway of acyclic, monocyclic, and bicyclic monoterpene biosynthesis. Isopentenyl pyrophosphate and dimethylallyl pyrophosphate undergo condensation by geranyl pyrophosphate synthase to produce geranyl pyrophosphate. Elimination of the pyrophosphate group results in formation of acyclic monoterpenes, such as myrcene. Cyclization of geranyl pyrophosphate results in formation of monocyclic monoterpenes, such as limonene. Further hydration of limonene ( $\alpha$ -terpineol), followed by cyclization results in formation of the bicyclic monoterpene, 1,8-cineole.

fluid [49]. Additionally, levels of pro-inflammatory cytokines, TNF- $\alpha$  and IL-1 $\beta$ , as well as expression of transcription factor NF- $\kappa$ B in lung tissue were reduced by 50% in 1,8-cineole-treated mice. The effects by 1,8-cineole were equivalent to an inhibitory response of 0.5 mg/kg of prednisone.

In another study, 1,8-cineole significantly reduced airway hyperresponsiveness in ovalbumin-sensitized guinea pigs [50]. Guinea pigs were sensitized with multiple peritoneal injections of ovalbumin, followed by inhalation of a single dose of 1 mg/mL 1,8-cineole which was aerosolized with an ultrasonic nebulizer. Airway constriction in isolated tracheas was measured following induction with an acetylcholine receptor agonist (carbachol). Animals treated with 1,8-cineole demonstrated 30-40% reduction in tracheal constriction when compared with guinea pigs without 1,8-cineole treatment. In addition, 1,8-cineole treatment reduced leukocyte infiltration by 40%, eosinophils and neutrophils by 50%, lymphocytes by 20%, and macrophages by 30% in bronchoalveolar lavage fluid. 1,8-cineole also decreased pro-inflammatory cytokines levels of TNF- $\alpha$  and IL-1 $\beta$  by 40%, while increasing expression of anti-inflammatory cytokine, IL-10, by 50%.

In a further study, mice were exposed to cigarette smoke (12 cigarettes per day for 5 days) to induce COPD-like symptoms [51]. 1,8-cineole was administered to the treatment group in aerosol form. Histological examination of lung tissue showed that mice exposed to 12 cigarettes per day for five days disrupted normal lung parenchymal architecture, with significant leukocyte infiltration observed in alveoli and parenchyma. Lung tissue of mice treated with 3 mg/kg and 10 mg/kg 1,8-cineole showed normal lung parenchyma and significantly less leukocyte infiltration. These dosages reduced leukocyte infiltration by 40-50%, along with a reduction in myeloperoxidase activity by 60%,

IL-1 $\beta$  expression by 50%, and interleukin-6 (IL-6) expression by 40%. A 10 mg/kg dosage of 1,8-cineole reduced TNF- $\alpha$  levels by 80%.

Finally, 1,8-cineole significantly reduced inflammation in a TNBS-induced (2,4,6-trinitrobenzenesulfonic acid) colitis rodent model. Rats that were pre-treated intra-rectally with 1,8-cineole doses of 200 and 400 mg/kg histologically showed only mild inflammation in colonic tissue as compared with the TNBS-only control group. These dosages also reduced pro-inflammatory TNF- $\alpha$  and IL-6 expression by 40-50%.

## Molecular Observations

Studies aimed at elucidating the molecular mechanisms of 1,8-cineole anti-inflammatory activity have led to reports indicating an inhibitory function of key signaling events in the innate immune response. *In vitro* analysis of 1,8-cineole activity on isolated lipopolysaccharide-induced human lymphocytes and monocytes showed that pro-inflammatory cytokine expression, including TNF $\alpha$ , IL-1 $\beta$ , and IL-6, were significantly reduced with IC<sub>50</sub> values of 0.2  $\mu$ M, 0.8  $\mu$ M, and 7.0  $\mu$ M, respectively [52]. A later study more closely examined the effects of 1,8-cineole on activation of signaling molecules following LPS-challenge and reported elevated levels of Inhibitor of kappa B ( $\text{I}\kappa\text{B}$ ) leading to a decrease in activation of NF $\kappa$ B. In addition to blunted NF $\kappa$ B signaling, decreases in pERK, p38 MAPK, and pJNK activation were also noted.

## Conclusion

*In vivo* and *in vitro* studies have established that 1,8-cineole has potent anti-inflammatory activity and in some cases can reduce or replace current therapeutic modalities that often have complex and detrimental side effects. Many of these studies have focused on respiratory illnesses of which several clinical trials show substantial



promise that 1,8-cineole may become a primary treatment, or at the very least, an adjunct therapy for current corticosteroid use.

Although its pharmacokinetic and pharmacodynamics properties require further study, preliminary reports show that 1,8-cineole demonstrates excellent bioavailability following oral administration and maintains sufficient bioactivity to significantly inhibit an immunological challenge in lung and colon tissues. In several human clinical trials, patient compliance taking 1,8-cineole was considered good and few side effects were reported when consuming therapeutic doses. Based on these reports, use of 1,8-cineole as an anti-inflammatory agent needs greater study in other diseases with a chronic inflammatory component, including atherosclerotic cardiovascular disease, type 2 diabetes mellitus, and arthritic complications.

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