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Invivo study to demonstrate the therapeutic role of 1,8-Cineole in respiratory disorders

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Abstract: *Eucalyptol* also known as 1,8-Cineole is a monoterpenoid compound that occurs in the essential OIls of leaves of various species belonging to different families, including *Eucalyptus*, *Rosemary & Bay* Laurel. Due to its anti-inflammatory, antibacterial, expectorant, analgesic, and other activities, this compound has attracted much attention. 1,8-Cineole has a large therapeutic potential use, such as respiratory treatments, pain relief and in aromatherapy. *Lobelia* has found widespread use in medicinal preparations as an adjunct in relieving air-passage restrictions and in assisting with mucus expulsion in the management of asthma, bronchitis, and sinusitis. Additionally, the antinociceptive properties of 1,8-Cineole provide an alternative mechanism of pain relief that is less reliant on established pathways of pain hypersensitization which have shown efficacy across numerous preclinical and clinical pain paradigms in addition to peripheral central sensitization in a host of pain models.

Keywords: 1,8-Cineole, Therapeutic, Aerosol Dilator, Analgesic, Anti-inflammatory

دراسة معمالية سريرية علي اثبات دور 1.8 سينول في علاج امراض الربو الشعبي وفرط التحسس وتسكين الالام

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المستخلص: يُعرف الأوكالبتول أيضًا باسم 1,8–سينول، وهو مركب أحادي التربين، ويوجد في الزيوت العطرية لأوراق أنواع مختلفة من النباتات الطبية التي تنتمي إلى عائلات مختلفة، بما في ذلك الأوكالبتوس وإكليل الجبل والغار. وقد حظي هذا المركب باهتمام كبيرمن قبل الباحثين في مجال العقاقير الطبية نظرًا لخصائصه المضادة للالتهابات والبكتيريا وطاردة للبلغم ومسكنة للألم وغيرها. ويتميز 1,8–سينول بإمكانيات علاجية واسعة، مثل علاجات الجهاز التنفسي يعمل على توسيع الشعب التنفسية عند مرضى الازمة التنفسية وحساسية الربيع بالاضافة. كما استُخدم نبات اللوبيليا

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ايضا على نطاق واسع في المستحضرات الطبية كعامل مساعد في تخفيف ضيق مجرى الهواء والمساعدة في طرد المخاط في علاج الربو والتهاب الشعب الهوائية والتهاب الجيوب الأنفية. بالإضافة إلى ذلك، توفر الخصائص المضادة للألم لـ 1,8-سينول آلية بديلة لتسكين الألم تعتمد بشكل أقل على المسارات الراسخة لفرط حساسية الألم والتي أظهرت فعاليتها عبر العديد من نماذج الألم السريرية وما قبل السريرية بالإضافة إلى التحسس المركزي المحيطي.

الكلمات الدالة. 1,8-سينول العلاجيات موسع للشعب التنفسية مسكن للام مضاد للالتهابات

Introduction

Natural products have been a mainstay for agent discovery and development as therapeutic agents for many years. Essential oils are one of them which have developed as effective bioactive mixtures having a wide spectrum of applications, for instance, in medicine, aromatherapy, cosmetics and the food industry. A very important compound in this regard is 1,8-Cineole, or *eucalyptol*. This monoterpenoid cyclic ether is associated with its characteristic aromatic fragrance and various biological activities, such as anti-inflammatory, antimicrobial, expectorant, and analgesic activity. With broad therapeutic range and low toxicity, the 1,8-Cineole is being increasingly investigated in both traditional and modern medicine.

The vast majority of 1,8-cineole is contained in *Eucalyptus* species; Eucalyptus globulus has essential oil containing 90% of 1,8 cineole. However, it is also found in significant amounts in many other aromatic plants like *Rosmarinus officinalis (rosemary), Laurus nobilis (bay laurel), Melaleuca spp. (tea tree)* and some members of the *Myrtaceae, Lamiaceae, Zingiberaceae* families. This compound's broad distribution among plant species makes it more available and relevant for various industrial and pharmaceutical uses.

1,8-Cineole has received an evergrowing amount of supporting experimental and clinical studies with respect to its pharmacological significance. Due to its bronchodilatory and mucokinetic effects, it has been effective in the treatment of respiratory diseases, including asthma, bronchitis, and sinusitis. Alternatively, its use in topical applications and aromatherapy products capitalizes on its antimicrobial and comforting properties.

Material and methods

Natural Sources of 1,8-Cineole

1,8-Cineole, commonly referred to as eucalyptol, is a monoterpene that occurs naturally and has been applied extensively medicinally and industrially. This compound is found abundantly in certain plant families and is highly valued for its anti-inflammatory, antimicrobial, and expectorant properties. Eucalyptus species of the *Myrtaceae* family are regarded as the most commercial source, but species in other families (e.g. *Lamiaceae* and *Zingiberaceae*) also yield significant amounts. More unusual botanicals also provide share of the global output of 1,8-cineole, an option for those who want to create essential oil.

Myrtaceae

Myrtaceae is the richest natural source of 1,8-cineole of all botanical families to date and several species, in particular, have been shown to contain very high levels. Due to its antibacterial and respiratory-enhancing properties, this family has become widely widespread in pharmaceuticals and fundamental medicine.

Eucalyptus:

The Eucalyptus genus, with almost 900 species, is considered the largest and most industrially important source of 1,8-cineole production(Southwell & Russell, 2002). Its leaves yield essential oils rich in the highest concentrations of cineole in nature, making it crucial in both medicinal and industrial usage.

Eucalyptus kochii subsp. borealis is the undisputed leader, boasting an astonishing 97.32% 1,8-cineole content, the highest concentration recorded to date (Russo, 2011).

Eucalyptus globulus (Blue Gum), one of the most widely cultivated species, contains 70% to 90% 1,8-cineole, making it a preferred choice for pharmaceutical and aromatherapy industries (Batish et al., 2008; Brophy & Boland, 1991).

Eucalyptus radiata and Eucalyptus smithii, though slightly lower in concentration, still hold impressive levels of 60% to 80% 1,8-cineole, further reinforcing the genus's importance in essential oil production (Brophy & Boland, 1991).

Thyme and Rosemary

Thymus mastichina belongs to the *Lamiaceae* family and 1,8-cineole constitutes 67.4% of its essential oil, suggesting its possibility to work as an antifungal (Chabir et al., 2011). On the other hand, *Rosmarinus officinalis* (Rosemary) shows a considerable variation of cineole response, between 15% and 55%, which depends predominantly on the chemotype, climate and soil (Pintore et al., 2002).

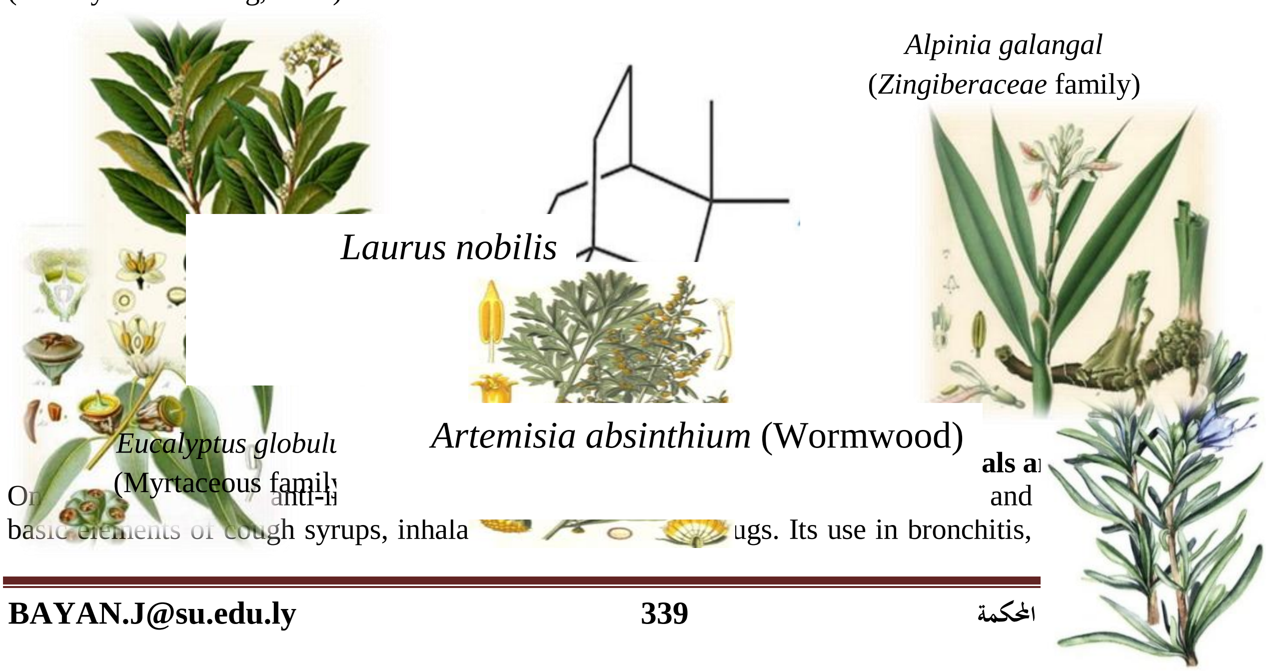
Other Species of *Lamiaceae*:

Various members of the *Lamiaceae* family contain significant quantities of 1,8-cineole and are subsequently valuable as aromatics in herbal medicine, aromatherapy and cooking. *Salvia officinalis* (Sage) is one of them, which contains 10%-35% 1,8-cineole, and is commonly used as a medicinal herb. Rich in antimicrobial and antioxidant compounds, sage has been used both traditionally and in modern herbal therapy to support respiratory health and general well-being (Raal et al., 2007).

Likewise, *Hyptis suaveolens*, which is of tropical American origin, is renowned for its high yield of cineole. While the specific content of 1,8-cineole varies across species, it still holds significant value as a medicinal and aromatic plant with extensive applications in folk medicine and essential oil (EO) production (Abdullah et al., 2015).

The other notable cineole producing plant in *Lamiaceae* is Ocimum basilicum (Basil). 5%–20% 1,8-cineole, depending on the chemotype and cultivation conditions of the basil essential oil. The pinene varieties have been characterized for having medicinal and aromatherapy usage due to their abundant terpenes (Javanmardi et al., 2002), especially cineole.

Cymbopogon citratus (Lemongrass) is another plant, the most famous being *Mentha piperita* (Peppermint), with the same properties, although the menthol and menthone are mainly responsible for the characteristic flavour and fragrance, other components account for around 3% to 10% of the 1,8-cineole content. Although not the major player, cineole is an important contributor to the therapeutic benefits of peppermint oil, including its cooling feelings and benefits for the respiratory system. As a result, peppermint is used in various pharmaceutical, personal care, and food products (McKay & Blumberg, 2006).



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basic elements of cough syrups, inhala ugs. Its use in bronchitis, asthma is due to its ability to clear airway obstructions and decrease mucus production(Moteki & Hibasami, 2002). In fact, studies reveal that it even inhibits bacterial and fungal growth, thus making this compound valuable in the formulation of antiseptics (Hammer et al., 2003).

Synthesis of 1,8-Cineole

Heteropoly acid $H_3PW_{12}O_{40}$ (PW) catalyzes the isomerization of α-terpineol in homogeneous and heterogeneous systems to generate 1,8-cineole (Leão Lana et al., 2006b), which has potential for flavor and pharmaceutical applications. With 1,8-cineole as product, the homogeneous system gave 50% α-terpineol conversions with a 25% selectivity (in a nitrobenzene solution at 40°C). In a heterogeneous system, 1,8-cineole was achieved with 35% yield at 70–100% conversion in a cyclohexane solution at 60°C with silica-supported PW as a solid acid catalyst that was reusable. In comparison to conventional acid catalysts (e.g. H_2SO_4 and Amberlyst-15), PW exhibited much more catalytic activity and selectivity.

Tercineoles can be prepared synthetically by treating terpene fractions or isoprene with mineral acids (usually sulfuric acid). The acid catalysed rearrangements of terpineols and terpin hydrate have been used for many years to provide methods to prepare cineoles (Leão Lana et al., 2006b), the details thereof however being relatively scant. The traditional approaches approach left over products like menthadienes, cymenes, and terpinenes with a complicated mixture of low-yielding cineole and require a large excess of mineral acids for each substrate. Final mixture is typically less than 15% 1,8-cineole. These traditional approaches present significant environmental challenges, as they lead to the generation of substantial waste residues. Thus, the finding of a cleaner synthetic route towards 1,8-cineole remains a challenge.

Heteropoly acids (HPAs) have emerged as useful and effective catalysts for cleaner syntheses of fine and specialty chemicals with applications in homogeneous and heterogeneous systems. HPAs have been applied effectively to the hydration, acetoxylation, cyclization, and isomerization of terpenes (Khaled et al., 2015).

In nitrobenzene, α-terpineol was isomerized to give a complex mixture of products including 1,8-cineole (Pinto et al., 2009), limonene, terpinene, and oligomeric products. The mechanism is most likely a carbenium-ion mechanism wherein PW promotes isomerization. At 40°C, α-terpineol conversion was 90% with selectivity of 1,8-cineole of 25%. At 60°C, the reaction was finished in 0.5 hours; however, the selectivity decreased as other terpenes were produced.

In the case of the heterogeneous system, α-terpineol is isomerized in cyclohexane solution over PW/SiO_2 catalyst, which is more selective and environmentally benign than the equivalent homogeneous process. The catalyst is a solid and reusable, and no leaching of PW into the solution was found. High concentration in the PW caused a higher rate of reaction without influencing selectivity.

Extraction Techniques of Essential Oils and Bioactive Components

Crucial for the chemical composition, yield and potential applications of essential oils (EOs) and bioactive compounds is their extraction. Different extraction methods have been studied including traditional and advanced which brought important pros and cons. At this point, we review the various extraction methods identified in recent studies.And chromotogrphy technology.

Hydrodistillation (HD) and Steam Distillation (SD)

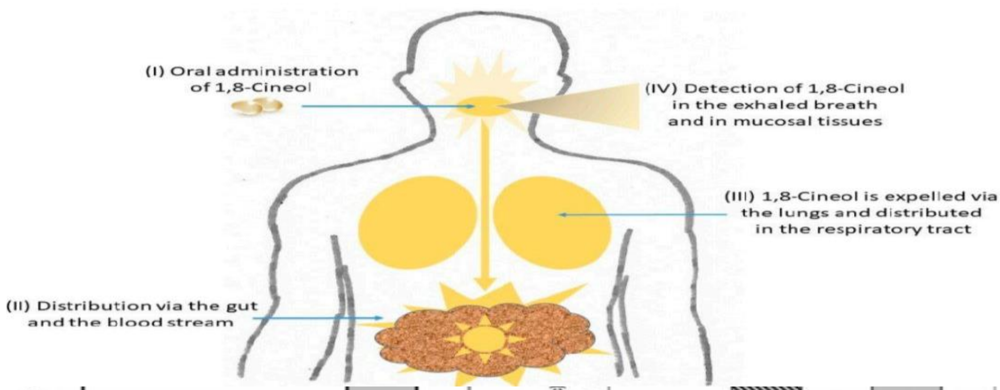
Hydrodistillation (HD) and steam distillation (SD) are two of the most commonly used traditional methods for EO extraction. These methods are used to heat up plant physicals with the addition of water or steam, such that vaporized compounds are pulled along with the vapor, and the resulting vapor is then condensed into a liquid phase. HD is commonly used following the Chinese Pharmacopoeia for the extraction of essential oils with a boiling point higher than 100°C (Zhou et al., 2023). SD works in a similar way but with no direct contact between plant materials and water, thus limiting hydrolysis or decomposition of thermolabile compounds. Although widely used, these procedures have some limitations such as long incubation times and loss of heat-sensitive fractions (Juergens et al., 2004).

Resultes and Discusion

Testing of In Vitro Cytotoxicity and Anti-Inflammatory Activity: Antioxidant and anti-inflammatory effects of essential oils can be determined in cell culture models, such as in human gingival fibroblasts (HGF-1 cells). In fact, a survey on *Salvia officinalis* L. infusion revealing that 1,8-cineole, borneol, camphor and thujone products activated the release of IL-6 and IL-8 cytokines in a manner indicating that they reduce IL-6 and IL-8 cytokine release with an inhibition of 50–76% (Ehrnhöfer-Ressler et al., 2013), as shown recently by other researchers confirming their anti-inflammatory effects.

Pharmacokinetics and Systemic Distribution

Following oral administration, 1,8-cineole is quickly absorbed and metabolized in the liver by cytochrome P450 enzymes (CYP3A4/5), generating the metabolites 2α-hydroxy-1,8-cineole and 3α-hydroxy-1,8-cineole, eliminated by the urine (Pries et al., 2023a).Studies of pharmacokinetics have demonstrated that 1,8-Cineole can be found in blood plasma as quickly as 18 minutes following inhalation, exemplifying its rapid and complete systemic bioavailability (C. C. Hoch et al., 2023b). Moreover, it is liberated via pulmonary decomposition, which makes it performed the local anti-inflamatory and mucomtic properties in repiratory tract (Juergens et al., 2020).



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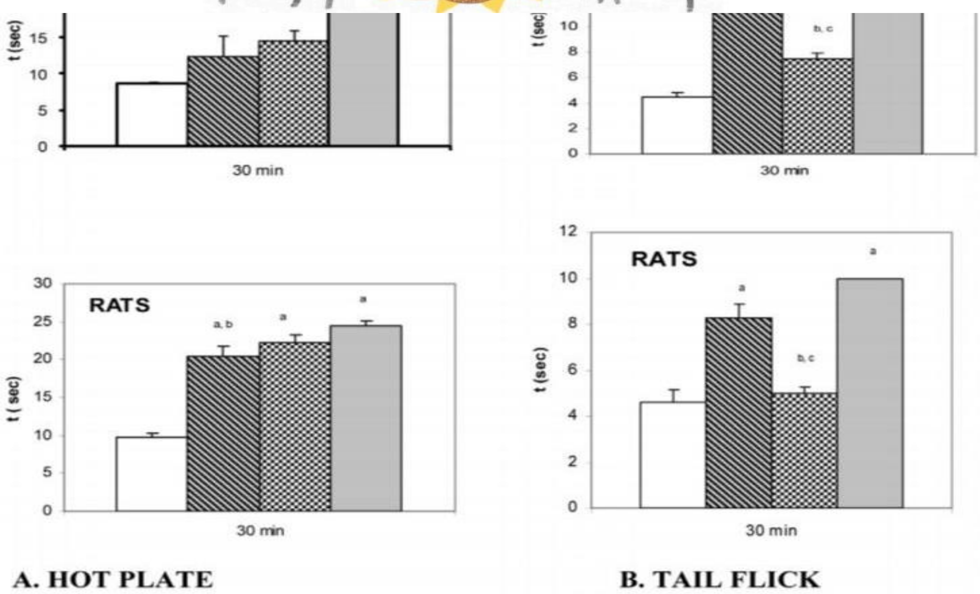

Figure 4: Effects of 1,8-cineole, β-pinene and morphine (1 mg/kg bw) on hot-plate and tail-flick reaction time in mice and rats at 30 min after administration. A Hot-plate: mice [$F(3,20) = 33.104$, ($p < 0.001$)]; rats: [$F(3,25) = 47.190$, ($p < 0.001$)]; B Tail-flick: mice: [$F(3,20) = 19.142$, ($p < 0.001$)]; rats: [$F(3,25) = 18.840$, ($p < 0.001$)]. a: $p < 0.001$ vs. control; b: $p < 0.01$ vs. M; c: $p < 0.05$ vs. C.

accumulating experimental evidence supports the role of 1,8-cineole as a potent antinociceptive agent. Its effectiveness in both peripheral and central models of pain, its independence from opioid pathways, and its interaction with adenosine receptors point to a multifaceted mechanism that warrants further exploration. As natural product-based therapies gain popularity, 1,8-cineole stands out as a promising candidate for the development of safe, non-opioid analgesics in both acute and chronic pain management(Liapi et al., 2007; Santos & Rao, 2000).

1. The Pharmacological Role of 1,8-Cineole in Respiratory Health

Eucalyptol is a natural monoterpene oxide, which is a natural occurring in the essential oils of Eucalyptus species, Rosemary (*Rosmarinus officinalis*) and camphor laurel (Cinnamomum camphora) and known as 1,8-cineole 1,8-Cineole is well-known phytopharmaceutical which displays broad spectrum pharmacological activity and therapeutic role commonly found with respiratory diseases, especially asthma, chronic obstructive pulmonary disease (COPD), bronchitis and sinusitis (C. C. Hoch et al., 2023b). Because of its anti-inflammatory, mucolytic, bronchodilatory, and antimicrobial activities, it may be a promising lass of compounds as adjuvant therapy in chronic airway disease (Pries et al., 2023b).Numerous clinical trials provide evidence of decreases in airway inflammation, improved lung function, and decreased exacerbation rates in patients with COPD and asthma (Juergens et al., 2020). Herein we examine the pharmacological actions of 1,8-Cineole, where activity potentially exists in separate respiratory disease processes and address the translational utility.

Anti-Inflammatory Effects of 1,8-Cineole

Therapeutic Effects of 1,8-Cineole as an Inflammatory Modulator An essential characteristic of asthma, COPD, and bronchitis is inflammation, primarily regulated by pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and IL-8 (Pries et al., 2023b).

The anti-inflammatory mechanism of action of 1,8-Cineole has got a base on the inhibitory action on the nuclear factor-kappa B (NF-κB) pathway, a relevant mediator in development of the inflammatory process and airway remodeling driven by cytokines. Thus, 1,8-Cineole inhibits airway inflammation, excessive mucus production and oxidative stress via mitigation of NF-κB activation (C. C. Hoch et al., 2023b).In addition, 1,8-Cineole activates the Nrf2 pathway, one of the most important regulators of the antioxidant defense mechanism in lung tissues. This, in turn, triggers the production of antioxidant enzymes that protects against oxidative lung damage, an important contributor to COPD advancement (Cai et al., 2020a).

a. Mucolytic and Bronchodilatory Actions

Chronic diseases of respiratory system are associated with excessive mucus production and
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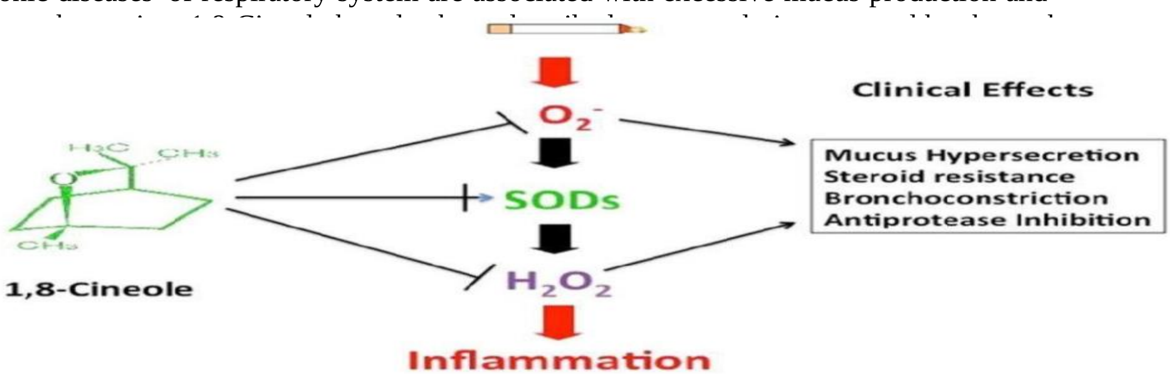

1,8-Cineole has been shown to be useful in studies for COPD as well. For instance, one 6-month randomized controlled trial of 1,8-Cineole (3 × 200 mg/day) found a 38.5% reduction in COPD exacerbations as well as statistically significant increases in lung function determined by FEV1 and quality of life (Juergens et al., 2020).

Asthma

1,8-Cineole reduces airway hyperresponsiveness in asthma patients. Mechanism of asthma control − 1,8-Cineole via inhibition airway inflammation strong inducers IL-4 and IL-5 cytokines, can regulate asthma (C. C. Hoch et al., 2023b). 1,8-Cineole is also reported to have steroid-sparing effect and to reduce corticosteroid doses without lulling out of control of symptoms (Juergens et al., 2020).

Bronchitis and Sinusitis

In a 10-day clinical study, patients with acute bronchitis receiving 1,8-Cineole experienced substantial symptom relief within four days compared with a placebo group (Juergens et al., 2020). Moreover, its mucolytic and antimicrobial abilities make it particularly effective in the management of chronic sinusitis, leading to decreased nasal inflammation and better sinus drainage (Pries et al., 2023b).

1,8-Cineole: Its Role in Respiratory Medicine and Pharmacological Profile Due to its anti-inflammatory, mucolytic, bronchodilatory and antimicrobial properties, it represents an important adjunctive treatment for COPD, asthma, bronchitis and sinusitis. Clinical evidence supporting its efficacy is already strong and further studies should now focus on optimizing formulations to improve bioavailability and realize its full therapeutic potential.

Conclusion

1,8-Cineole (Eucalyptol), has emerged as a multifunctional monoterpenoid with diverse therapeutic and pharmacological activities. Reconstituted from Eucalyptus and similar aromatic vegetation, it facilitates multiple biological activities such as anti-inflammatory, anti-microbial, and antioxidant, as well as respiratory-enhancing effects. Its uses range from pharmaceutical and aromatherapy to food preservation and green solvents.

Research studies have proven its effectiveness for managing respiratory diseases, neurological disorders, cardiovascular diseases.

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