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Research Article

Therapeutic Effects of Cajuput Oil (Melaleuca Cajuputi) in Respiratory Health

A Systematic Review of Preclinical and Clinical Studies

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Abstract: Respiratory tract diseases present significant challenges to global public health, requiring the development of multi-targeted, therapeutic interventions. Cajuput oil (Melaleuca cajuputi or Melaleuca leucadendra) and its primary monoterpene constituent, 1,8-cineole (eucalyptol), have demonstrated a broad spectrum of anti-inflammatory, antioxidant, spasmolytic, and antimicrobial properties. This systematic review synthesizes preclinical and clinical evidence to evaluate the therapeutic efficacy, underlying molecular mechanisms, clinical safety, and formulation advancements of cajuput oil and 1,8-cineole in managing upper and lower respiratory tract diseases. Methods: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, a systematic literature search was executed across PubMed, EuropePMC, and OpenAlex databases up to early 2026. Primary studies investigating the therapeutic effects of cajuput oil or 1,8-cineole in preclinical (in vitro and in vivo) and clinical respiratory disease models were selected. Six independent reviewers conducted the study screening, selection, data extraction, and risk of bias assessment. Result: Thirteen original studies met the rigorous eligibility criteria. In vivo animal models of pulmonary emphysema, pulmonary fibrosis, and allergic asthma showed that 1,8-cineole significantly attenuates tissue destruction, inflammatory cell infiltration, and fibrotic deposition. These cellular responses were mediated by the upregulation of Nrf2-driven antioxidant cascades and the suppression of NF-κB, p38 MAPK, and STAT6 inflammatory signaling pathways. Spasmolytic activities in human bronchial tissues were achieved via reversible H_1-receptor blockade and H_2-receptor/α-adrenoceptor activation. Furthermore, 1,8-cineole exhibited strong antimicrobial and antibiofilm properties against multidrug-resistant Klebsiella pneumoniae, Staphylococcus aureus, and Pseudomonas aeruginosa. In clinical trials and observational studies, oral administration of 1,8-cineole (including a novel amoxicillin-clavulanate-cineole formulation) significantly improved symptom severity and accelerated recovery in acute bronchitis, rhinosinusitis, and lower respiratory tract infections with excellent tolerability.

Keywords: Clinical Studies; Melaleuca Cajuputi; Preclinical; Respiratory Health; Therapeutic.

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1. Introduction

Pathological conditions of the respiratory system, including acute airway infections and progressive chronic disorders, are major contributors to global morbidity and mortality. Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow limitation and parenchymal destruction, has emerged as the third leading cause of death worldwide. Similarly, progressive interstitial lung disorders, such as idiopathic pulmonary fibrosis (IPF), cause irreversible destruction of the alveolar architecture with limited therapeutic alternatives. Obstructive airway conditions such as asthma are characterized by airway hyperresponsiveness, chronic inflammation, and tissue remodeling driven by epithelial-mesenchymal transition (EMT). Moreover, pulmonary arterial hypertension (PAH) causes severe pulmonary vascular remodeling, right ventricular hypertrophy, and eventual right heart failure, with current vasodilatory therapies failing to fundamentally halt disease progression.

In addition to these non-communicable disorders, acute lower respiratory tract infections (LRTIs) and community-acquired pneumonia remain significant causes of global disease burden. The clinical management of respiratory infections is increasingly compromised by the rapid rise of antimicrobial resistance (AMR) among opportunistic pathogens, such as *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. These bacteria often reside within structured extracellular polymeric substance (EPS) biofilms, which physically barrier antibiotic penetration and increase bacterial tolerance up to a thousand-fold compared to planktonic cells.

Conventional therapies for these conditions, such as inhaled corticosteroids (ICS) and bronchodilators, carry long-term risks, including increased susceptibility to pneumonia and systemic adverse events. Consequently, there is an urgent need for safe, bio-derived, multi-targeted therapeutic agents that can simultaneously reduce inflammation, alleviate oxidative stress, promote tissue repair, and disrupt resistant microbial biofilms.

Cajuput oil, an essential oil traditionally steam-distilled from the leaves of *Melaleuca cajuputi* (synonym *Melaleuca leucadendra*, Myrtaceae family), is a well-known natural therapeutic agent. The primary bioactive component of cajuput oil is 1,8-cineole (eucalyptol), a saturated monoterpene cyclic ether that exhibits robust lipophilic, volatile, and biologically active properties. While historical applications of cajuput oil and eucalyptol have focused primarily on their secretolytic, expectorant, and mild antiseptic effects, modern molecular research has revealed their capacity to modulate complex cell signaling pathways, suppress pro-inflammatory transcription factors, upregulate host antioxidant enzymes, and disrupt bacterial cell membranes. However, the primary literature evaluating these properties remains fragmented across diverse in vitro, in vivo, and clinical domains.

This systematic review was conducted to synthesize the available preclinical and clinical evidence regarding the therapeutic effects of cajuput oil and 1,8-cineole in respiratory health. Under the PRISMA 2020 framework, this study systematically evaluates their efficacy in reducing airway inflammation, mitigating oxidative tissue damage, preventing pathological remodeling, promoting bronchodilation, and eradicating resistant biofilms, while assessing their safety and clinical translation potential.

2. Materials and Method

Eligibility Criteria

Studies were selected according to predefined eligibility criteria based on the Population, Intervention, Comparator, Outcomes, and Study Design (PICOS) framework and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. Eligible studies were primary original research articles, including preclinical in vitro studies (e.g., cell cultures, organotypic tissue slices, and isolated tissue preparations), in vivo animal studies (e.g., mice, rats, and guinea pigs), and clinical investigations, including randomized controlled trials, prospective observational studies, and pharmacy-based surveys. Studies were required to evaluate cajuput oil (*Melaleuca cajuputi* or *Melaleuca leucadendra*) or its principal bioactive monoterpene, 1,8-cineole (eucalyptol), as the primary intervention. Eligible studies also had to report at least one outcome related to respiratory diseases, including anti-inflammatory, antioxidant, bronchodilator, mucolytic, immunomodulatory, or antimicrobial effects, as well as clinical symptom improvement, pulmonary function, or safety outcomes. Only full-text articles published in English or Indonesian were included.

Studies were excluded if they were secondary literature, including narrative reviews, systematic reviews, meta-analyses, clinical practice guidelines, or consensus statements. Editorials, letters to the editor, comments, conference abstracts or proceedings, patents, books, book chapters, theses, and dissertations were also excluded. Studies investigating essential oils or herbal formulations without clearly specifying cajuput oil or 1,8-cineole as the primary intervention, or without reporting their concentration or composition, were not considered eligible. Additionally, studies that did not investigate upper or lower respiratory tract diseases, lacked sufficient quantitative outcome data, or had unavailable full-text articles were excluded.

Information Sources

A comprehensive literature search was conducted across PubMed, Europe PMC, and OpenAlex to identify relevant studies evaluating the therapeutic effects of cajuput oil in respiratory diseases. Only studies published between 2016 and 2026 were considered for inclusion. To ensure comprehensive study identification, the reference lists of all eligible articles were also manually screened for additional relevant studies.

Search Strategy

A search strategy was developed using Medical Subject Headings (MeSH) and free-text terms. Boolean operators (AND, OR) and truncation wildcards (*) were applied to capture all relevant variations[3]. The exact search string utilized across all databases was: ("Melaleuca cajuputi" OR "Melaleuca leucadendra" OR "cajuput oil" OR "cajeput oil" OR "cajuput essential oil" OR eucalyptol OR cineole OR "1,8-cineole" OR "1,8 cineole") AND ("respiratory tract disease*" OR "respiratory tract infection*" OR "respiratory disease*" OR "lung disease*" OR "pulmonary disease*" OR "airway disease*" OR asthma OR COPD OR bronchitis OR pneumonia OR sinusitis OR rhinitis OR influenza OR COVID-19).

Data Collection Process and Data Items

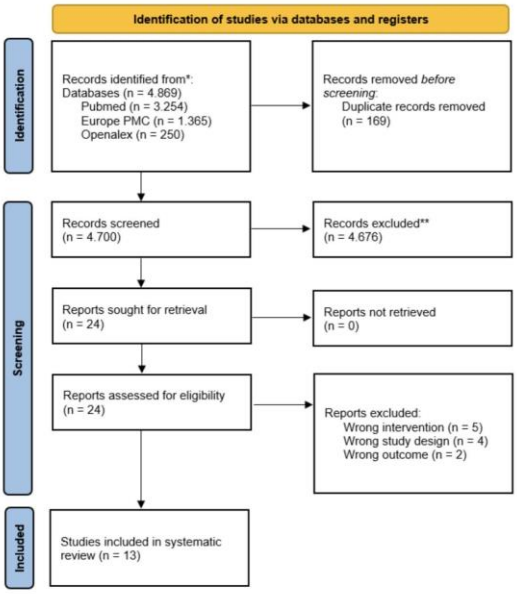
Data extraction was performed independently by the review team using a standardized and pilot-tested data extraction form to ensure consistency and accuracy across the included studies. Any discrepancies identified during the extraction process were resolved through discussion until consensus was reached.

The extracted data included study characteristics (first author, year of publication, country of origin, and study design); characteristics of the study population or experimental model, including animal models (species, strain, age, and sex), cell lines, clinical isolates, or human participants (sample size, age distribution, and clinical condition); intervention characteristics, including the type of intervention, dose or concentration, route of administration, frequency, duration of treatment, and vehicle where applicable; outcome measures, including histological, biochemical, immunological, physiological, microbiological, and clinical outcomes; and the main efficacy and safety findings, including both quantitative and qualitative results as well as the molecular mechanisms or biological pathways reported by the authors.

Synthesis Methods

Due to the substantial heterogeneity in study designs, animal models, clinical populations, drug formulations, and outcome parameters, a quantitative meta-analysis was not feasible. Instead, a structured, qualitative narrative synthesis was conducted[3]. Studies were grouped into distinct thematic domains based on their specific therapeutic mechanism (e.g., anti-inflammatory, antioxidant, bronchodilatory, antifibrotic, and antimicrobial effects) and their clinical application (e.g., emphysema, asthma, fibrosis, rhinosinusitis, and LRTIs). Within each thematic domain, the findings were synthesized to highlight the underlying molecular pathways, therapeutic efficacy, safety profiles, and advanced delivery systems.

3. Results and Discussion



Gambar 1. PRISMA 2020.

Study Selection

The initial electronic search retrieved a total of 4,869 records. Database-specific yields were: 3,254 records from PubMed, 1,365 records from EuropePMC, and 250 records from OpenAlex. A total of 169 duplicate records were identified and removed, leaving 4,700 unique records for title and abstract screening. Based on the eligibility criteria, 4,676 records were excluded during the initial screening phase.

Twenty-four reports were identified for full-text retrieval and eligibility assessment. No reports were lost or untraceable during the retrieval process. Following a comprehensive full-text review of these 24 reports, 11 were excluded because they did not utilize cajuput oil or 1,8-cineole as the primary intervention, focused on non-respiratory outcomes, or lacked sufficient quantitative primary data. Ultimately, 13 original studies were included in the systematic review. The flow of the study selection process is detailed in Table 1.

Study Characteristics

The 13 included studies represented a diverse range of geographical origins and experimental designs. Preclinical studies were conducted in Brazil, Germany, Bulgaria, China, Portugal, Indonesia, and Argentina, while clinical trials and observational cohorts were conducted in Russia, Germany, and Morocco. The study designs included 5 in vivo/in vitro combined animal and cell culture studies, 2 in vitro human tissue studies, 1 pure in vitro microbiological biofilm study, 1 Phase III randomized controlled trial, and 2 clinical observational studies. The experimental models covered acute and chronic airway pathologies, including cigarette smoke and elastase-induced emphysema, bleomycin-induced pulmonary fibrosis, allergic asthma, monocrotaline-induced pulmonary hypertension, *Staphylococcus aureus*-induced pneumonia, and bacterial biofilms. Table 1 presents the detailed characteristics of the 13 included studies.

Table 1. The Detailed Characteristics of the 13 Included Studies.

No	Author, Year	Country	Study Design	Sample Size / Experimental Model	Route of Administration	Disease / Model	Outcomes Measured	Main Findings
1	Kennedy-Feitosa et al., 2019	Brazil	In vivo (Mouse)	40 mice (10/group)	Nebulized inhalation (15 min/day)	Cigarette smoke-induced emphysema	Lung histology, MPO, TNF-α, IL-1β,	10 mg/mL eucalyptol promoted de novo alveolar formation, reduced

							Nrf2/NF-κB	inflammation, and normalized collagen deposition.
2	Cai et al., 2022	China	In vivo (Mouse)	25–30 mice	Inhalation using Microsprayer® (HA-coated liposomes)	Porcine pancreatic elastase (PPE)-induced emphysema	BALF analysis, mean linear intercept (MLI), TUNEL apoptosis assay	HA-coated liposomes improved pulmonary retention of eucalyptol and significantly reduced inflammation, oxidative stress, and apoptosis.
3	Rui et al., 2022	China	In vivo (Mouse) & In vitro	5 mice/group	Intraperitoneal injection (50 mg/kg)	Bleomycin-induced pulmonary fibrosis	Masson's trichrome histology, hydroxyproline, M2 macrophage polarization	Eucalyptol attenuated pulmonary fibrosis by suppressing M2 macrophage polarization through the p38 MAPK and STAT6 pathways.
4	Alves-Silva et al., 2025	Portugal	In vivo (Rat), Ex vivo & In vitro	5 rats/group (molecular analysis)	Daily transdermal administration	Pulmonary arterial hypertension (PAH)	Pulmonary arterial wall thickness, collagen deposition, BMPR2/Smad signaling	Transdermal eucalyptol prevented pulmonary vascular remodeling and restored endothelial barrier integrity and Cx43 signaling.
5	Cao et al., 2025	China	In vivo (Mouse) & In vitro	48 mice (12/group)	Nebulized inhalation (30 mg/kg)	*Staphylococcus aureus*-induced pneumonia	Survival rate, bacterial load (CFU), cytokines, metabolomics	Eucalyptol improved survival and reduced bacterial burden by modulating tryptophan (IDO1) and arginine (iNOS) metabolism.
6	Wang et al., 2026	China	In vivo (Mouse) & In vitro	30 mice (6/group)	Oral gavage (50 mg/kg)	Ovalbumin (OVA)-induced acute asthma	Airway resistance, serum IgE, BALF cytokines (IL-4, IL-13), NF-κB/COX-2	Eucalyptol alleviated airway hyperresponsiveness and remodeling through inhibition of the NF-

								κB/COX-2 pathway.
7	Kardos et al., 2021	Russia	Phase III randomized open-label clinical trial	132 patients	Oral (200 mg capsule, three times daily)	Acute bronchitis / tracheobronchitis	Cough frequency, Bronchitis Severity Score (BSS)	Adjunctive eucalyptol accelerated recovery, with 96.9% of patients recovering within 4–9 days.
8	Werkhäuser et al., 2023	Germany	Non-interventional observational survey	350 participants	Oral (Sinolpan® capsules, up to 800 mg/day)	Acute and chronic rhinosinusitis	RhinoQol, Bronchitis Severity Score (BSS)	Significant improvements in symptom frequency (64%) and disease impact (53.9%) with excellent tolerability.
9	Benjelloun et al., 2025	Morocco	Nationwide observational study	936 patients	Oral (Amoxicillin–clavulanate–cineole sachet)	Lower respiratory tract infection (LRTI)	Clinical recovery, radiological improvement	Clinical recovery was achieved in 94.9% of patients, and 57.8% became symptom-free within 3–4 days.
10	Beer et al., 2019	Germany & Bulgaria	In vitro experimental	Human bronchial tissue	Direct exposure in organ bath	Bronchial smooth muscle contraction	Spontaneous Contractile Activity (SCA)	Eucalyptol acted as an H1 receptor antagonist and H2 receptor agonist, producing bronchodilatory (spasmolytic) effects.
11	Vazquez et al., 2022	Argentina	In vitro experimental	Multidrug-resistant *Klebsiella pneumoniae* biofilm	Direct exposure (1% solution)	Drug-resistant bacterial biofilm	Cell viability (CFU), biofilm biomass	A 1% eucalyptol solution eradicated bacteria throughout the biofilm and reduced biomass by 30–62% within 1 hour.

12	Schürmann et al., 2019	Germany	In vitro & clinical experimental	*Staphylococcus aureus* biofilm and human respiratory mucosal explants	Direct exposure to organotypic tissue	Chronic rhinosinusitis (CRS)	MBIC50, biofilm gene expression, host cytokines	Eucalyptol inhibited *S. aureus* biofilm formation and attenuated host inflammatory responses by enhancing negative regulators of the NF-ϰB pathway.
13	Wibowo et al., 2024	Indonesia	Laboratory experimental	*Pseudomonas aeruginosa* culture	Agar diffusion assay (well/disc diffusion)	Gram-negative pneumonia pathogen	Inhibition zone diameter	Cajuput oil containing 72.3% eucalyptol inhibited *P. aeruginosa*, with maximal antibacterial activity at a 20% concentratio.

Discussion

Interpretation of Results

The synthesized evidence establishes that cajuput oil and its primary active component, 1,8-cineole, exert multi-targeted therapeutic actions on the respiratory system. The therapeutic benefits observed across preclinical models and human clinical cohorts can be integrated into four core mechanisms: parenchymal repair and redox homeostasis, immunomodulatory and cellular signal regulation, structural remodeling and tissue transition, and mechanical bronchodilation.

Parenchymal Repair and Redox Homeostasis in Emphysema

Pulmonary emphysema involves progressive alveolar septal destruction, protease-antiprotease imbalance, and persistent oxidative stress.[13] In a cigarette smoke-induced emphysema model in mice, treatment with eucalyptol (1,8-cineole) promoted de novo alveolar regeneration, as demonstrated by restoration of the septal volume fraction (SVF) and a reduction in the mean linear intercept (MLI), indicating improvement in alveolar structure.[13]

At the molecular level, 1,8-cineole functions as a potent antioxidant modifier[14]. Specifically, it upregulates the transcription factor Nrf2, which coordinates the expression of phase II detoxifying enzymes, including superoxide dismutase (SOD) and catalase (CAT), thereby enhancing the antioxidant response.

The upregulation of these antioxidant pathways is directly coupled with suppression of NF-ϰB signaling, leading to a significant reduction in myeloperoxidase (MPO) activity, lipid peroxidation, as reflected by reduced malondialdehyde (MDA) levels, and the production of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and the chemokine KC. Concurrently, eucalyptol mitigates tissue proteolysis by suppressing neutrophil elastase (NE) and upregulating elastin and TIMP-1 levels, thereby restoring extracellular matrix integrity[13].

These findings were further corroborated in a Porcine Pancreatic Elastase (PPE)-induced emphysema model, in which quantitative pulmonary delivery of 1,8-cineole arrested airspace enlargement, reduced apoptotic cell death in the lung parenchyma, and restored the antioxidant/oxidant balance.

The effectiveness of 1,8-cineole in restoring pulmonary parenchymal structure largely depends on its ability to reach the distal lung tissue through inhalation or quantitative pulmonary delivery. In a cigarette smoke-induced emphysema model, aerosolized eucalyptol administered by ultrasonic nebulization for 15 minutes daily significantly promoted lung

repair by inducing de novo alveolarization and normalizing collagen deposition in the peribronchiolar region. To further optimize drug delivery to the alveolar units, nanocarrier technologies, such as hyaluronic acid (HA)-coated liposomes, have demonstrated superior therapeutic performance compared with conventional formulations. Furthermore, quantitative pulmonary administration using the Microsprayer® aerosolizer achieved greater pulmonary deposition than free drug delivery, significantly reducing the mean linear intercept (MLI) and parenchymal cell apoptosis through activation of the Nrf2/NQO1 antioxidant signaling pathway.

Spasmolytic Activity and Bronchodilation

The mechanical regulation of airway smooth muscle tone plays a crucial role in maintaining airway patency in patients with asthma and chronic obstructive pulmonary disease (COPD). Using human segmental bronchial tissue preparations, 1,8-cineole demonstrated a dose-dependent and reversible spasmolytic effect on bronchial smooth muscle. This bronchodilatory activity is mediated through a dual pharmacological mechanism.

The first mechanism involves selective H_1-receptor antagonism. Specifically, 1,8-cineole acts as a reversible antagonist of H_1 histamine receptors located on bronchial smooth muscle fibers, thereby preventing histamine-induced bronchoconstriction. Importantly, this antagonistic effect is selective, as eucalyptol does not interfere with muscarinic acetylcholine (ACh) receptors.

The second mechanism involves agonistic activity at H_2 histamine receptors and β-adrenoceptors. Through activation of these receptors, 1,8-cineole suppresses spontaneous contractile activity (SCA), thereby contributing to relaxation of the bronchial smooth muscle. Collectively, these two mechanisms reduce intracellular calcium sensitivity and facilitate bronchodilation, supporting the clinical use of eucalyptol for relieving acute bronchospasm.

In clinical settings, the spasmolytic effects of 1,8-cineole on airway smooth muscle are most commonly achieved through oral administration in the form of enteric-coated soft capsules. Following absorption in the small intestine, the compound enters the systemic circulation and is partially excreted unchanged through the lungs, allowing direct therapeutic activity on the respiratory epithelium through an inside-out mechanism. This mechanism is consistent with the findings of a phase III clinical trial, in which oral administration of 1,8-cineole at a dose of 200 mg three times daily significantly reduced both cough frequency and the Bronchitis Severity Score (BSS) within four days.

At the molecular level, eucalyptol exerts its bronchodilatory effects through direct interaction with bronchial tissue by acting as a reversible histamine H_1 receptor antagonist and an agonist of H_2 receptors and β-adrenoceptors, thereby producing dose-dependent relaxation of bronchial smooth muscle.

Antifibrotic Mechanisms and Macrophage Polarization

Pulmonary fibrosis is characterized by persistent injury to alveolar epithelial cells, fibroblast activation, and excessive deposition of extracellular matrix proteins. In a bleomycin-induced pulmonary fibrosis model in mice, treatment with 1,8-cineole significantly attenuated fibrotic remodeling, as evidenced by the downregulation of hydroxyproline content, α-SMA expression, and fibronectin levels in lung tissue.

The antifibrotic effects of 1,8-cineole are mediated through the regulation of macrophage plasticity within the fibrotic microenvironment. Macrophages are capable of polarizing into either the pro-inflammatory M1 phenotype or the profibrotic M2 phenotype. Eucalyptol disrupts M2 macrophage polarization and suppresses macrophage-mediated secretion of the profibrotic factor transforming growth factor-β (TGF-β)

At the signaling level, eucalyptol inhibits the phosphorylation and nuclear translocation of signal transducer and activator of transcription 6 (STAT6) and p38 Mitogen-Activated Protein Kinase (p38 MAPK). This inhibition suppresses downstream transcription factors, including Kruppel-like Factor 4 (KLF4) and peroxisome proliferator-activated receptor-gamma (PPAR-γ), thereby preventing alternative macrophage activation and the subsequent progression of tissue fibrosis.

The immunomodulatory effects of 1,8-cineole generally require sustained systemic bioavailability, which can be achieved through intraperitoneal injection, oral gavage, or transdermal administration. In a pulmonary fibrosis model, intraperitoneal administration at

a dose of 50 mg/kg in corn oil effectively inhibited M2 macrophage polarization through suppression of the STAT6 and p38 MAPK signaling pathways, thereby reducing the production of profibrotic cytokines, particularly transforming growth factor-β1 (TGF-β1). Likewise, oral gavage administration in an asthma model suppressed epithelial–mesenchymal transition (EMT) through inhibition of the NF-κB/COX-2 signaling pathway, thereby attenuating airway remodeling. Furthermore, transdermal administration via daily topical application has emerged as an innovative strategy to circumvent hepatic first-pass metabolism, allowing systemic delivery to the pulmonary vasculature and restoration of the BMPR2 signaling cascade in pulmonary hypertension.

Regulation of Epithelial-Mesenchymal Transition in Asthma

In chronic bronchial asthma, persistent airway hyperresponsiveness and structural remodeling are driven by Epithelial-Mesenchymal Transition (EMT), where ciliated epithelial cells acquire a profibrotic mesenchymal phenotype under the influence of TGF-β. In ovalbumin (OVA)-induced asthmatic mice and human bronchial epithelial (BEAS-2B) cells, 1,8-cineole significantly reduced airway resistance (R_l) and improved dynamic compliance (Cdyn). Eucalyptol prevented EMT by suppressing the NF-κB/COX-2 signaling cascade. This regulatory action reduced the expression of mesenchymal markers (α-SMA, N-cadherin) while restoring E-cadherin levels, thereby maintaining epithelial barrier integrity and preventing airway wall remodeling.

Pulmonovascular Remodeling and Gap Junction Integrity

In addition to airway disorders, 1,8-cineole demonstrates a protective effect on the pulmonary vasculature. In monocrotaline (MCT)-induced pulmonary arterial hypertension (PAH) in rats and human pulmonary artery endothelial cells (HPAECs), 1,8-cineole prevented pulmonary vascular remodeling, interstitial collagen deposition, and medial wall thickening.

This protective effect was achieved by restoring the deregulated Bone Morphogenetic Protein Receptor Type II (BMPR2) cascades specifically the BMPR2/Smad1/5 and BMPR2/PPAR-γ pathways. Concurrently, eucalyptol preserved the integrity of endothelial gap junctions, restored pulmonary surfactant expression, maintained mitochondrial structure, and inhibited pathological angiogenesis.

Antimicrobial, Antibiofilm, and Host Metabolic Reprogramming Efficacy

The therapeutic utility of cajuput oil and 1,8-cineole extends to their antimicrobial properties. In a murine model of *Staphylococcus aureus*-induced pneumonia, treatment with 1,8-cineole improved survival rates while reducing pulmonary bacterial burden and inflammatory cell infiltration.

Metabolomic profiling further revealed that 1,8-cineole induces immunometabolic reprogramming in the host by modifying 19 key metabolites across the tryptophan-kynurenine (TRP-KYN) and arginine-nitric oxide (arginine-NO) pathways. This effect is achieved through suppression of the enzymatic activities of Indoleamine 2,3-Dioxygenase 1 (IDO1) and Inducible Nitric Oxide Synthase (iNOS), thereby mitigating inflammatory damage to the lung parenchyma.

Against Gram-negative opportunistic pathogens, cajuput oil obtained by steam distillation from *Melaleuca leucadendra* exhibited direct, concentration-dependent antibacterial activity against *Pseudomonas aeruginosa*. Well-diffusion assays demonstrated inhibition zones of 15.73 mm, 20.82 mm, 17.91 mm, 11.83 mm, 11.25 mm, 10.92 mm, 10.46 mm, 9.93 mm, and 9.57 mm at concentrations of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, and 90%, respectively. Interestingly, no inhibition zone was observed at a concentration of 100%, suggesting that the presence of aqueous co-solvents is necessary to facilitate the solubility and diffusion of the volatile oil through the agar matrix.

Furthermore, 1,8-cineole exhibits potent antibiofilm activity. In biofilms of multidrug-resistant, extended-spectrum β-lactamase (ESBL)-producing *Klebsiella pneumoniae*, treatment with 1% (v/v) 1,8-cineole for 1 hour killed bacteria throughout all biofilm layers and reduced biofilm biomass by 30% to 62%. Similarly, in clinical isolates from chronic rhinosinusitis (CRS), 1,8-cineole disrupted *Staphylococcus aureus* biofilm formation on organotypic respiratory epithelial slices and attenuated host inflammatory responses through the NF-κB pathway.

To combat bacterial infections and biofilm formation, 1,8-cineole has been formulated for both nebulized delivery and oral combination therapy. Nebulized administration using hydroxypropyl-β-cyclodextrin (HP-β-CD) inclusion complexes significantly enhances the aqueous solubility and stability of the compound, resulting in improved survival in a *Staphylococcus aureus* pneumonia model through modulation of the immunometabolic IDO1 and iNOS pathways. In addition, an oral sachet formulation combining amoxicillin, clavulanic acid, and cineole, marketed as Olipen®, demonstrated a clinical recovery rate of 94.9% in patients with lower respiratory tract infections. Furthermore, the lipophilic nature of 1,8-cineole facilitates its penetration into the extracellular matrix of multidrug-resistant (MDR) bacterial biofilms, including those formed by *Klebsiella pneumoniae*, thereby disrupting biofilm integrity and eradicating bacterial cells throughout all biofilm layers. Similar antibiofilm activity has also been reported against *Staphylococcus aureus* in chronic rhinosinusitis and against *Pseudomonas aeruginosa* using the agar well diffusion method.

Clinical Translation, Safety, and Advanced Formulations

The multi-targeted mechanisms identified in preclinical studies align with clinical outcomes observed in human trials.

Clinical Trials in Acute Bronchitis and Rhinosinusitis

In a Phase III randomized, open-label, parallel-group clinical trial involving 132 patients with acute bronchitis or tracheobronchitis, oral cineole (3 × 200 mg/day) administered as an adjunct to standard therapy significantly reduced cough frequency and Bronchitis Severity Scores (BSS) within four days of treatment. Cineole was well tolerated, with only a few mild adverse events reported, including gastrointestinal discomfort and the characteristic odor of eucalyptol. This odor reflects the systemic pharmacokinetics of cineole, which is absorbed enterally and partially exhaled through the lungs, allowing it to exert direct secretolytic and anti-inflammatory effects on the respiratory epithelium.

Clinical benefits have also been demonstrated in patients with rhinosinusitis. A prospective observational study involving 350 patients with acute or chronic rhinosinusitis reported significant improvements in RhinoQol outcomes, including symptom frequency, symptom burden, and health-related quality of life after approximately seven days of cineole treatment. More than 90% of participants rated the therapeutic effectiveness as good or very good, with excellent tolerability, supporting the role of cineole as an effective symptomatic therapy.

The therapeutic efficacy observed in both bronchitis and rhinosinusitis is supported by the multimodal pharmacological actions of cineole. Beyond its anti-inflammatory and mucoregulatory properties, cineole suppresses mucus hypersecretion and inhibits biofilm formation by common respiratory pathogens, particularly *Staphylococcus aureus*, through the downregulation of key biofilm regulatory genes. These complementary mechanisms may enhance mucociliary clearance, reduce persistent sinonasal inflammation, and support antibiotic stewardship by providing effective symptom control while minimizing unnecessary antibiotic use.

Integration with Antibacterial Formulations in Lower Respiratory Infections

The clinical efficacy of 1,8-cineole is further illustrated by its incorporation into multi-target antibacterial formulations. In a nationwide, observational study in Morocco evaluating 936 adult outpatients with mild-to-moderate lower respiratory tract infections (LRTIs), including community-acquired pneumonia and acute exacerbations of chronic bronchitis or COPD, patients were treated with Olipen®.

This formulation combines amoxicillin 500 mg, clavulanate 62.5 mg, and 1,8-cineole 100 mg per sachet, administered twice per sachet, three times daily for 7–14 days. Clinical recovery was achieved in 94.9% of the cohort, with 57.8% of patients becoming completely symptom-free within 3 to 4 days of initiating therapy.

Radiological improvements were observed in 81% of patients. The addition of 1,8-cineole to the amoxicillin-clavulanate regimen enhances clinical efficacy by improving amoxicillin bioavailability and reducing the affinity of bacterial β-lactamases for the antibiotic, helping to overcome resistance in ESBL-producing strains.

Advanced Nano-Delivery and Pulmonary Target Optimization

Despite its therapeutic potential, the clinical translation of 1,8-cineole is limited by its high volatility, hydrophobic nature, chemical instability, and short biological half-life *in vivo*. To overcome these pharmacodynamic limitations, advanced drug delivery systems have been developed.

Cai *et al.* (2022) engineered a bio-inspired, hyaluronic acid (HA)-coated liposomal formulation to encapsulate 1,8-cineole (HA-Lips/1,8-cineole). When delivered directly to the lungs using a Microsprayer® aerosolizer, this formulation demonstrated significant advantages:

1. The liposomal matrix protected 1,8-cineole from rapid volatilization and enzymatic degradation, ensuring sustained release and prolonged therapeutic retention within the lung parenchyma.
2. The surface modification with hyaluronic acid facilitated active targeting of the CD44 receptors, which are overexpressed on inflamed alveolar macrophages and activated epithelial cells, enhancing localized cellular uptake.
3. In porcine pancreatic elastase-induced emphysema models, HA-Lips/1,8-cineole achieved superior therapeutic outcomes compared to free 1,8-cineole or uncoated liposomes, significantly reducing alveolar airspace enlargement, inflammatory cell infiltration, and apoptosis.
4. This enhanced protective effect was driven by the efficient target delivery of eucalyptol to CD44-expressing cells, resulting in the upregulation of the Nrf2/NQO1 antioxidant pathway and the suppression of the pro-inflammatory NF-κB/IκBα axis.

These findings indicate that the development of targeted nanocarriers represents a critical strategy to optimize the clinical efficacy and bioavailability of volatile monoterpenes in respiratory medicine.

Limitations of the Evidence and Review Process

Several limitations within the primary evidence and the systematic review process should be considered:

1. Reliance on Animal Models: A significant portion of the mechanistic evidence is derived from induced animal models (e.g., chemical, elastase, or smoke-induced injuries). These models are valuable for studying specific pathways but do not fully replicate the chronic, progressive, and multi-factorial pathophysiology of human diseases.
2. Clinical Trial Design and Population Demographics: Some of the clinical evidence, such as the trial by Kardos et al. (2021), utilized open-label designs, which can introduce bias in symptom reporting. Additionally, clinical cohorts were geographically localized, highlighting the need for larger, multi-ethnic, double-blind randomized trials.
3. Heterogeneity of Interventions: The included studies evaluated various interventions, ranging from pure 1,8-cineole to steam-distilled cajuput oil and multi-component formulations. This heterogeneity, combined with diverse outcome measures, precluded a quantitative meta-analysis, restricting the review to a qualitative narrative synthesis.
4. Database and Language Restrictions: The systematic search was limited to PubMed, EuropePMC, and OpenAlex, and restricted to studies published in English and Indonesian, which may have omitted relevant research indexed in other databases or published in other languages.

4. Conclusion

This systematic review confirms that cajuput oil (*Melaleuca cajuputi* / *Melaleuca leucadendra*) and its primary active monoterpene, 1,8-cineole (eucalyptol), exert multi-targeted therapeutic actions across several upper and lower respiratory tract conditions. Preclinical studies demonstrate that 1,8-cineole modulates key signaling pathways including Nrf2, NF-κB, STAT6, p38 MAPK, and BMPR2 to suppress oxidative stress, reduce inflammatory cytokine release, prevent pathological remodeling, and preserve cellular barrier integrity. Clinically, oral and adjunctive formulations of 1,8-cineole significantly reduce symptom severity, accelerate recovery, and are well tolerated in patients with acute bronchitis, rhinosinusitis, and lower

respiratory tract infections. Advanced delivery platforms, such as hyaluronic acid-coated liposomes, successfully address the challenges of volatility and low bioavailability, representing a promising strategy to optimize localized drug delivery. Future clinical research should focus on large-scale, double-blind randomized trials to validate the efficacy of targeted pulmonary inhalation formulations in patients with chronic respiratory diseases.

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