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Review Article

A SYSTEMATIC REVIEW OF EUCALYPTOL AS AN INNOVATIVE THERAPEUTIC AGENT FOR RESPIRATORY DISEASES

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ABSTRACT

Eucalyptol (1,8-cineole), a natural monoterpenoid found in eucalyptus essential oil, has long been used in traditional medicine for its anti-inflammatory, mucolytic, antimicrobial, and mild bronchodilatory properties. Recent pharmacological studies have further validated its therapeutic potential, making it a promising candidate for managing chronic respiratory diseases. This study systematically reviews the available evidence on eucalyptol's effects in treating these conditions. The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a clear and reproducible process for selecting articles, extracting data, and analyzing results. Literature was collected from reliable databases such as PubMed, ScienceDirect, and Scopus. The bibliometric analysis incorporated in this study further strengthens its novelty, providing a quantitative overview of research trends and highlighting key themes and emerging areas of interest. A total of 35 studies met the inclusion criteria, evaluating the pharmacological effects of eucalyptol on respiratory diseases. Eucalyptol has demonstrated anti-inflammatory effects through cytokine modulation, enhances mucus clearance, and reduces airway resistance. Several studies showed improvement in lung function and symptom relief in patients. Eucalyptol holds significant potential as an adjunctive therapy for chronic respiratory diseases due to its anti-inflammatory, mucolytic, antimicrobial, and mild bronchodilatory properties. In addition to improving lung function and patient quality of life, eucalyptol also reduces the risk of side effects associated with long-term therapy. Despite these benefits, challenges remain, including low bioavailability, volatility, and the need for optimized pharmaceutical formulations. Future research should focus on nanoemulsions, inhalable drug delivery systems, and controlled-release technologies to enhance its therapeutic efficacy. Large-scale clinical trials targeting vulnerable populations, including pediatric and geriatric patients, are essential to establish eucalyptol's clinical utility.

Keywords: Eucalyptol, Respiratory diseases, Systematic review, Pharmaceutical formulation

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INTRODUCTION

Eucalyptol (1,8-cineole) is a primary component of eucalyptus essential oil and has long been used in traditional medicine to address various respiratory disorders. Modern studies have revealed that eucalyptol exhibits a wide range of pharmacological effects, including anti-inflammatory, mucolytic, and antimicrobial activities, making it a potential therapeutic candidate in the management of chronic respiratory diseases [1–3]. Eucalyptol has been shown to inhibit the production of pro-inflammatory mediators such as TNF-α and IL-1β, which play a crucial role in the inflammatory processes underlying various lung diseases [4, 5]. Eucalyptol inhibits inflammation by blocking ERK-dependent NF-κB activation, reducing nuclear NF-κB expression and lowering pro-inflammatory cytokines like TNF-α [6]. Additionally, eucalyptol's mucolytic effects aid in thinning mucus and enhancing sputum clearance, which is critical in reducing airway obstruction in diseases like chronic bronchitis and COPD [7].

Respiratory diseases, such as asthma, chronic bronchitis, and Chronic Obstructive Pulmonary Disease (COPD), are leading causes of global morbidity and mortality, affecting over 500 million people worldwide. These conditions significantly impact the quality of life and contribute to the healthcare cost burden [8]. Research on four common respiratory diseases in the Asia-Pacific region estimated that the average annual cost per patient is approximately $4,191, with total expenses reaching $22 million for the study sample. These costs stem primarily from medical treatments, hospital visits, and reduced work productivity, highlighting the urgent need for more cost-effective therapeutic options [9]. Current therapies for these respiratory conditionstypically include a combination of inhaled corticosteroids, bronchodilators, and anti-inflammatory drugs. While effective in symptom management, long-term use of these therapies often leads to serious side effects, including osteoporosis, hypertension, and an increased risk of infections [10, 11]. In this context, there is an urgent need to identify safe and effective therapeutic agents as alternatives or adjuncts to conventional treatments. This highlights the urgent need for safer and more effective therapeutic agents as alternatives or adjuncts to conventional treatments. Eucalyptol's potential as an adjunct therapy for respiratory diseases has been evaluated in numerous clinical and preclinical studies, with results showing improved lung function, reduced exacerbation rates, and enhanced quality of life for patients [12]. Despite these promising findings, there remain several unanswered questions regarding the specific mechanisms of action, long-term safety, and potential interactions between eucalyptol and conventional therapies. Beyond pharmacological approaches, patient education and counseling have also been shown to improve medication adherence, disease management, and health outcomes [13].

This article aims to systematically review the existing body of literature on eucalyptol as an innovative therapeutic agent for managing respiratory diseases, with the overarching goal of establishing a comprehensive scientific foundation that supports the development of safer and more effective treatment options. By examining the pharmacological properties and therapeutic potential of eucalyptol, this review seeks to highlight its capacity to address unmet needs in the treatment of respiratory conditions, particularly chronic disorders. Furthermore, it explores eucalyptol's role as a promising alternative in the management of chronic respiratory diseases, thereby contributing to the diversification of therapeutic approaches and enhancing patient outcomes in a field where innovation and safety are critical priorities.

MATERIALS AND METHODS

Data collection

This systematic review was conducted following the guidelines of the PRISMA to ensure transparency and high quality in the screening and selection process of relevant articles [14]. In addition to the systematic review, a comprehensive bibliometric analysis was performed to identify and analyze research trends in the field of eucalyptol and its use in the therapy of respiratory diseases. This approach aimed to map future research directions and provide insights into emerging research trends and collaborations in this area.

Eligibility criteria

Studies were included if they investigated eucalyptol in the context of respiratory diseases, focusing on its effects or mechanisms of action, either in clinical or preclinical settings. Only original research articles were considered, while book chapters, review articles, and bibliographies were excluded. The studies had to focus on the therapeutic effects of eucalyptol, including improvements in respiratory function, symptom relief, or other relevant clinical outcomes. Studies written in English were included, provided eucalyptol was a central focus or discussed as a primary therapeutic agent in respiratory disease treatment. Studies could be included with or without a comparison group, where applicable, to assess the effects of eucalyptol.

Search strategy

A comprehensive search strategy was developed across three databases: PubMed, ScienceDirect, and Scopus. Keywords and Boolean operators (AND, OR) were used to combine terms in various permutations to ensure the identification of all relevant articles. The following search string was applied: ["Eucalyptus globulus" OR "Eucalyptol"] AND ["Respiratory disease" OR "Respiratory tract infection"]. The search was not restricted by publication date to maximize the scope of included studies, ensuring comprehensive coverage of the literature.

Selection process

The search results were screened by two independent reviewers in two phases. First, the titles and abstracts of all retrieved studies were reviewed, and studies that clearly did not meet the inclusion criteria were excluded. In the second phase, the remaining articles were assessed in full for eligibility based on the criteria outlined above. Disagreements between reviewers were resolved through discussion, and consensus was reached before final selection.

Data collection

Data were collected using the reference management software Zotero. Relevant articles that met the eligibility criteria were exported in. ris format for further analysis. Each article's publication details, study design, outcomes, and findings were extracted for subsequent synthesis.

Data analysis process

VOSviewer software was used to visualize and evaluate research trends through bibliometric mapping. This process involved identifying and mapping keywords that appeared at least twice across the reviewed literature. Irrelevant or less significant terms were systematically excluded to ensure a focused analysis. The mapping helped identify clusters of research topics and the relationships between them, providing an overview of the main themes and trends related to the role of eucalyptol in respiratory disease therapy.

This structured methodological approach, adhering to PRISMA guidelines, ensures comprehensive, transparent, and accurate insights into the scientific landscape of eucalyptol in respiratory disease therapy.

RESULTS AND DISCUSSION

Literature search

The literature search process identified 486 relevant articles from three major databases: PubMed (n=9), ScienceDirect (n=412), and Scopus (n=65). The search process is depicted in the PRISMA flow diagram (fig. 1), which involves the stages of identification, screening, eligibility assessment, and final selection of articles for review.

After removing 10 duplicate articles, 476 unique articles were analyzed further. From this total, 261 articles were excluded based on the following criteria: book chapters (n=62), review articles (n=124), non-English articles (n=2), conference proceedings (n=4), and others (n=24). During the eligibility assessment phase, 215 articles remained and were re-screened to ensure relevance to the topic. A further 180 articles were excluded because the keywords were not the primary focus of the study. Ultimately, 35 articles met the inclusion criteria and were included in the systematic review, as shown in fig. 1.

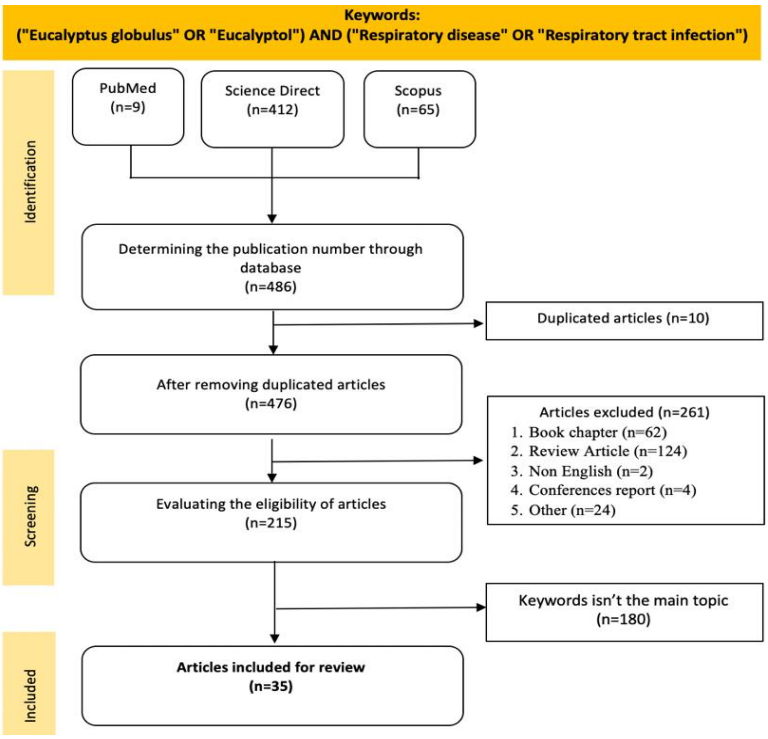

Fig. 1: Screening literature flowchart based on PRISMA method

Pharmacological potential of eucalyptus in respiratory disease therapy

Eucalyptus has long been utilized in traditional medicine to treat respiratory disorders owing to its bioactive compounds, such as eucalyptol and cineole, which possess antibacterial, anti-inflammatory, mucolytic, and bronchodilatory activities. Recent research has uncovered the mechanisms and therapeutic potential of these compounds, particularly in the treatment of respiratory tract diseases.

Recent studies indicate that eucalyptus is effective as a complementary agent in alleviating symptoms of respiratory infections such as cough, bronchitis, and asthma. Its active compounds work on the respiratory tract and the immune system, providing protective and restorative effects for patients with both acute and chronic respiratory disorders. Table 1 summarizes the plant parts, active compounds, analytical methods, and pharmacological mechanisms, offering a comprehensive overview of eucalyptus's role in respiratory therapy.

Clinical evidence supports eucalyptol's role in improving lung function and reducing airway inflammation. A randomized controlled trial (ISRCTN07600011) in 242 COPD patients showed that 200 mg of eucalyptol, taken thrice daily for six months, significantly reduced exacerbation frequency, severity, and duration while improving lung function, dyspnea, and quality of life [7]. Similarly, a multicenter trial in 247 asthma patients found that eucalyptol treatment led to significant improvements in lung function ($p = 0.0398$), asthma symptoms ($p = 0.0325$), and quality of life ($p = 0.0475$) compared to placebo, highlighting its potential as an adjunct therapy for respiratory diseases [15]. While clinical trials have used a standard oral dose of 200 mg three times daily, preclinical studies have tested a wider range of doses (e. g., 50–500 mg/kg in animal models). This discrepancy highlights the challenge of dose translation from preclinical to human studies, where factors such as metabolism and bioavailability may impact efficacy. Future research should focus on optimizing dosing strategies to ensure therapeutic consistency between preclinical and clinical findings.

Advancements in pharmaceutical technology have enabled the development of various eucalyptol-based formulations, such as aerosols, capsules, essential oils, and nanoemulsions, which enhance the delivery efficiency of active compounds via inhalation, topical application, and oral administration. Specifically, nanoemulsion technology improves the stability and penetration of these compounds, resulting in more effective therapeutic effects for infectious and inflammatory conditions. Table 2 presents various eucalyptus-based formulations and their pharmacological effects, providing a comprehensive view of eucalyptus-based therapies for respiratory disorders.

Bibliometric analysis: computational mapping in eucalyptol research

This study generates a bibliometric map based on keyword co-occurrence to identify the main clusters in eucalyptol research. This visualization provides valuable insights for researchers to recognize dominant themes and highlight underexplored areas in the field. From the 35 selected articles, keyword co-occurrence analysis was used to identify research trends and thematic clusters. The frequency of each keyword is represented by the size of the nodes on the bibliometric map (fig. 2). The largest node, "eucalyptol," reflects the most frequently discussed topic in the literature, while smaller nodes, such as "trachea" and "aerosol," indicate more specific areas of research focus.

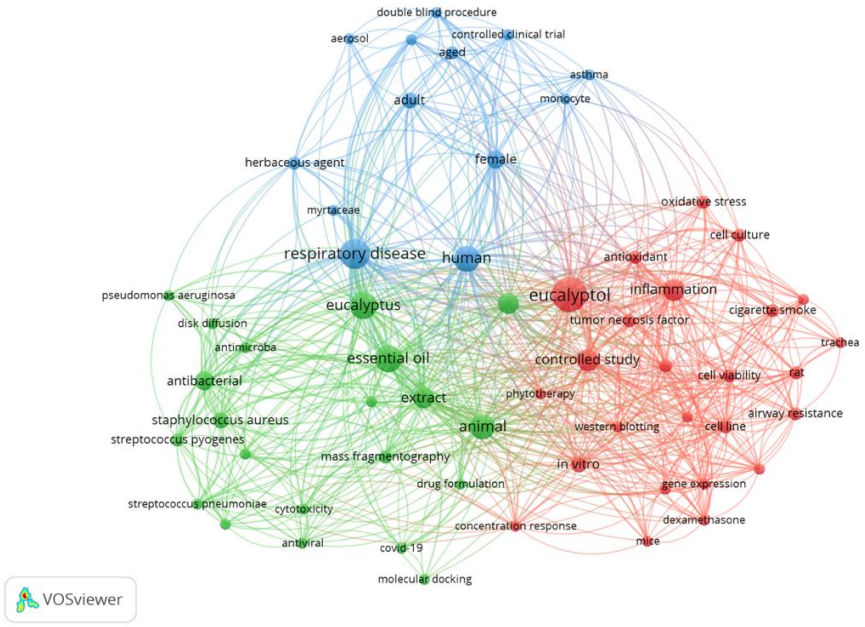

Fig. 2: Bibliometric map of keyword Co-occurrence network in eucalyptol research

The bibliometric mapping revealed three main thematic clusters that cover various aspects of eucalyptol research. The first cluster highlights the antimicrobial effects of eucalyptol, particularly its ability to combat respiratory tract pathogens. This positions eucalyptol as an effective antimicrobial agent for respiratory infections. Studies in this cluster emphasize eucalyptol's ability to inhibit bacterial growth, making it a promising candidate for respiratory disease treatments. The second cluster focuses on eucalyptol's anti-inflammatory and antioxidant properties, which help reduce inflammation and protect tissues from oxidative stress-induced damage. Research within this cluster indicates that eucalyptol plays a protective role against tissues by reducing the damaging effects of free radicals and inflammation, reinforcing its potential as an antioxidant agent. The third cluster examines the clinical applications of eucalyptol in respiratory therapy, particularly its potential as a bronchodilator and its ability to enhance the efficacy of treatment when used as an adjunct therapy. Research in this cluster explores the practical applications of eucalyptol in the management of respiratory diseases, offering deeper insights into its use in complementary therapy.

These three clusters provide a comprehensive understanding of the role and potential of eucalyptol in health, particularly in respiratory treatment. Each cluster contributes unique insights into the pharmacological effects and clinical applications of eucalyptol, allowing researchers to identify key trends and opportunities for further exploration. This analysis underscores the need for further investigation into eucalyptol's benefits as an adjunct component in respiratory therapy to maximize its potential.

Table 1: Summary of eucalyptus species' plant part, compound, site of action, pharmacological mechanism, dosage form, delivery method, formulation, description, and comparative drugs

S. No.	Type/Cultivar	Part of plant	Compound	Site of action	Mechanism of pharmacology	Dosage form	Delivery method	Formulation	Reference
1	*Eucalyptus camaldulensis*	Leaves	Eucalyptol	Respiratory tract	Antibacterial (*Pseudomonas aeruginosa*)	Aerosol	Inhalation	Eucalyptol in 40% olive oil solution	[16]5/4/2025 7:23:00 AM
2	*Eucalyptus citriodora*	Leaves	Eucalyptol	Alveolar macrophages	Immunomodulatory	Aerosol	Inhalation	Eucalyptol 10 mg/ml	[17]
3	*Eucalyptus citriodora*, E. *globulus*, *Mentha piperita*, Origanumsyriacum, *Rosmarinusofficinalis*	Multiple	Essential Oils	Upper Respiratory Tract	Provides rapid symptom relief in upper respiratory tract infections through anti-inflammatory and analgesic effects	Fluids for *in vitro* research	*In vitro* Delivery (Laboratory)	Eucalyptol, dissolved in culture medium at a concentration of 100 µM	[18]
4	*Eucalyptus deglupta*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial	Liquid extracts and essential oils	Inhalation, Oral (Green Pharmacy)	Essential oil from Eucalyptus tereticornis leaves with the main content of eucalyptol, coumarin, α-pinene, β-pinene, p-cymene, limonene, γ-terpinene, α-terpineol, and aromadendrene	[19]
5	*Eucalyptus globulus*	Leaves	Cineole	Respiratory tract	Mucolytic, anti-inflammatory, bronchodilator; reduces inflammation, enhances mucus clearance, improves lung function	*E. globulus* leaf extract	Antibacterial	Methanol extract of eucalyptus leaves; MIC for *Staphylococcus aureus* (64 mg/l), *Streptococcus pyogenes* (32 mg/l), *S. pneumoniae* (16 mg/l), and *Haemophilus influenzae* (16 mg/l)	[20]
6	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory Tract	Inhibits Wnt/β-catenin signaling pathway by dephosphorylating GSK-3, reducing inflammatory gene expression	Inhaler	Inhalation	Eucalyptus inhaler (contains 28 mg eucalyptol, 3 mg thymol, 10 mg menthol)	[21]
7	*Eucalyptus globulus*	Leaves	Eucalyptol	Mice lungs	Reduces airway hyperresponsiveness	Capsule	Oral	Cineole 200 mg per capsule	[15]
8	*Eucalyptus globulus*	Leaves	Eucalyptol	Nasal polyps	Reduces phosphorylation of eNOS, anti-inflammatory	Enteric-coated capsules	Oral (Enteric Capsule)	Eucalyptol, limonene, and pinene	[3]
9	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antioxidant, anti-inflammatory; inhibits superoxide anion (O2−) production, partially inhibits SOD, reduces H2O2 and TNF-α	Oral Solution	Oral (Through the Mouth)	Eucalyptol (99% purity) was diluted in 1% Tween-80 solution.	[22]
10	*Eucalyptus globulus*	Leaves	Eucalyptol	Grass carp hepatocytes	Antioxidant, anti-inflammatory	Aerosol	Inhalation	Eucalyptol (50 mg/kg)	[23]
11	*Eucalyptus* spp.	Leaves	Eucalyptol	Human bronchial tissue	Anti-inflammatory (asthma treatment)	Capsule	Oral	Cineole 200 mg per capsule	[24]
12	*Eucalyptus* spp.	Leaves	Eucalyptol	Mouse lungs	Lung repair, antioxidant, anti-inflammatory	Pure Essential Oils	Topical	Essential oils of some Eucalyptus species (main components: eucalyptol and citronellal)	[25]
13	*Eucalyptus globulus*	Leaves	Eucalyptol	Nervous system, microglia	Reduces inflammation and nerve damage by inhibiting GSDMD-mediated pyroptosis, lowering IL-1β, TNF-α, TLR4/NF-κB expression, and microglia activation	Pure Essential Oils	Topical	*Eucalyptus globulus* essential oil (79% cineole) combined with antibiotics	[26]
14	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antiviral, molecular docking against COVID-19	Aerosol	Inhalation	Eucalyptol (50 mg/kg)	[27]
15	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial, anti-inflammatory	Aerosol	Inhalation	Eucalyptol (1 mg/ml)	[28]
16	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial, anti-inflammatory for COVID-19	Nano-Emulsion solution in nebulizer	Inhalation	Eucalyptol nano-emulsion (4% v/v) with Tween 80 as surfactant	[29]
17	*Eucalyptus* spp.	Leaves	Eucalyptol	Mouse macrophages	Antioxidant, immunomodulatory	Solution (culture	*In vitro* (cell culture)	Eucalyptol (5 µM)	[30]

S. No.	Type/Cultivar	Part of plant	Compound	Site of action	Mechanism of pharmacology	Dosage form	Delivery method	Formulation	Reference
						medium)			
18	*Eucalyptus* spp.	Leaves	Eucalyptol	Olfactory system	Enhances olfactory sensitivity through repeated smell training that triggers increased aroma identification and discrimination	Smell exercise	Olfactory	Eucalyptol, phenyl ethyl alcohol, citronellal, and eugenol	[31]
19	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Anti-inflammatory, antioxidant	Solution (culture medium)	*In vitro* (cell culture)	Eucalyptol (10^{-10}–10^{-5} M)	[32]
20	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antibacterial (*S. aureus*, *S. pyogenes*)	Spray	Inhalation	Essential oils: *E. citriodora* (10%), *E. globulus* (20%), *M. piperita* (20%), Origanumsyriacum (30%), *R. officinalis* (20%)	[33]
21	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Cross-protection against influenza virus	Suspension in Tween-80 0.5%	Oral	Eucalyptol (30, 60, and 120 mg/kg)	[34]
22	*Eucalyptus griffthsii*	Leaves	Eucalyptol	Respiratory tract	Antioxidant, immunomodulatory	Plant tissue isolation method	Topical	Eucalyptol (100 μM)	[35]
23	*Eucalyptus globulus*	Leaves	Eudesmol, α-pinene, β-pinene, γ-terpinene, α-terpineol	Nervous system, microglia	Reduces inflammation and nerve damage by inhibiting GSDMD-mediated pyroptosis, lowering IL-1β, TNF-α, TLR4/NF-κB expression, and microglia activation	Pure Essential Oils	Topical	*E. globulus* essential oil with eudesmol content	[36]
24	*Eucalyptus* spp.	Leaves	Not specified	Digestive and respiratory tracts	Antimicrobial, used in traditional medicine for digestive and respiratory diseases	Computer Model	In Silico (Molecular Interactions)	Eucalyptol, citronellol, alpha-terpineol, d-limonene	[27]
25	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial, anti-inflammatory	Essential oils	Inhalation	Essential oils from Eucalyptus species	[25]
26	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antiviral, cross-protection against influenza virus	Solution (oral)	Oral	Eucalyptol (200 mg per capsule)	[24]
27	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial, anti-inflammatory	Aerosol	Inhalation	Eucalyptol (1 mg/ml)	[28]
28	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Reduces bronchial inflammation and hyper responsiveness	Inhalation	Inhalation	Eucalyptol nano-emulsion in nebulizer	[23]
29	*Eucalyptus radiata*	Leaves	Eucalyptol	Airway epithelium	Mucolytic, bronchodilator	Pure Essential Oils	Topical	Eucalyptol-rich essential oils	[24]
30	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Adjuvant to flu vaccine	Oral solution	Oral	Eucalyptol (99%)	[34]
31	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial, anti-inflammatory	Inhaler	Inhalation	Eucalyptol (20 mg per inhaler)	[21]
32	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Antimicrobial and anti-inflammatory effect for asthma patients	Capsule	Oral	Eucalyptol (200 mg per capsule)	[24]
33	*Eucalyptus globulus*	Leaves	Eucalyptol	Respiratory tract	Bronchodilator and anti-inflammatory	Nebulizer	Inhalation	Eucalyptol-rich essential oils	[28]

Identification of research gaps through cluster mapping

This bibliometric analysis reveals key gaps in eucalyptol research through the mapping of three major clusters: biomedical research related to inflammation and oxidative stress, antimicrobial studies and formulation development, and clinical studies in respiratory diseases. The analysis highlights the need for more in-depth clinical data in humans to confirm preclinical findings, particularly in the context of respiratory inflammation. Furthermore, there is a lack of research focusing on the bioavailability and stability of eucalyptol in innovative pharmaceutical formulations, which is crucial for enhancing its therapeutic effectiveness.

Another gap identified is the scarcity of data regarding the effectiveness of eucalyptol in vulnerable populations, such as pediatric and geriatric patients, as well as the limited evaluation of its long-term safety. This underscores the urgent need for comprehensive clinical trials, the development of more stable formulations, and studies involving specific populations to ensure that eucalyptol can be optimized as an effective therapeutic agent.

Table 3 presents a summary of these research gaps and offers recommendations for future studies, including innovations in pharmaceutical formulations and broader clinical evaluations, to maximize eucalyptol's potential in the treatment of various respiratory diseases.

Table 3: Research gaps in eucalyptol studies based on keyword mapping

Research cluster	Dominant areas in research	Identified gaps	Further research recommendations	Ongoing research efforts
Cluster 1: Biomedical Research. Inflammation and Oxidative Stress	Focus on the anti-inflammatory effects of eucalyptol, especially through *in vitro* studies, animal testing (rats/mice), and molecular mechanisms such as IL-6 and TNF-α expression.	1. Lack of clinical data confirming *in vitro* and animal results at the human level. 2. Lack of research on the interaction of eucalyptol with specific molecular pathways in the human respiratory system.	1. Conduct large-scale clinical trials in patients with inflammatory respiratory conditions (asthma, COPD) to confirm preclinical results. 2. Identify and map the major molecular pathways of eucalyptol in human respiratory epithelial cells.	Some clinical trials are investigating eucalyptol's effects in respiratory conditions (e. g., COPD, asthma), but large-scale human studies remain limited.
Cluster 2: Antimicrobials and Drug Formulation Development	Studies on the antibacterial and antiviral effects of eucalyptol against respiratory pathogens, as well as the use of *disk diffusion methods, molecular docking,* and the development of essential oil-based formulations.	1. Lack of clinical data regarding the effectiveness of eucalyptol as an antimicrobial agent in patients with acute respiratory infections. 2. Lack of research on the bioavailability and stability of eucalyptol in new formulations. 3. Limitations of research into the effectiveness of eucalyptol against viruses other than SARS-CoV-2.	1. Develop a clinical trial to evaluate the effectiveness of eucalyptol in patients with acute respiratory infections. 2. Research new formulations (e. g., nanoparticles or liposomes) to improve the bioavailability and stability of eucalyptol. 3. Conduct *in vitro* and *in vivo* studies on the antiviral activity of eucalyptol against other respiratory viruses such as influenza or RSV.	Nanoparticle-based eucalyptol formulations are being explored to enhance bioavailability. Some preliminary antiviral studies are expanding beyond SARS-CoV-2. However, clinical validation remains scarce.
Cluster 3: Clinical Research in Respiratory Diseases	Clinical trials have investigated the effectiveness of eucalyptol in respiratory diseases (asthma, COPD) in adult patients, often via aerosol or inhalation formulations.	1. Limited data on the effectiveness of eucalyptol in different populations, especially pediatric and geriatric patients. 2. Lack of direct comparative studies evaluating the efficacy of different administration routes. 3. Lack of data regarding the safety of long-term use of eucalyptol in humans. 4. Lack of evaluation of side effects in patients with respiratory comorbidities.	1. Conduct studies covering a wider population, including pediatric and geriatric patients, to evaluate the effectiveness and safety of eucalyptol in vulnerable groups. 2. Future research should explore head-to-head comparisons to determine the most effective route for specific respiratory conditions. 3. Develop long-term studies to monitor the side effects and safety of long-term use of eucalyptol. 4. Conduct specific studies in patients with respiratory comorbidities to understand the risks and benefits of eucalyptol in this population.	Some moderate-scale trials have included geriatric patients, but pediatric studies remain lacking. Long-term safety data is still insufficient.

Future research directions based on these findings

This research not only identifies gaps in eucalyptol studies but also provides strategic directions for future research to enhance the understanding and clinical application of eucalyptol in respiratory disease therapy. The bibliometric findings highlight several key areas for further development.

Large-scale clinical trials involving diverse populations, such as pediatric, geriatric, and patients with comorbidities, are needed to confirm the safety profile and efficacy of eucalyptol in managing conditions like asthma and COPD. Additionally, the development of innovative pharmaceutical formulations, such as nanoparticles or slow-release systems, could improve the bioavailability and stability of eucalyptol, thereby maximizing its therapeutic effects. Further research into the pharmacological interactions between eucalyptol and other respiratory medications is also crucial to ensure safe and effective therapeutic combinations, particularly in relation to pharmacokinetics and pharmacodynamics.

Exploration of the molecular pathways influenced by eucalyptol at the cellular and genetic levels will provide deeper insights into its anti-inflammatory and antioxidant mechanisms, which are relevant for the treatment of chronic inflammatory conditions. Studies on the antimicrobial activity of eucalyptol against acute respiratory pathogens such as influenza, RSV, and pneumonia-causing bacteria are also important to confirm its potential as an adjunctive antimicrobial agent in respiratory infections.

Lastly, long-term safety testing is essential to assess potential side effects, particularly in vulnerable populations, to establish safe dosages for prolonged use. Focusing on these areas is expected to address the existing research gaps and propel eucalyptol toward becoming a more effective, safe, and widely applicable therapy for respiratory diseases.

CONCLUSION

Eucalyptol exhibits significant pharmacological potential as an adjunct therapy for asthma, chronic bronchitis, and COPD, with documented effects on lung function, airway responsiveness, and symptom relief. Studies indicate that eucalyptol contributes to improved lung function, reduced airway resistance, and modulation of inflammatory cytokines (TNF-α, IL-1β, and IL-6), leading to better respiratory outcomes. Additionally, its mucolytic and antimicrobial properties support its role in alleviating symptoms and reducing the

severity of exacerbations in chronic respiratory diseases. These benefits position eucalyptol as a valuable complementary therapy that may help reduce corticosteroid dependence and associated adverse effects. However, bioavailability limitations, volatility during inhalation, and formulation challenges must be addressed to maximize therapeutic effectiveness. Future research should prioritize nanoemulsion-based formulations, targeted inhalation therapies, and long-term safety studies. Large-scale clinical trials focusing on pediatric, geriatric patients and those with respiratory comorbidities are crucial to validating eucalyptol's efficacy in real-world applications. Addressing these gaps will facilitate the integration of eucalyptol into mainstream respiratory disease management, offering a safer and more effective alternative to long-term corticosteroid therapy.

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ETHICS STATEMENT

This research did not involve human participants, animal subjects, or any material that requires ethical approval.

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AUTHORS CONTRIBUTIONS

Literature Review: I N. G. T. S., Ni N. A. D., D. K. W.; Data Curation: I N. G. T. S., Ni N. A. D., D. K. W.; Conceptualization: I N. G. T. S., Ni M. L., I M. A. G. W.;Visualization: I N. G. T. S., Ni M. L.; Writing-Original Draft: I N. G. T. S., Ni N. A. D., D. K. W., Ni M. L., I M. A. G. W.; Evaluation: D. K. W., Ni M. L., I M. A. G. W.; Supervision: Ni M. L., I M. A. G. W.

CONFLICT OF INTERESTS

The authors have no conflicts of interest regarding this investigation.

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