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REVIEW ARTICLE

THE USE OF ESSENTIAL OILS AS ANTI-INFECTIVE AGENTS IN THE TREATMENT OF RESPIRATORY TRACT BACTERIAL INFECTIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Respiratory tract infection is a life-threatening infection in clinical medicine that affects both the upper and lower respiratory tract. Bacteria or viruses mainly cause them. Treating this infection involves using antibiotics to combat the bacteria, but the growing antimicrobial resistance hinders this process. The use of a natural substance called essential oils has been widely explored as it is said to possess both antibacterial and anti-viral properties. Therefore, a systematic review and meta-analysis was conducted to determine essential oils' anti-infective activity against respiratory bacterial related infections.

Databases of EBSCOhost, Google Scholar and Science Direct were used to search for related literature. This review included research on clinical trials and *in vivo* tests on bacterial related infection/diseases involving the use of essential oils published in English between 2000-2020, and excluded *in vitro* studies and studies published before 2000. A qualitative and quantitative analysis (forest plot & funnel plot) was conducted on collected data. Studies were retrieved by following the PRISMA guidelines, and the data extracted was analysed using the Mantel-Haenszel random effect model. A total of 11 eligible studies were identified, 7 clinical trials and 4 *in vivo* studies. Meta-analysis suggests a significant effect of essential oils on respiratory bacterial infections (OR = 5.09, 95% CI = 2.30-11.28).

Overall, the qualitative and quantitative analysis suggests that essential oils possess antimicrobial activity, making it a promising futuristic approach in treating respiratory bacterial infections.

KEY WORDS: Respiratory bacterial infections; Essential oils; Antimicrobial agents; Natural products; Medicinal plants; Systematic literature review; Meta-analysis; Phytomedicine.

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INTRODUCTION

During inhalation, the respiratory tract is the first channel for pollutants and microorganisms before reaching the lungs, with the average person inhaling about 10,000 L of air daily.[1] The presence of sophisticated host defence mechanisms in the lungs protects healthy individuals from these microorganisms and pollutants.[2] The local defence mechanisms in the respiratory airway are important for our well-being.[3] The presence of the cilia and a mucosal membrane on the epithelial surface promotes the clearance and trapping of particles and microorganisms.[4]

A breakdown in these defence mechanisms promotes pathogenic colonisation of the respiratory tract, which causes respiratory tract diseases or infections.[5] Respiratory infections are described as one of the most common infections affecting humans worldwide, accounting for 50 million deaths annual-

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ly.[6] These infections are classified according to their site of infection in the organs (middle ear, larynx and pharynx, trachea, nose, bronchi, sinuses, and lungs) of the upper and lower respiratory tract.[7,8] Infections of the respiratory tract are mainly caused by bacteria or viruses. Common bacterial causes of respiratory infections include *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus, Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, while viral causes include rhinovirus, coronavirus, parainfluenza virus, enterovirus, respiratory syncytial virus, meta pneumonia virus and adenovirus.[9,10]

Antibiotics are crucial, as they are used as primarily to treat or eradicate pathogenic respiratory bacterial infections.[11] However, the increasing antibiotic or antimicrobial resistance in pathogens poses a massive threat in the healthcare system as it reduces the efficacy of antibiotic treatment, which leads to an increase in morbidity and mortality, clinical failure and extended inpatient stay.[12,13] According to a peer-reviewed article published by the European Centre for Disease Prevention and Control (ECDC), antibiotic resistance accounts for about 25 000 deaths annually in each respective continent.[14] This resistance creates difficulty in standardised antibiotic treatment methods, making infection control impossible or more challenging.[15] The transmission of the resistant gene from one bacterial species to another or the proliferation of the resistant bacterium also contributes to antibiotic resistance.[16,17] This form of resistance was imitated in the carbapenems resistant *Klebsiella pneumoniae* (KPC), which spread across the United States of America, Greece and Israel; It was related to the spread of a single clone of KPC [sequence type 258 (ST258)] found in Europe as reported by Grundmann et al.,[18], Kitchel et al., [19], Maltezoou et al.,[20], Navon-Venezia et al*.,* [21] and Samuelsen et al.,[22] . The continuous rise in antimicrobial resistance has prompted the exploitation of natural products such as essential oils for medicinal purposes due to their active chemical compounds.[23]

Essential oils (EO) are volatile metabolites of aromatic plants obtained from the twig, bark, flowers, buds, wood, herbs, seeds, fruits, leaves and roots of plants.[24,25] EO has been used over the years to produce cosmetics, beverages, food, preservatives, feed, and perfumes.[26] Presently the most common method of extraction is steam distillation.[27] EOs have been widely explored and are said to possess antibacterial and antiviral properties, which provides a future perspective into the reversal/eradication of microbial resistance.[28]

The method used in the extraction of essential oils is dependent on the quality of the essential oil. Using wrong extraction techniques can cause a change or damage in the chemical properties of the essential oil as many natural products are thermally unstable.[29] About 93% of essential oil are extracted using steam distillation, and the remaining 7% are extracted using other methods.[30] The steam distillation process involves the heating up of plant material using the Clevenger system.[31] Botanicals are placed in a still, and pressurised steam from the steam generator is passed through the plant material. The steam passed breaks down the plant material; therefore, releasing the essential oil through vapour. The vapour and essential oil mixture further go through a condenser to create a liquid consisting of water and volatile essential oil. This mixture is then separated and collected in a florentine vessel.[32,33]

Multiple *in vitro* studies conducted to determine and confirm the antibacterial effects of EOs have shown positive outcomes.[34] Their antimicrobial effect has been demonstrated against multiple bacterial species such as *Enterococcus faecalis, Escherichia coli, Staphylococcus aureus*, methicillin-sensitive *Staphylococcus aureus* (MSSA), *Listeria monocytogenes, Proteus mirabilis, Salmonella typhimurium, Branhamella catarrhalis*.[34,35] Reports have also demonstrated their efficacy against potential respiratory bacterial pathogens such *as Pseudomonas aeruginosa, Klebsiella pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes, Streptococcus pneumoniae*.[35-37] Although multiple *in vitro* tests confirm essential oils' antibacterial activity, limited clinical trials and *in vivo* tests have been conducted to determine this.

Therefore, this systematic review and meta-analysis aimed to analyse the effectiveness of essential oil as an anti-infective agent in treating respiratory bacterial infections using clinical trials and *in vivo* test-based research.

MATERIALS AND METHODS

Study design

To determine the use of essential oils (EO) as an anti-infective agent in the treatment of respiratory tract bacterial infection, a systematic review and meta-analysis was conducted using the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines.[38] The PRISMA checklist was used to ensure the appropriate inclusion and exclusion criteria were applied to select relevant information.

Literature search design and strategy.

Electronic databases of EBSCOhost, Google scholar and Science direct were systematically screened for papers published between the year 2000 - 2020. Table 1 reflects the search terms and syntax method used to retrieve data form the different electronic databases. The retrieved data for these search terms were further screened for relevance to the study, completeness of information and quality of research

based on the inclusion and exclusion criteria.

Table 1: Search syntax.

No.	Search syntax
1	Essential oils OR Aromatic herbs OR Aromatherapy
2	Treatment OR Therapies OR protective effects OR antibacterial activity
3	Respiratory infections OR Rhinosinusitis OR bronchitis OR Respiratory bacteria
4	Clinical trial OR double-blind placebo OR controlled trial OR randomised controlled trial OR *in vivo*
5	1 AND 2 AND 3 AND 4

Inclusion and exclusion criteria

This analysis considered full-text primary research articles published between the year 2000 - 2020. Primary papers focused on *in vivo* testing methods, and clinical trials were the primary inclusion criteria for this systematic review and meta-analysis. Papers published in English and bacteria related respiratory infections or diseases were also included in the search.

Literature reviews, systematic reviews, and meta-analyses, *in vitro* studies, abstracts and studies not published in English, research papers without free access or without full text were excluded from the selection criteria. Primary research papers focused on viral, and fungi infections were also excluded in this search.

Study quality and Risk of Bias Assessments

Initially, two independent reviewers screened the titles and abstracts of all retrieved articles based on the inclusion and exclusion criteria for identifying eligible studies. Each of the identified eligible studies was evaluated by the two investigators for quality using the eight-item Newcastle-Ottawa Scale (NOS) [39,40] and quality assessment was further strengthened using the principle described by Bell and colleagues[41]. Any discrepancies were resolved through discussion by both investigators. For articles that met the inclusion criteria during screening, the following data were retrieved and entered into Microsoft Excel: Full reference; URL; Study identifier (authors and year of publication); methodologies; abbreviations and terminology used; participant details; location details; essential oils intervention details (botanical/traditional name; clinical trial or *in vivo* animal studies; doses; duration of study); outcome measures; concluding remarks. A funnel plot was used to assess publication bias. Selection, detection, attrition and reporting biases were assessed according to the guidelines provided in the Cochrane handbook for systematic reviews of interventions.[42]

Statistical and meta-analysis

All the data collected were analysed for a meta-analysis using Review Manager (RevMan)[43] version 5.4.1 software obtained from the Cochrane training website.[44] Mantel-Haenszel method was used to analyse 95% CI, Chi-square, heterogeneity and I^2 statistics. The heterogeneity of samples and overall test results were included in the forest plots. Results were analysed and interpreted using the Cochrane Handbook for Systematic Reviews of Intervention.[42]

RESULTS

Characteristics of retrieved data

After screening for primary research papers using the search syntax shown in Table 1, a total of 210 papers were identified. The identified papers were screened for duplicates, leaving a total of 180 papers. Title and abstracts were screened, which led to a further exclusion of 161 research papers that did not meet the inclusion criteria (literature reviews, systematic reviews, and meta-analysis, *in vitro* studies, publication date, without free access and full text). After full-text screening, eight research papers were further excluded leaving a total of 11 research papers. Out of the eight excluded papers, three full-text studies not published in English missed out in initial exclusion were further excluded (one was published in Chinese and two were German). Two papers focused on antiviral and antifungal activities of essential oils; one was an ex-vivo study; two were unconvincing clinical trials. Finally, 11 studies were included for this study; four studies focused on the effects of 1.8-cineole of eucalyptus [45,46,47,48]; one on tea catechin extract[49]; one on eucalyptus oil[50]; one on GeloMyrtol (Myrtol oil) [51]; one on nano tea tree oil (nanoTTO)[52]; one on TTO-β-cyclodextrin [53]; one on *Artemisia vestita* [54]; and one on Spicae aetheroleum[55].

Activity of eucalyptus and 1,8 cineole in the treatment of chronic obstructive pulmonary disorder (COPD) exacerbation, rhinosinusitis, acute bronchitis and bronchial asthma

Kehrl et al., [45] conducted a study to determine the therapeutic effect of 1.8 cineole (eucalyptol) on patients with acute rhinosinusitis. There was a decrease in sinusitis symptoms after 4 and 7 days, with a higher significance in the verum group when compared with the placebo group ($p < .0001$). Treatment with 1.8-cineole and placebo significantly improved clinical symptoms of rhinosinusitis (e.g., headache when bending, frontal headache, nasal obstruction, rhinological secretion, the sensitivity of pressure points of the trigeminal nerve, secretion quantity and secretion viscosity) after 4 and 7 days.

In the study by Lin et al., [50], eucalyptus essential oil showed anti-infective properties in male Sprague-Dawley rats with *Klebsiella pneumoniae* induced COPD. Eucalyptus oil administered at

30, 100, and 300 mg/kg showed significant effects in the reduction of emphysematous damage, bronchiolitis, secretion of AB-PAS-positive goblet cell, secretion of pro-inflammatory cytokines (TNF-α and IL-1β), malondialdehyde (MDA) production in lung homogenate and an increase in superoxide dismutase (SOD) activity.

Juergens et al., [46] performed a study to determine the anti-inflammatory effect of 1.8-cineole (eucalyptol) on patients with bronchial asthma by evaluating its efficacy on oral glucocorticosteroid reduction. After the study, participants on 1.8-cineole had their levels of concomitant oral glucocorticosteroids reduced by a mean of 3.7 mg, and they remained clinically stable; although, this was significantly lower in the placebo group ($p=0.006$). They also recorded a decreased dyspnoea score in both 1.8-cineole patients and placebo group, with significantly higher scores ($p=0.0063$) in the placebo group (2.8 ± 1.3, n=15) compared to 1.8-cineole patients (1.3 ± 1.3, n=16).

Worth et al.,[47] determined the effects of 1.8-cineole (eucalyptol) by conducting a 6-month concomitant therapy in the winter season on patients with stable COPD. After six months, there was an improvement in quality of life, with a mean symptom score of -9.1 in the cineole group and -4.1 in the placebo group. Symptom score was measured using the Saint George's respiratory questionnaire (SGRQ). The improvement in symptom scores between both groups was statistically significant ($p=0.0224$)..

Worth & Dethlefsen, [48] conducted a trial to determine cineole (eucalyptus) effect on bronchial asthma patients. Cineole improved lung function after six months, with a statistically significant increase in Forced Volume Capacity (FVC) and peak flow rate, respectively ($p = 0.0226$; $p= 0.0197$). There was also a change in Vital Capacity (VC) in both treatment groups, but the values retrieved were not statistically significant ($p = 0.0682$).

GeloMyrtol (Myrtol oil) in the treatment of Acute Bronchitis

Gillissen et al., [51] conducted a multi-centre, randomised, double-blind, placebo-controlled clinical trial to determine the effectiveness of GeloMyrtol essential oil (formulated from Myrtaceae and Rutaceae plant family) in the treatment of acute bronchitis. 4 daily doses of 300mg GeloMyrtol EO or placebo capsules were randomly administered to eligible participants for two weeks. After a 2-week treatment with GeloMyrtol essential oil, the frequency of daily coughing fits was significantly lowered compared with the placebo capsules ($p <0.0001$). It also lowered the Bronchitis Severity score (BSS), and BSS-subscore in the EO treated group at each visit (day 1, 7, 10 and 14).

Tea catechin in the treatment of patients with Multi-drug resistant *Staphylococcus aureus* (MRSA)

Yamada et al.,[49] conducted a clinical trial to investigate the effect of tea catechin extract on MRSA infections in patients of a hospital ward. After one week, there was a significantly high decrease/disappearance of MRSA in the tea catechin group than in the control group ($p < 0.05$). There was a significant increase in hospital discharges in the tea catechin group compared with the control group ($p < 0.05$).

Tea tree oil against *Acinetobacter baumannii*

A stable thermodynamic emulsion of Nano-emulsion tea tree oil (Nano TTO) was used as an inhalation therapy to treat bacterial pneumoniae in an experiment conducted by Li et al., [52]. In this study, Nano TTOs effectively reduced immune response and killed *Acinetobacter baumannii* by significantly decreasing the secretion of cytokines (TNF-α and IL-1β) and immune cells (neutrophils and leukocytes) induced bacterial inflammation. In the overall experiment, nanoTTO showed the highest therapeutic effect against the *Acinetobacter baumannii* rat model compared to tea tree oil and penicillin (positive control).[52]

Li et al.,[53] conducted a further experiment to determine the efficacy of a new TTO formulation called tea tree oil- β-cyclodextrin (TTO-β-CD), which promotes pulmonary absorption and delivery of tea tree oil due to the presence of a hydrophilic outer membrane (cyclodextrin). *Acinetobacter baumannii* was used to induce bacterial pneumonia in 30 male Sprague-Dawley rats. This experiment showed that pneumonic rats treated with TTO-β-CD showed a significant result ($p <0.05$) than the untreated group.

Artemisia vestita* (wormwood) against *Streptococcus pyogenes

The EO of *Artemisia vestita* and its major component grandisol, demonstrated novel antibacterial activity in treating *Streptococcus pyogenes* infections in mice.[54] The treatment of *S. pyogenes* infections with Artemisia vestita EO and grandisol at a concentration higher than 100 μg/mouse and 135 μg/mouse respectively administered twice a day, reduced *Streptococcus pyogenes* colonisation in the lungs.[54] Active treatment of *artemisia vestita* at 100 μg/mouse and grandisol at 135 μg/mouse had no toxic effects on renal and hepatic function in mice.[54]

Efficacy of *Spicae aetheroleum* (Spike lavender essential oil) on patients suffering from acute bronchitis

Kahler et al.,[55] conducted a double-blind, randomised clinical trial to determine the effectiveness of lavender spike essential oil (*Spicae aetheroleum*). The primary outcome at day 7 showed an improvement in the individual signs and symptoms that make up the BSS (cough, dyspnoea, rales/rhonchi, cough and sputum production) in the treatment group in comparison with the placebo ($p < 0.005$). BSS improved with a mean score point of

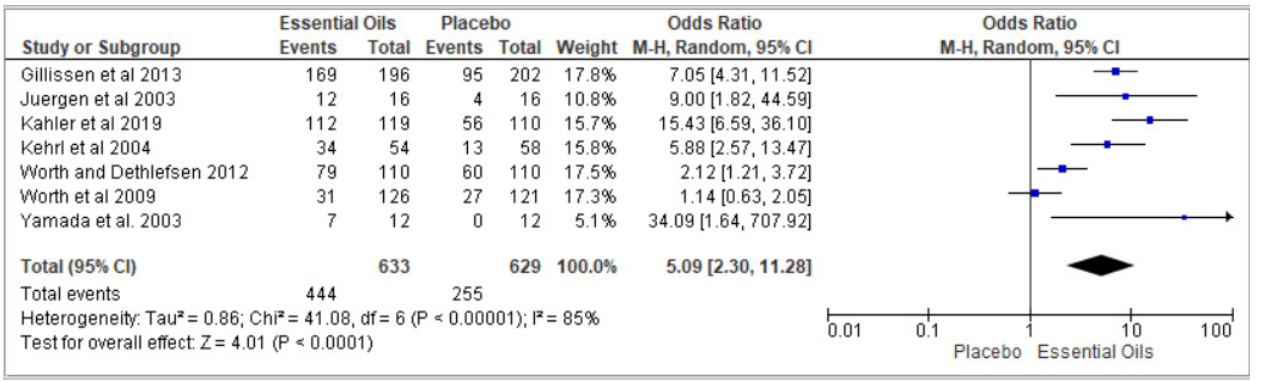

Figure 1: Forest plot of essential oils in the treatment of respiratory infections using the number of responders in each group.

4.73 (57.1%) and 3.20 (38.8%) in the treatment and placebo groups. Secondary outcome endpoint at day 10 showed a significantly reduced BSS in the treatment group than the placebo group ($P < 0.009$), with score points of 6.47 and 4.32, respectively. All investigated symptoms reflected statistically significant differences between the treatment group and the placebo after both 7 (residual parameter: < 0.0001; acute rhinitis $p < 0.005$) and 10 days (all parameters: $p < 0.0001$).

Quantitative analysis (Meta-analysis)

Figure 1 represents a forest plot determining the significance of each study. The data presented represents the number of patients who reflected a positive clinical therapeutic effect of the essential oils or placebo. The heading stating 'events' represents patients who responded to either method of treatment. The overall Odds Ratio, OR from this meta-analysis is 5.09 with a 95% CI of 2.30 to 5.33 (OR = 5.09, 95% CI = 2.30 – 11.28). This reflects that the true Odd ratio (5.09) in this study is greater than one, which means that EO has a significant effect in treating respiratory bacterial infections compared to the placebo. An overall test for effect represents an overall chi-squared test of studies. This also reflects an overall significance ($p < 0.001$) in the use of EO in the treatment of respiratory infections. Analysing the forest plot on the right, the study by Worth et al.,[47] can be described as not significant as it passes through the line of no effect (vertical line) while the other studies by Kehrl et al., [45], Juergen et al., [46], Gillissen et al., [51], Kahler et al.,[55], Worth & Detlefsen,[48] and Yamada et al.,[49] were significant. The diamond on the forest plot indicates the overall Odds Ratio and 95% CI. Significant heterogeneity was observed between these studies ($I^2 = 85\%$, $p < 0.00001$).

DISCUSSION

A total of seven (7) clinical trials and four (4) *in vivo* studies were collected, of which three were on acute bronchitis patients, two on *Acinetobacter baumanii* infections in rats, two on COPD exacerbation, one on MRSA decolonisation, one streptococcus pyogenes patients, one on acute rhinosinusitis and the last on asthma patients.[45,46,47,48,49,50,51,52,53,54,55] As this meta-analysis intended to focus on both clinical trials and *in vivo* trials, a total of 11 research was retrieved, out of which 7 were clinical trials, and 4 were *in vivo* studies. All retrieved research was to be used in the meta-analysis, but a difficulty in extrapolating the data from the *in vivo* study occurred during data collection. This was due to results being presented as figures alone and not as text. Therefore, these four pieces of research [50,52,53,54] were only used in the qualitative analysis and not the quantitative analysis (forest plot). According to *invitro* studies and data collected from clinical trials and *in vivo* studies for this systematic review and meta-analysis, essential oils displayed anti-infective properties in treating respiratory bacterial infections/diseases. Overall, all clinical trials and *in vivo* studies observed statistically significant results when essential oils were used as a form of treatment for respiratory bacterial infection.

The data retrieved in this systematic review and meta-analysis data suggests a significant efficacy in the use of essential oils as anti-infective agents, with a random effect model reflecting a significant overall Odd ratio, (OR=5.09 at 95%CI = 2.30 - 11.28) and high statistical heterogeneity, ($I^2 = 85\%$; $p < 0.00001$) across all clinical trials presented for this meta-analysis. Analysing individual odds ratio, all studies except Worth et al.,[47] reflect a significant odds ratio (0.63). This could be related to the distribution of events between both groups. No significant difference was observed in the events (responders) of either group. Therefore, there was no major difference between patients in the essential oil or placebo group. The high heterogeneity can be attributed to varying study duration, placebo dosage strength, study design (placebo-controlled, double-blind trial/ control clinical trial), the definition

of outcomes and patient size.[56]

The study of unconventional alternatives from medicinal plants against respiratory bacterial infections/diseases has become a priority concern worldwide, with essential oils becoming a possible alternative.[11] Essential oils are made up of secondary metabolites such as terpenoids (carvacrol and 1,8-cineole), terpenes and aromatic compounds (eugenol and cinnamaldehyde), which are responsible for its antimicrobial effect against pathogens.[35,37] Some studies propose that they possess antimicrobial activity through the penetration of cells and the impairment of cellular metabolism.[58] Although all essential oils used in the data retrieved show a practical activity of essential oils in alleviating or treating respiratory bacterial infections, limited studies explain their mechanism and mode of action as it remains unclear.[54]

Kehrl et al.,[45], Juergen et al.,[46], Worth et al., [47], Worth & Dethlefsen[48] and Lin et al., [50], demonstrated that the major component of eucalyptus oil (1.8–cineole) has anti-inflammatory properties in the alleviation of COPD exacerbation, asthma and acute rhinosinusitis. COPD, asthma and rhinosinusitis are characterised by a progressive airflow restriction caused by a heightened chronic inflammatory response in the lungs and airways.[59] Inflammation and overproduction of mucus in the airways are significant hallmarks of COPD, rhinosinusitis and bronchia; asthma.[60] *Moraxella catarrhalis, Haemophilus influenzae, Klebsiella pneumoniae* and *Streptococcus pneumoniae* are the three predominant bacterial species responsible for about 70% of COPD exacerbations.[59] Acute rhinosinusitis and bronchial asthma are associated with facultative aerobic bacteria, i.e., *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*.[61] The anti-inflammatory mechanism of 1,8-cineole involves inducing the inhibitory protein kappa-light-chain-enhancer of activated B cells (Iκbα), the impediment of NF-Kb translocation and the control of the synthesis of pro-inflammatory mediators.[62] This activity was studied and proven in an ex-vivo and *invitro* model on COPD, asthma and rhinosinusitis. 1,8-cineole significantly decreased NF-kB activity by decreasing MUC2 and MUC19 gene expression levels in human nasal turbinate slices with induced bacterial rhinosinusitis (ex-vivo).[60] An *invitro* study also agreed with this mechanism where 1.8-cineole decreased synthesis or inhibition of IL-1β, TNF-α, IL-8, IL-5, IL-4, Th1 and Th2 cytokines in monocytes and lymphocytes of inflammation-induced mice models.[63,64]

Nano tea tree oil (nanoTTO) and tea tree oil-beta-cyclodextrin (TTO-β-CD) showed anti-infective activity against *Acinetobacter baumanii. Acinetobacter baumanii* is an opportunistic gram-negative bacterium that causes pneumonia.[65] However, the specific mode of action of TTO has not been thoroughly researched.[66] It is said that TTO induces a toxic effect on Gram-negative bacteria by inducing cell membrane structure damage which promotes cell death as a result of its monoterpene component.[66] This mechanism was imitated by nanoTTO and TTO-β-CD in the *invivo* studies by Li et al., [52] and Li et al.,.[53]

Acute bronchitis is characterised by acute inflammation of the tracheobronchial tree, leading to desquamation of epithelial cells, thickening of the bronchial and tracheal mucosa and exposure of the basement membrane.[4] This infection can be caused by bacteria such as *Mycoplasma pneumoniae, Bordetella pertussis,* and *Chlamydia pneumoniae*.[4] As initially stated, there are limited resources broadly explaining the anti-infective mechanism of essential oils. Therefore, the mechanism of 1.8 – cineole, GeloMyrtol (myrtol oil) and spicae aetheroleum on acute bronchitis, *Artemisia vestita* on *Streptococcus pyogenes*, and tea catechin extract on MRSA cannot be thoroughly discussed.

Essential oils were associated with multiple adverse effects like heartburn, eructation, stomach ache, diarrhoea, itching, cough, gastritis, nausea, urticaria, and urticaria exanthema over the body. Essential oils are volatile substances with an apparent chemical structure that reacts independently or in collaboration with biomolecules such as proteins; it is possible to attribute the observed adverse effects to the high dosage administered to patients.[67,68] Although, publications confirming this fact have not been conducted yet, but possible reduction or dilution of EO administered to patients could reduce or eradicate the level of adverse effects observed. The FDA's adopted no-significant-risk level of administered essential oil is 1.5 μg/d.[67]

Results from the Qualitative analysis shows that all studies observed different changes after treatment with essential oils and its compounds (eucalyptus oil, Artemisia vestita, Spicae aetheroleum, nanaTTO, TTO-β-CD, 1.8-cineole, tea catechin extract and GeloMyrol/Myrtol oil). Generally, it reduced emphysematous and bronchiolitis damage in COPD models. Clinical symptoms of acute rhinosinusitis and bronchopneumonia were alleviated. It also increased lung function and quality of life in asthma and COPD models, decolonisation of MRSA and *Streptococcus pneumoniae* in the lungs, mouth, and sputum etc. Further highlighting their usefulness in the treatment of respiratory bacterial infections.

CONCLUSION

This systematic review and meta-analysis reviewed clinical trials conducted in animals and humans to determine the effectiveness of essential oils as an anti-infective agent in the treatment of respiratory infections. Based on the qualitative data, essential oils are effective in the treatment of respiratory bacterial related infections like COPD, acute rhinosinusitis,

MRSA bronchopneumonia infections and MRSA nasal colonisation. Quantitative data also supports the proposed hypothesis with a statistically significant *p*-value ($p < 0.01$) and odds ratio (5.09, 95% CI = 2.30 – 11.28). Although 4 studies were excluded from this meta-analysis, there is no evidence that the inclusion of these studies would make a huge difference in the results acquired. This is because the excluded studies were *invivo* experiments; therefore, an entirely new forest plot which would be analysed independently would be required. However, high heterogeneity, publication bias, disparity in study size and parameters measured in our data sources limits the quality of papers presented; therefore, necessitating further studies.

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.