Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Herbal Medicine 28 (2021) 100451

Contents lists available at ScienceDirect

Journal of Herbal Medicine

journal homepage: www.elsevier.com/locate/hermed

Appropriate use of essential oils and their components in the management of upper respiratory tract symptoms in patients with COVID-19

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ARTICLE INFO

Keywords:
Aromatherapy
Essential oils
Eucalyptol
Menthol
Coronavirus
COVID-19

ABSTRACT

Introduction: The involvement of the upper respiratory tract is common in COVID-19, and the majority of patients are treated at home with a mild-to-moderate form of the disease. Many approaches based on essential oils have been proposed for the symptomatic treatment of COVID-19. This work aims to outline the potential and safe evidence-based uses of essential oils and their major components for the clinical management of mild respiratory symptoms caused by uncomplicated coronavirus infections, including SARS-CoV-2. Due to their wide use, a focus on the constituents eucalyptol and menthol has been provided.

Methods: An overview of the scientific literature with a critical discussion of retrieved evidence and clinical recommendations.

Results: In general, eucalyptol and essential oils or blends whose content is rich in it, may be used as an integrative remedy for the symptomatic improvement of patients with mild and uncomplicated infections caused by coronaviruses. Menthol is not recommended in patients with COVID-19, due to a potential reduction of the self-perception of dyspnea, which can lead infected patients to underestimate the actual disease severity and to delay medical attention.

Discussion: Based on available evidence, symptomatic remedies for COVID-19, such as essential oils and their isolated compounds, can be useful, but are not an alternative to standard medical therapy and do not exempt patients from following precautionary measures issued by health authorities. Clinical recommendations on the appropriate use of essential oils for the management of upper airway symptoms of COVID-19 are provided. Further studies on the topic are advised.

1. Introduction

The global community is currently facing a pandemic disease caused by a novel human coronavirus named "SARS-CoV-2", first reported in China. The virus is responsible for an infectious disease called COVID-19 and is often characterized by fever and respiratory symptoms, with an estimated 1 out of 5 infected subjects requiring hospital care (World Health Organization, 2020). The World Health Organization (WHO) reports that the most common symptoms of COVID-19 are fever, tiredness, and dry cough. Some patients may develop aches and pains, nasal congestion, runny nose, sore throat, and gastrointestinal problems like diarrhea, in addition to other less frequent manifestations (World Health Organization, 2020). Available therapeutic options are limited, mostly providing symptomatic relief in mild cases and support of vital functions in severe cases (Li and De Clercq, 2020): in particular, among current evidence-based therapies, corticosteroids are recommended to treat the inflammatory response in patients with COVID-19 bilateral pneumonia and respiratory insufficiency (Ma et al., 2021), and monoclonal antibodies like Tocilizumab are used to treat hospitalized subjects with severe disease (Fu et al., 2020). Moreover, different types of COVID-19 vaccinations were rapidly developed in 2020 and, afterwards, large vaccination campaigns have already been initiated by many countries worldwide in attempt to achieve mass immunization (Dagan et al., 2021).

The majority of COVID-19 patients show a mild-to-moderate disease severity involving the upper respiratory tract and are treated at home. As such, essential oils may have a role in the management of these symptoms (Horváth and Ács, 2015). From the beginning of this

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https://doi.org/10.1016/j.hermed.2021.100451
Received 30 July 2020; Received in revised form 25 September 2020; Accepted 24 March 2021
Available online 26 March 2021

epidemic, many "natural" approaches have been suggested as valid options for patients with COVID-19, with an "infodemic" of misinformation spreading on the Internet (Hrabovszki, 2020; Office of the Commissioner, 2020). In particular, aromatherapy, defined as the therapeutic use of plant-derived essential oils and their active components (Valussi, 2013), has been proposed for the treatment and prevention of COVID-19. This has created a dangerous stream of misleading and unproven claims, advertisements and commercials, which may induce many people to take do-it-yourself treatments without any scientific evidence. These concerns have been publicly expressed by regulatory authorities like the American Food and Drug Administration and the Federal Trade Commission (Coronavirus (COVID-19) Pandemic, 2020; Office of Regulatory Affairs, 2020). Moreover, self-prescribed and uncontrolled aromatherapy-based COVID treatments may lead to worse outcomes. For example, consumers can surf the Internet and be deceived by fraudulent advertisers to believe that essential oils can effectively prevent COVID-19. This may lead some people to refuse evidence-based vaccinations and preventive measures, thus being eventually exposed to high risks of getting the disease with its potential complications.

The primary aim of this research work is to outline the potential and evidence-based uses of essential oils and their major components for the safe clinical management of mild respiratory symptoms associated with uncomplicated infections caused by human coronaviruses like SARS−COV-2. A secondary aim is to discourage the spread of misinformation by providing an evidence-based dissertation on the topic. Due to their frequent use for the symptomatic management of acute respiratory ailments of infectious origin (Horváth and Ács, 2015), a special focus on eucalyptol and menthol, as individual compounds and in branded products, was included as they are both major essential oils components. Therefore, a brief explanation of possible mechanisms of action of eucalyptol and menthol, together with a description of their toxicological profile, was provided to better understand the rationale behind their potential uses in clinical practice. Practical considerations about their clinical applications in patients with COVID-19 were also discussed.

2. Materials and methods

In order to outline the topic amidst an ongoing pandemic, whilst quickly providing a synthesis of available evidence for proper management of COVID-19 symptoms, it was decided to design this work as a narrative and qualitative review of the scientific literature.

Medline (accessed via PubMed), Cochrane Library, and Google Scholar were searched using the following keywords: "essential oil*", "eucalyptol", "eucalyptus", "menthol", "peppermint", "rhinitis", "pharyngitis", "bronchitis", "respiratory infection*", "respiratory disease*", "coronavirus*", "SARS", "COVID".

All articles which described the efficacy of essential oils and their components (with a keen focus on eucalyptol and menthol) for the symptomatic management of acute infectious respiratory diseases, especially of likely or certain viral origin, were included. Studies were considered eligible for inclusion regardless of their specific design, but priority was given to systematic reviews of clinical studies and, when unavailable, to single Randomized Controlled Trials (RCT). There were no restrictions imposed regarding comparison type, but results of placebo-controlled studies were highlighted above others. Relevant outcomes were included the severity and duration of respiratory symptoms. Results of laboratory experiments were briefly described to report the potential mechanisms of action of the compounds studied. All studies with at minimum an English abstract/summary and published in peer-reviewed journals were included.

The literature was independently searched by two authors (M.V., M. A.), who agreed upon a set of studies to be included in consideration of the main objectives of this review. The other two authors (D.D., F.F.) provided a critical appraisal of retrieved evidence, thus combining available data with their field experience in the clinical management of COVID-19. Implications for public health were also underscored for better comprehensiveness. Finally, clinical recommendations on the appropriate use of essential oils were provided.

3. Results

Various essential oils have been studied for the symptomatic treatment of respiratory diseases (Horváth and Ács, 2015). In regard to their route of administration, essential oils, after selection and adequate dilution, can be administered orally, inhaled, or topically applied on the subject's skin as ointments (Valussi, 2013). Their effects on respiratory functions and symptoms have been reported in several clinical studies (Horváth and Ács, 2015; Valussi, 2013; Wagner et al., 2015).

The two components of essential oils most studied are eucalyptol and menthol: for this reason, these substances have been described individually (Table 1).

3.1. A focus on eucalyptol

Eucalyptol is a natural organic compound which forms the majority of the essential oil distilled from various eucalyptus species, mainly *Eucalyptus globulus* (Boland et al., 1991). From a chemical point of view, eucalyptol is a cyclic ether and a monoterpene (1,8-cineole), and naturally appears as a colorless liquid with aromatic properties (National Center for Biotechnology Information, 2021a,b).

It has been suggested that eucalyptol can act both as an antimicrobial and as an antiphlogistic agent, thus also potentially reducing the production of inflammatory mediators (TNF-α, IL-6, and IL-8) by inducing modifications at an epigenetic level in white blood cells (Juergens et al., 2020, 2004). This possible mechanism of action of eucalyptol deserves further investigations since IL-6 seems to play an important role in the pathophysiology of lung damage and in the onset of the so-called "cytokine release syndrome", which is associated with poor clinical outcomes in patients with COVID-19 (Zhang et al., 2020). Additionally, findings of in vitro or animal experiments indicated that eucalyptol might have some antimicrobial and protective activity against viral microorganisms like herpes simplex virus type 1 (HSV-1) or influenza A virus (Astani et al., 2010; Li et al., 2016). Interestingly, a recent molecular docking study currently only available as a preliminary report, shows that eucalyptol may be a potential inhibitor of SARS-CoV-2, due to its capability to bind viral proteinase (Sharma and Kaur, 2020). Moreover, e*ucalyptus* essential oil can increase the ciliary activity of human nasal epithelial cells, thus potentially boosting natural defenses of the upper airways (Neher et al., 2008). In mice, eucalyptol demonstrated a synergic action with oseltamivir for the treatment of influenza A (Lai et al., 2017), and provided cross-protection against the influenza virus if co-administered with the vaccination (Li et al., 2017). Finally, eucalyptol has a Transient Receptor Potential (TRP)-mediated activity, exerting an antinociceptive effect with inhibition of pain perception, as summarized in Table 2 (Bautista et al., 2007; Haeseler et al., 2002;

Table 1
A brief summary of eucalyptol and menthol's properties and an example of practical evidence-based uses (Valussi, 2013).

Compound	Properties	Example
Eucalyptol	Antitussive Mucolytic Antimicrobial Bronchodilator Mucociliary function promoter	Adults: oral administration, 200 mg encapsulated t.i.d.
Menthol	Antitussive Analgesic Refrigerant Mucociliary function promoter	Adults: inhalation, 10 mg nebulized b.i.d.

Table 2
Transient Receptor Potential (TRP) thermoreceptors-mediated activities of eucalyptol (1,8-cineole) and menthol.

	TRPM8	TRPV3	TRPA1	Other	References
1,8-Cineole	Activation, less than menthol (reduced nociceptive effect).	Desensitization Decreases allyl isothiocyanate-induced-TRPV3 currents.	Blocking, less than menthol (anti-inflammatory and antinociceptive effects).	Suppresses smoke respiratory irritation.	Santos, Rao 2000; Takaishi et al., 2012; Liedtke and Heller, 2007
Menthol	Bimodal action. Low-to-moderate concentrations reduce cinnamaldehyde- and capsaicin-induced irritation, heat hypersensitivity or hyperalgesia mediated by TRPV1, and headaches. High concentrations cause cold allodynia and hyperalgesia.	Desensitization.	Bimodal action: activating at submicromolar doses, inhibiting at higher concentrations.	In inhalation, it reduces cough sensitivity to inhaled capsaicin, influences respiratory flow, suppressing smoke respiratory irritation.	Haeseler et al., 2002; Bautista et al., 2007; Sherkheli et al., 2009; Millqvist et al., 2013

Liedtke and Heller, 2007; Millqvist et al., 2013; Santos and Rao, 2000; Sherkheli et al., 2009; Takaishi et al., 2012).

In a recent review, the therapeutic role of eucalyptol for respiratory diseases such as Chronic Obstructive Pulmonary Disease (COPD), bronchial asthma, and sinusitis was explored, and respiratory symptoms, function and quality of life were demonstrated (Juergens et al., 2020). In a placebo-controlled trial involving 32 patients with bronchial asthma, eucalyptol (200 mg t.i.d. taken orally for 12 weeks) had anti-inflammatory activity (Juergens et al., 2003). At the same daily dose, it was demonstrated that cineole significantly improved nasal congestion, secretion, pain, and headache in patients with acute rhinosinusitis (Kehrl et al., 2004). Cineole was also shown to be an effective remedy for the symptomatic management of acute bronchitis, especially with regard to cough, after only 4 days of oral administration at a dose of 200 mg 3 times daily (600 mg/day) (Fischer and Dethlefsen, 2013).

Eucalyptol has the following therapeutic properties:

- Antitussive (Fischer and Dethlefsen, 2013).
- Mucolytic (Juergens et al., 2020).
- Anti-inflammatory (Juergens et al., 2003).
- Antimicrobial (Juergens et al., 2020).

Since eucalyptol has bronchodilating effects and can promote mucociliary and respiratory function, it was proposed by some authors for the symptomatic treatment of a wide range of respiratory ailments (Horváth and Ács, 2015).

From a toxicological perspective, eucalyptol is considered safe and well-tolerated if consumed at normal doses, but, when taken at high doses or for excessively prolonged periods, its consumption via oral ingestion, inhalation, or skin application can be hazardous (Bhowal and Gopal, 2016). The lethal dose of eucalyptol in human subjects is estimated to be between 0.0461 and 0.461 g/kg, and death by overdose occurs due to central nervous system depression and respiratory failure (Bhowal and Gopal, 2016). No proof of genotoxicity or carcinogenicity associated with eucalyptol administration has been found to date (Bhowal and Gopal, 2016). Eucalyptol use is contraindicated in infants aged 30 months old or younger, but caution should be exercised when using it with the pediatric population (Bhowal and Gopal, 2016).

3.2. A focus on menthol

Menthol is a natural analgesic, antitussive, and cooling compound, which can be found in several essential oils (Galeotti et al., 2002). Its name derives from plants in the *genus Mentha*, from which it is often extracted (Galeotti et al., 2002). Menthol's chemical formula is 2-isopropyl-5-methylcyclohexanol, and this substance often appears as a crystalline solid with a peppermint odor and taste (National Center for Biotechnology Information, 2021a,b).

Menthol, apart from its action on smooth muscles, can interact with the Transient Receptor Potential (TRP) thermoreceptors, thus reducing pain, acting as a counter-irritant, and eliciting a subjective sensation of cold (Harris, 2006). The majority of menthol effects on the respiratory system has been traditionally attributed to its activity on cold receptors (Harris, 2006; Mahieu et al., 2007). Moreover, menthol was found to increase the ciliary beat frequency of human nasal epithelial cells, which can contribute to mechanical defenses against microorganisms (Neher et al., 2008). The TRP-mediated activity of menthol is summarized in Table 2 (Bautista et al., 2007; Haeseler et al., 2002; Liedtke and Heller, 2007; Millqvist et al., 2013; Santos and Rao, 2000; Sherkheli et al., 2009; Takaishi et al., 2012).

At a dose of 10 mg (nebulized, b.i.d., for 4 weeks), menthol may reduce bronchial hyperexcitability, but did not significantly improve the airflow in asthmatic patients (Tamaoki et al., 1995). Although menthol has not shown to significantly influence airway resistance in human subjects (Eccles et al., 1990; Pereira et al., 2013), menthol can provide symptomatic relief from rhinosinusitis-related congestion when taken

orally at a dose of 11 mg due to its specific interaction with cold-sensitive receptors on the nerve endings in the upper airways (Eccles, 2003).

Menthol has the following properties:

- Antitussive and sedative at low doses (Morice and Kardos, 2016; Plevkova et al., 2011).
- Gives a sensation of freshness and is subjectively perceived to act as a decongestant, without a real effect on measures of airflow (Kenia et al., 2008).
- Can inhibit pulmonary ventilation and reduce the sensation of dyspnea, especially when administered at high doses (Horváth and Ács, 2015).

Menthol is generally considered a safe substance and is widely used by the food, drug, and cosmetic industry, yet cases of toxicity due to the ingestion of high doses have been reported in scientific literature (Kumar et al., 2016). The lethal oral dose of menthol is between 50 and 150 mg/kg, and adverse events due to overdose include respiratory and kidney failure along with neurological, cutaneous, and gastrointestinal manifestations (Kumar et al., 2016). Therefore, prolonged and heavy exposure to menthol is to be avoided.

3.3. Blends with eucalyptol and/or menthol

Menthol and eucalyptol, administered together in a blend or added to a more complex formulation including other compounds, have been shown to improve respiratory symptoms. In a small study, the vapor inhalation of a blend composed of menthol, eucalyptol, and camphor was reported to ameliorate the subjects' respiratory function (Cohen and Dressler, 1982). A spray with *Eucalyptus citriodora*, *Eucalyptus globulus*, *Mentha piperita*, *Origanum syriacum*, and *Rosmarinus officinalis* significantly reduced cough when compared to placebo (Ben-Arye et al., 2011). The inhalation of menthol (75 %) in *Eucalyptus* spp. essential oil diminished the frequency of induced cough in healthy individuals (Morice et al., 1994). Eucalyptol, when orally administered in a formulation including limonene and pinene, was effective for the symptomatic management of chronic sinusitis during the perioperative period in a cohort of 576 cases (Jiang and Yan, 2014).

3.4. Branded products with eucalyptol and/or menthol

In a 2015 systematic review assessing the efficacy of herbal medicines for cough, four controlled trials (1231 participants) analyzed the use of essential oil-based preparations (Myrtol®, Pinimenthol®, and Vicks® VapoRub™) (Wagner et al., 2015). In the majority of the included studies, it was reported that essential oils significantly ameliorated the severity and frequency of cough among patients, with mucolytic effects and an overall improvement of other respiratory symptoms (Wagner et al., 2015). However, adverse effects like skin irritation were reported and the authors reported a high level of study design heterogeneity, which prevented any meta-analysis of retrieved data (Wagner et al., 2015).

Three placebo-controlled clinical trials, involving 1666 patients, tested the effects of Myrtol®, a branded phytomedicine obtained through essential oil distillation, on upper and lower respiratory tract inflammation. The product consisted of mainly monoterpenes such as (+)-alpha-pinene, d-limonene, and 1,8-cineole (Federspil et al., 1997; Gillissen et al., 2013; Matthys et al., 2000; Meister et al., 1999; Paparoupa and Gillissen, 2016). For the treatment of acute bronchitis, Myrtol® was administered orally every day for 2 weeks and it was reported to be superior to placebo in terms of disease improvements, evaluated with pulmonary auscultation and sputum consistency assessments. Cough, sleep quality, and general wellbeing symptoms were also improved (Gillissen et al., 2013; Matthys et al., 2000). In one study, Myrtol® was comparable to cefuroxime or ambroxol in the treatment of acute bronchitis of a nonspecific etiology (Matthys et al., 2000). In another multicenter clinical trial which involved 331 patients, Myrtol® was superior to placebo in the treatment of uncomplicated non-purulent acute sinusitis when administered for 1 week, roughly (Federspil et al., 1997). The intervention was generally regarded as well tolerated by patients (Gillissen et al., 2013; Matthys et al., 2000; Meister et al., 1999), however, in some cases, adverse effects like nausea, mild diarrhea, and eructation were reported by patients (Gillissen et al., 2013).

A potential role of a mixture of essential oils (mostly extracted from *Mentha piperita*, *Eucalyptus globulus*, and *Melaleuca Leucadendron*) for acute rhinitis in pediatric patients has been hypothesized by some authors, with observed beneficial effects in terms of improved symptoms duration and severity, as well as of reduced drug consumption (Kilina and Kolesnikova, 2011). In a study involving 138 children (aged 2–11 years old), the cutaneous application on the upper chest and neck area of Vicks® VapoRub™ with camphor (4.8 %), menthol (2.6 %), and *Eucalyptus* spp. essential oil (1.2 %), was compared to petrolatum application or no treatment for upper respiratory tract infections (Paul et al., 2010). The intervention was associated with improved symptoms (cough, congestion, and sleep quality) when compared to the active control and no treatment, but some mild irritant adverse effects were recorded (Paul et al., 2010). In another study, Vicks® VapoRub™ was shown to be effective in decreasing restlessness in children suffering from acute bronchitis (Berger et al., 1978). When topically applied or vapors inhaled after being added to hot water, Vicks® VapoRub™ is associated with subjective nasal cooling and relief from nasal congestion in adults (Eccles et al., 2015) and can significantly improve sleep quality in subjects affected by common cold symptoms (Santhi et al., 2017). However, long-term use of Vicks® VapoRub™ is contraindicated both in children and in adults due to the potential onset of adverse effects like chemical leukoderma or exogenous lipoid pneumonia (Boyse and Zirwas, 2008; Cherrez Ojeda et al., 2016). Additionally, a laboratory model suggested that the product might paradoxically increase mucus production in the respiratory airways of small children, thus acting as an irritant substance (Abanses et al., 2009).

In an observational study with data from 3060 subjects (adults and adolescents; minimum age 12 years old), Pinimenthol® ointment (containing eucalyptus essential oil, along with essential oil extracted from pine needles (*Pinus sylvestris*), and menthol) administered through inunction and/or inhalation was rated as well tolerated by 96.7 % of physicians and 95.7 % of patients. It was subjectively reported to be highly effective against respiratory tract conditions like the common cold, hoarseness, and bronchitis by 88.3 % of physicians and 88.1 % of patients (Kamin and Kieser, 2007). A total of 22 patients (0.7 % of the study population) reported skin or mucosal adverse reactions (Kamin and Kieser, 2007).

Beneficial effects superior to placebo in the symptomatic treatment of uncomplicated acute respiratory infections were also observed for Tavipec®, a phytomedicine obtained through the steam distillation of spike lavender (*Lavandula latifolia*) flowering tops (a preparation traditionally called "*Spicae aetheroleum*"), which are rich in linalool and 1,8-cineole (Kähler et al., 2019). The safety analysis, involving 258 patients, revealed that Tavipec® was well tolerated and no severe adverse events were reported in the sampled patients (Kähler et al., 2019). Apart from this product, it can be difficult to find essential oils obtained from *L. latifolia* in the general market; additionally, the camphor content, potentially responsible for adverse reactions like mucosal irritation and gastrointestinal problems, can be high and account for 10–23 % of the overall essential oil composition (Blumenthal et al., 1999; Council of Europe, 2021; Health Canada, 2004; Millqvist et al., 2013; Nair, 2001; Tisserand and Young, 2013). It is worth mentioning that, amongst *Lavandula* species, which are all rich in linalyl acetate and linalool, lavandin (*Lavandula* × *intermedia*) has the highest content of 1,8-cineole, accounting for up to the 13 % of its composition (Renaud et al., 2001), but with far less camphor (between 5% and 11 %) (Blumenthal et al., 1999; Council of Europe, 2021; Health Canada, 2004; Millqvist et al.,

Table 3
Safety summary for essential oils derived from *Eucalyptus* spp. and *Mentha x piperita*.

	Eucalyptus spp. (high cineole content)	*Mentha x piperita*	References
Hazards	Essential oils rich in 1,8-cineole can cause problems with breathing and in the central nervous system in young children.	Choleretic, mucous membrane irritation (low risk).	Liedtke and Heller, 2007; Tisserand and Young, 2013
Contraindications	Oral: inflammatory diseases of the gastrointestinal tract and bile ducts, and severe liver disease (Commission E). Topical: do not apply to or near the face of infants or children under ten years of age. (Tisserand & Young 2014).	All routes of administration: cardiac fibrillation (low-quality studies), G6PD deficiency. Oral: cholestasis, gastroesophageal reflux disease. Topical: do not apply to or near the face of infants or children.	Liedtke and Heller, 2007; Tisserand and Young, 2013; Blumenthal et al., 1999
Maximum adult daily oral dose	600 mg (Commission E).	152 mg	Tisserand and Young, 2013; Blumenthal et al., 1999
Maximum dermal use level	20 % (Commission E).	5.4 %	Tisserand and Young, 2013; Blumenthal et al., 1999
State regulations	**Canada:** it is recommended not to use at a concentration of more than 25% in cosmetic products. **Australia**: "Schedule 6" poison, with "a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label".	**USA:** GRAS status. The Cosmetic Ingredient Review Expert Panel has concluded that peppermint essential oil is safe when used in cosmetic formulations, as long as the pulegone content of the essential oil does not exceed 1.0%. **EU:** The CEFS of the Council of Europe has set a group TDI for menthofuran and pulegone of 0.1 mg/kg bw. **Germany (Commission E)**: it allows 5–20% in oily and semisolid preparations, 5–10% in aqueous-alcoholic preparations, 1–5% in nasal ointments and 6–12 drops (or 0.6 mL in enterically coated capsules) as an average daily oral dose.	Tisserand and Young, 2013; Blumenthal et al., 1999; Nair, 2001b; Health Canada Cosmetic Ingredient Hotlist

2013; Nair, 2001; Tisserand and Young, 2013) when compared to *L. latifolia*, thus making lavandin a safer and easier alternative to *L. latifolia*. Beyond the action of eucalyptol, linalyl acetate and linalool, which are derived from lavender essential oil, showed some in vivo anesthetic activity when tested on rabbits (Ghelardini et al., 1999). Additionally, linalyl acetate demonstrated spasmolytic properties on smooth muscles in a laboratory experiment (de Sousa et al., 2011). Other studies have indicated that lavender essential oil has analgesic and anti-inflammatory effects (da Silva et al., 2015) and seems capable of increasing ciliary beat frequency of human nasal epithelial cells (Neher et al., 2008), thus acting at different levels on respiratory symptoms.

4. Discussion

4.1. Focus on clinical practice

Most patients with COVID-19 can remain at home throughout the entire course of the disease with mild symptoms, similar to the common cold or flu. For these individuals, the standard treatment is essentially symptomatic and it is based on an antipyretic therapy (paracetamol or non-steroid anti-inflammatory drugs) and antitussive agents, along with proper hydration and sometimes vitamin C supplementation. In addition to this symptomatic treatment, based on local clinical guidelines and the patients' conditions and comorbidities, it is possible to prescribe an antiviral therapy, an antithrombotic prophylaxis, or, in case of bacterial superinfections, common antibiotics. In the symptomatic management of gastrointestinal manifestations of COVID-19, antidiarrheal, anti-emetic, and anti-nausea medicines can be useful. In cases with minor complications, which are often linked to preexistent baseline comorbidities, steroidal drugs can play an important role in treatment. In the home health care setting, it is important to have effective strategies and treatments to manage COVID-19 symptoms, which typically last for relatively long periods of time due to specific pathogenic characteristics of SARS-CoV-2.

Aromatherapy can have a useful role in the management of patients with mild COVID-19, especially for those presenting with upper respiratory tract symptoms. Considering available scientific evidence and common contraindications (allergies or patient-specific health conditions), eucalyptol (as an isolated substance or as a major compound of some essential oils) appears as the preferable therapeutic option, followed by terpenes such as limonene and pinene. Due to its ability to potentially reduce the self-perception of dyspnea and to inhibit pulmonary ventilation (Horváth and Ács, 2015), we suggest avoiding menthol in patients affected by COVID-19. This is because the disease is characterized by a paradoxical discrepancy between the occurrence of dyspnea and blood oxygen saturation soon after the onset of respiratory distress (Marini and Gattinoni, 2020). Some authors have called this phenomenon the "shadow-syndrome discrepancy" (Wan et al., 2020). In fact, dyspnea tends to occur late in the overall clinical course of the disease, when actual blood oxygen levels are far worse than expected to be based on the sole dyspneic symptom (Couzin-Frankel, 2020). Moreover, in infected subjects who develop dyspnea, the disease more frequently evolves rapidly into a severe form, thus requiring urgent medical attention and hospital care (Cohen et al., 2020). The rapid identification of the early stages of respiratory failure in patients with COVID-19 is critical. Therefore, by potentially reducing the sensation of dyspnea, patients risk underestimating the actual disease severity, and medical attention could be delayed, resulting in poor clinical outcomes.

From a clinical perspective, common routes of essential oil administration include inhalation (ie.vaporization with hot water or ultrasonic air diffusers), oral ingestion (ie. encapsulated essential oils), and cutaneous application with transdermal absorption (ie. ointments and balsams with essential oils) (Valussi, 2013). Provided that all precautions for safe use are considered, evidence shows that aromatherapeutic remedies can be used in patients to improve upper tract respiratory symptoms like cough, mucus, nasal congestion, runny nose, or sore throat. Aromatherapy can help to monitor anosmia, a highly specific symptom of this infectious disease (Vaira et al., 2020), and essential oils may be used to detect its occurrence and its progressive amelioration during the course of the disease. Significant information regarding the tolerability and safety of eucalyptol and menthol in clinical practice is described in Table 3 (Blumenthal et al., 1999; Council of Europe, 2021; Health Canada, 2004; Millqvist et al., 2013; Nair, 2001; Tisserand and Young, 2013). In regard to drug interactions, data about orally administered eucalyptol and menthol are scant. In mice models, eucalyptol can induce P450 isoenzymes (CYP2B1 and CYP3A2) at doses of 500 and 250 mg/kg but not at a dose of 125 mg/kg (Hiroi et al., 1995), thus suggesting a potential role as an enzyme inducer when taken at high doses.

Table 4
Clinical recommendations for the use of essential oils in the management of COVID-19 symptoms of the upper airways (Tisserand and Young, 2013; Valussi, 2013).

Essential oils with a high eucalyptol content recommended for the management of COVID-19 symptoms of the upper airways		
Essential Oil	Active Compound	Content
Eucalyptus plenissima	Eucalyptol	85–95%
Eucalyptus polybractea	Eucalyptol	89–92%
Eucalyptus globulus	Eucalyptol	65–84%
Eucalyptus camaldulensis	Eucalyptol	85–85%
Eucalyptus smithii	Eucalyptol	~78 %
Eucalyptus maidenii	Eucalyptol	~77 %
Eucalyptus radiata	Eucalyptol	60–64%

Essential oils with a lower eucalyptol content recommended for the management of COVID-19 symptoms of the upper airways		
Essential Oil	Active Compound	Content
Melaleuca cajeputi	Eucalyptol	41–71%
Melaleuca quinquenervia (niaouli) CT cineole	Eucalyptol	55–65%
Cinnamomum camphora CT cineole	Eucalyptol	57–64%

Essential oils *NOT* recommended for the management of COVID-19 symptoms of the upper airways due to their menthol content		
Essential Oil	Active Compound	Content
Mentha x piperita	Menthol	19–54%
Mentha *arvensis*	Menthol	29–35%

Essential oils *NOT* recommended for the management of COVID-19 symptoms of the upper airways due their frequent association with allergic reactions		
Essential Oil	Active Compound	Content
Laurus nobilis	Eucalyptol	38–43%

Other essential oils recommended for the management of COVID-19 symptoms of the upper airways with a lower eucalyptol content but effective on some concurrent symptoms			
Essential Oil	Active Compound	Content	Effective on concurrent symptoms
Rosmarinus officinalis CT cineole	Eucalyptol	39–58%	Dyspepsia/nausea/vomiting
Elettaria cardamomum	Eucalyptol	26–45%	Dyspepsia/nausea/vomiting
Salvia tridentata	Eucalyptol	~59 %	Dyspepsia/nausea/vomiting
Myrtus communis	Eucalyptol	19–37%	Dyspepsia/nausea/vomiting
Lavandula intermedia	Eucalyptol	~10 %	Anxiety/headache

Other essential oils recommended for the management of COVID-19 symptoms of the upper airways with active compounds other than eucalyptol			
Essential Oil	Active Compound	Content	Effective on concurrent symptoms
Melissa officinalis*	Citral + Geraniol	25–70%	Anxiety/sore throat
Cymbopogon spp.*	Citral + Geraniol	72–92%	Anxiety/sore throat
Syzygium aromaticum**	Eugenol	~80 %	Sore throat

* Contraindicated in hypothyroidism.
** Especially effective if used for gargling as a mouthwash (diluted in an alcoholic solution).

Eucalyptol-rich products like *eucalyptus* essential oil may potentiate the pharmacological activity of oral antidiabetic agents due to an enhancement of their hypoglycemic effects (Firenzuoli, 2001). Animal studies showed that compounds like pepper mint (*Mentha piperita*) essential oil, characterized by a high menthol content, can reduce the activity of cytochromes 1A2, 1A1, 3A4, 2B1, and 2E1 (De-Oliveira et al., 1999; Firenzuoli, 2001), thus acting as an enzyme inhibitor. Case reports indicate that menthol may interact with warfarin and potentiate its anticoagulant effects (Coderre et al., 2010; Kassebaum et al., 2005). Professional supervision is therefore recommended, especially in patients with baseline comorbidities who take several drugs for chronic health conditions.

When choosing a specific essential oil or an essential oil-based commercial product for the management of COVID-19 symptoms of the upper airways, it is important to pay attention to the quantity of active compounds in the overall biochemical composition (e.g. active terpenes). Thus, it is possible to prefer one essential oil over another due to the different content of eucalyptol (active on symptoms of the upper airways) and of other active compounds useful for the management of non-respiratory symptoms that may arise during the course of COVID-19. For example, the essential oil obtained from rosemary (*Salvia rosmarinus)* may be effective not only on upper airway symptoms, but also on digestive symptoms like dyspepsia, nausea or vomiting (see Table 4). A brief clinical guide regarding how to choose proper essential oils was provided in Table 4. Unless the prescriber has solid experience with orally administered essential oils, the preferred route of administration should be through vaporization with boiling water or ultrasonic diffusers. Patients should be advised to inhale vapors from above, while ideally covering their head with a towel. Each treatment should last 10–15 min and should be repeated 2–4 times a day. Patients should rest for at least 15 min after the treatment in order to avoid vasovagal reactions and falls. After carefully evaluating all the patient's symptoms, the prescriber may also consider administering specific blends of recommended essential oils. Possible formulations may be composed of: 100 ml distilled water, 1–5 g of any selected essential oil (see Table 4 for suggestions), and polysorbate as an emulsifier, with a dose of 5 ml (Valussi, 2013).

Finally, it is important to emphasize that, by definition, essential oils as symptomatic remedies for mild SARS-CoV-2 infections still lack clinically-demonstrated effects on the etiology of the disease and they should not be used as a curative purposes remedy. Moreover, they do not reduce the patients' contagiosity and, therefore, their intake does not exempt infectees from strictly following all precautionary measures and recommendations issued by public health authorities to prevent the spread of the infection (ie. vaccinations, isolation, hygienic rules, validated diagnostic tests to demonstrate full recovery). As such, the use of essential oils for the management of symptoms should be used to ameliorate the patient's health-related quality of life during the course of the disease and it is not to be intended as an alternative, but as an adjunct therapy, to standard care. Another possible role of essential oils can be for post–COVID-19 rehabilitation: as an example, among others, eucalyptus essential oil, due to its aromatic properties, was proposed by some authors for olfactory training in post–COVID-19 patients with persistent olfactory dysfunction (Whitcroft and Hummel, 2020).

5. Conclusions

The mechanism of action of essential oils and their isolated components when used for the symptomatic treatment of acute respiratory ailments are essentially ascribable to their anti-inflammatory, spasmolytic, mucolytic, and anesthetic effects on the upper and lower airways. On the basis of their specific composition, which depends on their origin and production, different essential oils exert diverse effects on the respiratory system, as well as on other organs, thus providing relief for specific symptoms. For example, essential oils with anesthetic properties are more effective for dry cough control, whereas those with a mucolytic action are more useful for nasal congestion or catarrhal bronchitis.

In general, eucalyptol (as an isolated substance or as a major compound of essential oils) appears to be a useful remedy for the management of respiratory symptoms. Essential oils rich in eucalyptol may be used in patients with mild uncomplicated infections caused by coronaviruses like SARS-CoV-2. Available data outlined a favorable tolerability profile for essential oils with eucalyptol as a major compound, although professional supervision is required for their safe and proper use in clinical practice. Essential oils with high concentrations of menthol are not recommended in patients with COVID-19, due to their ability to

potentially reduce the self-perception of dyspnea, which can lead infected patients to underestimate the actual severity of their disease and to dangerously delay medical intervention. Other essential oils less rich in eucalyptol but with other active components may still be useful for COVID-19-related non-respiratory symptoms like nausea, vomiting, dyspepsia, sore throat, anxiety, and headache. Further research on the topic is advised and, in particular, eucalyptol deserves further investigations for its potential antiviral activity and its possible role in the modulation of cytokine production.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgment

We would like to thank Meghan Henshaw.

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