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REVIEW ARTICLE

EUCALYPTUS ESSENTIAL OIL; AN OFF-LABEL USE TO PROTECT THE WORLD FROM COVID-19 PANDEMIC: REVIEW-BASED HYPOTHESES

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Abstract

Objective: Severe acute respiratory syndrome Coronavirus 2 causes both health and economic crises and up till now no drug or vaccine has yet been approved. There is an increased demand to explore other complementary methods to protect the world. Eucalyptus essential oil; a popular off-label drug used to relieve nasal congestion via inhalation with promising effects on the upper respiratory diseases including viral infections.
Methods: In order to provide review-based hypotheses demonstrating eucalyptus essential oil beneficial role; several published studies were retrieved from different databases and websites till June 2020. The retrieved data declared the antiviral potentials against viruses of same subgenus or with same pattern and the beneficial effects on respiratory system, immunity and overall health improvement, along with declaring the application methods and safety.
Results: Off-label use of Eucalyptus essential oil by inhaling 12 drops /150 mL or 1.5% v/v solution boiling water may relief COVID-19 mild and moderate symptoms as pain, cough, respiratory inflammation, cytokine storm and dyspnea.
Conclusions: Experimental and clinical data proved that inhalation of eucalyptus essential oil may provide the ability to reduce COVID-19 patients symptoms and morbidity risk factors and may play a role as a preventative technique complementary to WHO guidance for beating COVID-19 virulence and transmission spread.
Keywords: Cineole, COVID-19, essential oil, eucalyptus oil, inhalation.

INTRODUCTION

Corona virus disease 2019 (COVID-19) is a global pandemic of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It first appeared in Wuhan, Hubei, China and then spreads all over the world through respiratory droplets, contact and the faecal-oral route[1]. World Health Organization (WHO) listed COVID-19 as a public health emergency of international concern due to its rapid and highly infectious pattern. The last WHO situation report-134 up to date June 2, 2020 has confirmed a total number of infected peoples to be 6194533 from which 376320 were died[2]. The nowadays pandemic is characterized by intensity variation between countries, misleading indication of case fatality rate and unclear data about the virus and its virulence. The absence of vaccines and treatments encouraged the control strategies role and non-pharmacological measurements for communities[3]. Several intervention therapeutic strategies were reported as an alternative approach to control the COVID-19 pandemic. From these strategies the inhalation of Eucalyptus essential oil (EEO) which reported in several publications in addition to folkloric traditional use in some countries during the few last days[4-9]. No clinical trial, in vivo or in vitro studies demonstrate the EEO activity against COVID-19; but several review-based expected potentials as antiviral, co-infection control, symptoms relief or just a safe hygienic lifestyle. Today many companies have advertised to EEO as a product for prevention or treatment of COVID-19[10]; but, US Food and Drug Administration (FDA) had sent a warning letters to such companies[11]. In this work I will declare both facts and problems of EEO use in controlling COVID-19 pandemic.

METHODS

Literature search was performed using diffrent databases as; Science Direct, Google Scholar, Web of Science, PubMed, ClinicalTrials.gov and Scopus using

main key word "Eucalyptus" in addition to "COVID-19, COPD, Antiviral, Anti-inflammatory, Immune modulation, Antimicrobial, clinical trials, FDA, Monograph, Inhalation and Potential".

DISCUSSION

Off-label use of EEO: EEO widely used as Over The Counter (OTC) drug in a single or combined form for relieving nasal congestion via inhaling a few drops either on a handkerchief or in a bowl of hot water[12]. Vapor inhalation of EEO relief symptoms of bronchitis, asthma, and chronic obstructive pulmonary disease (COPD) which are the risk factors in COVID-19 patients[13]. Traditional use of EEO for relief of cough associated with cold are accepted without the supervision of a medical practitioner via inhalation and as a bath additive and had been described for a long time[14]. 1,8-Cineole the major constituent of EEO (80-95%) is well tolerated in inhalation administrations and is registered as a licensed medicinal product which available for airways inflammation for many years[15]. As well Vicks VapoRub® vapors inhalation which containing eucalyptus, camphor and menthol acting on cold receptors in the nose are a common used off-label drug. The German Standard zulassung, the Pharmacopée Française and the WHO monograph 2002 had reported the use of EEO for the treatment of respiratory tract disorders, bronchial catarrh and stomach pain[14]. The Martindale reported that EEO effective as an inhalant, often in combination with other volatile oils for catarrh and coughs in a lot of preparations[16]. EEO is approved by the FDA for food use (EAFUS -Everything Added to Food in the United States- list No 2081) [FDA 2013] and as OTC (Over the counter) drug in cough/cold monograph sub-categories nasal decongestant (mouthwash or lozenge), antitussive and expectorant and in external analgesic monograph sub-categories counter irritant, fever blister/cold sore and poison ivy/oak/sumac and in skin protectant monograph sub-categories astringent and poison (ivy/oak/sumac)[17].

COPD control by EEO: COPD is associated with increased risk of morbidity in COVID-19 patients[18]. Pretreatment with EEO markedly reduced the production TNF-α and IL-β proinflammatory cytokines, superoxide dismutase (SOD) activity and malondialdehyde (MDA) level which indicates that EEO might have its potential in COPD treatment[19]. The anti-inflammatory effect EEO to reduce cytokine release was confirmed also in ex-vivo cultured and stimulated alveolar macrophages from patients with (COPD)[20]. Few weeks (1-8) therapy with 1,8-Cineole reduces exacerbations, dyspnea and specific airway resistance in patients with COPD and improves lung function parameters and health status by intervening in the mucus membrane pathophysiology of airway inflammation[14].

Antiviral activity of EEO: The antiviral activity of EEO was confirmed against an enveloped viruses (similar to COVID-19); mumps virus obtained from patients with respiratory tract infection[21], herpes simplex virus before or during host cell adsorption[22], H_1N_1 influenza virus[23]and inhibits avian influenza virus $H_{11}N_9$ in aerosol, vapor and if being captured on a fiber coating materials[9]. The inhibitory mechanism of EEO is based on the inactivation of hemagglutinin protein of the virus in its vapor phase[9]. As well, two preprint articles by (Sharma *et al.*) demonstrated that eucalyptol (1,8 cineole) and Jensenone from EEO represent potential COVID-19 main viral proteinase (M-pro/3CLpro) inhibitory effect by molecular docking studies. Inhaling concentrated EEO vapors for 30 minutes followed by periodical inhaling vapor mixture of EEO and tea tree oil (TTO) (50:50) with 30-120 minutes intervals; reduces the risk of infection with SARS-CoV which is a highly pathogenic coronavirus[23,24].

Co-infection control activity of EEO: The antibacterial potentials of EEO was confirmed by activity against respiratory infecting bacteria; *Haemophilus influenzae*, *H. parainfluenzae*, *Stenotrophomonas maltophilia* and *Streptococcus pneumoniae*[21] and by inhalation prophylactic use against colds, tuberculosis, flus and opportunistic infections of the human respiratory system[24]. In hospitals EEO used for controlling multidrug-resistant bacteria[25], reduce endotracheal tube biofilm microbial contamination during ventilation process[26] and showed antifungal potential against intensive care units (ICU) isolated yeast[24,27]. EEO fumes inhalation affords bactericidal components killing infections in the nasal passages, sinuses, bronchial tubes and lungs[24].

Anti-inflammatory and Immune modulation potentials of EEO: Dexamethasone today is the first and only drug that has made a significant difference to patient mortality for COVID-19 due to its anti-inflammatory and immune modulation effects. Surprisingly EEO can implement the innate cell-mediated immune response and anti-inflammatory properties[28,29]. COVID-19 hospitalized patients developed at latter phase a syndrome known as cytokine storm or hyperinflammatory syndrome due to immune overactivation that increases the acute respiratory distress and can lead to death[30]. Pretreatment with EEO markedly reduced the production of proinflammatory cytokines which indicates that EEO might have its potential to stop cytokine storm[19]. As well suppression of human lung macrophages inflammatory responses by EEO and its constituent 1,8-cineole was reported[31].

Other activities of EEO: EEO decreasing patient's pain[32], cough treatment[33], aid in the recovery from certain respiratory diseases[24], air freshener, fumigating agent[34] and effective in cleaning mixtures for degreasing, deodorizing and disinfection[33,35].

Dose and safety of EEO: The WHO monograph EEO reported doses were 12 drops/150 mL or 1.5% v/v solution boiling water for inhalation three times daily[36,37]. The oral LD_{50} in rats (2.5 g/kg)[38]. A toxicological study influenced the use of EEO with certain concentration less than (233.44 mg/kg) to avoid serious metabolic and cellular damage[39]. As well, EEO also may cause irritation to the skin, toxic effects especially in children and adverse effects as slurred speech, ataxia, muscle weakness progressing to

unconsciousness and seizures if used in high concentration[40-42]. Because of EEO strong odor, an accidental poisoning is not common, as intoxication occurs only via oral consumption of 4-5 ml EEO[5]. There is no danger of accumulating inhaled essential oils in the body even with repeated inhalation as the concentration of inhaled EOs decreases to half its original value within 30-40 minutes[24]. However the oils liquid phase are generally irritant and possibly toxic for nasopharyngeal and lung epithelial cells, the vapor phase of the same oils might be useful as inhalers for respiratory infections in low concentrations[15]. Studies on 1,8-cineole confirmed that it is well absorbed from breathing air. Upon inhalation of 2 ml 1,8-cineole 99% for 20 min. the blood serum concentration was increasing in a linear way with distribution half-life 2-13 min. and elimination half-life 31-281 min.

Clinical trials of EEO on human volunteers: The effect of 0.25 ml EEO inhalation for 10 minutes on cardiovascular responses using a disposable face mask was reported in (ClinicalTrials.gov Identifier: NCT02656004) and smelling of pure EEO in vial for training of the olfactory nerve for improving smell sense after radiation therapy also reported in (ClinicalTrials.gov Identifier: NCT03049358). EEO 100% concentration was confirmed as a safe method of protection from mosquito bites on human volunteers skin in indoor conditions[34]. Inhalation of EEO was effective in reducing blood pressure and pain after total knee replacement[32]. Another clinical study had concluded that the treatment with 1,8-cineole of patients with acute non-purulent rhinosinusitis was effective and safe with only mild side effects and can avoid antibiotic treatment[43]. Another study had concluded that acute rhinosinusitis can be managed by treatment with 1,8-cineole and confirmed its safety and significant benefit for bronchitis[44].

Precautions for using EEO: EEO should not be used during pregnancy or lactation as there is no information available on inhalation of EEO or its main constituent 1,8-cineole for pregnant women and 1,8-cineole has been reported to penetrate the rodents placenta. EEO should not be used for babies and very young children less than 12 years as the risk of reflex spasm is expected.

CONCLUSIONS

Off-label use of EEO as an inhaler via inhalation vaporizers, diffusers or as a fragrance in cleaning mixtures should be announced as a concomitant safe hygienic lifestyle to hand washing, face mask wearing and social distancing. The use of EEO for COVID-19 patients will reduce muscle and stomach pain, cough and dyspnea which are the common symptoms, and protect patients from co-infection susceptibility and decrease chance of hyper inflammatory syndrome and COPD associated risk morbidity. Researchers should start the clinical trials and in vivo studies on EEO safety and efficacy as soon as possible to confirm or reject its antiviral potentials against COVID-19 to evaluate the possibility of its use for treatment and/or prevention. Community pharmacies and essential oil manufactories should sell EEO just as an off-label drug not as treatment or preventative protocol for COVID-19 pandemic.

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AUTHOR'S CONTRIBUTION

Abbass HS: Writing original draft, review, literature survey, editing, methodology, data curation.

DATA AVAILABILITY

The datasets generated during this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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