

## **Eucalyptus Essential Oil; the Off-label Drug to Protect the World from COVID-19 Pandemic: an Evidence Based Perspective**

**Abstract:** Eucalyptus essential oil; a popular off-label drug used to relieve nasal congestion via inhalation. Non-clinical and clinical data prove a promising effect of Eucalyptus essential oil on upper respiratory diseases including viral infections. Off-label use of Eucalyptus essential oil by inhalation 12drops /150mL or 1.5% v/v solution boiling water may relief COVID-19 symptoms as cough, pain, respiratory inflammation, cytokine storm, and dyspnea in mild and moderate cases as well may provide a preventative technique complementary to WHO guidance for beating COVID-19 virulence and transmission spread.

**Key-words:** COVID-19; essential oil; Eucalyptus oil

### **1. Introduction:**

Corona virus disease 2019 (COVID-19) is a global pandemic of Severe Acute Respiratory Syndrome Coronavirus2 (SARS-CoV-2). It first appeared in Wuhan, Hubei, China and then spreads through respiratory droplets, contact and the fecal-oral route all over the world. 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. 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.<sup>1</sup> 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.<sup>2-7</sup> 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;<sup>8</sup> but, US Food and Drug Administration (FDA) issued warning letters to such companies.<sup>9</sup> In this work I will declare both facts and problems of EEO use in controlling COVID-19 pandemic.

### **2. Materials and methods**

Literature search was conducted in the following databases: Science Direct, Scopus, Web of Science, PubMed, ClinicalTrials.gov and Google Scholar using main key word “Eucalyptus” in addition to “COVID-19, COPD, Antiviral, Anti-inflammatory, Immune modulation, Antimicrobial, clinical trials, FDA, Monograph, Inhalation and Potential”

### **3. Results & Discussion**

**3.1 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.<sup>10</sup> Application of EEO by either vapor inhalation or oral route provides benefit for both purulent and non-purulent respiratory problems, such as bronchitis, asthma, and chronic obstructive pulmonary disease (COPD) which are the risk factors in COVID-19 patients.<sup>11</sup> 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 have been well described for a long time.<sup>12</sup> 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.<sup>13</sup> Vicks VapoRub<sup>®</sup> vapors inhalation which containing eucalyptus, camphor and menthol acting on cold receptors in the nose.<sup>14</sup> The German Standardzulassung, the Pharmacopée Française and the WHO monograph 2002 had reported the use of EEO for the treatment of disorders of respiratory tract, bronchial catarrh and stomach pain.<sup>12</sup> The Martindale reported that EEO effective as an inhalant, often in combination with other volatile oils substances for catarrh and coughs and as an ingredient of a lot of preparations.<sup>15</sup> 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)<sup>16</sup>

**3.2 COPD control by EEO:** COPD is associated with increased risk of morbidity in COVID-19 patients.<sup>17</sup> Pretreatment with EEO markedly reduced the production of proinflammatory cytokines TNF- $\alpha$  and IL- $\beta$  in lung homogenate, significantly decreased the elevated malondialdehyde (MDA) level and increased superoxide dismutase (SOD) activity which indicates that EEO might have its potential to be a proper candidate drug in the treatment of COPD.<sup>18</sup> The anti-inflammatory effect EEO to reduce cytokine release was confirmed also in ex-vivo cultured and stimulated alveolar macrophages from patients with (COPD).<sup>19</sup> Several studies dealt with effects of 1,8-Cineole on pulmonary diseases were reported as an active controller of airway inflammation in COPD by intervening in the pathophysiology of airway inflammation of the mucus membrane and reduces exacerbations as well as dyspnea and improves lung function and health status.<sup>20</sup> Parameters of lung-function, peak-flow and symptom-score of patients with COPD showed better improvements under therapy with 1,8-cineole for one week.<sup>21</sup> Lung function parameters, airway resistance and specific airway resistance were reduced by 21% and 26%, in patients with COPD treated by 1,8-cineole for 8 weeks.<sup>21</sup>

**3.3. 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),<sup>22</sup> herpes simplex virus (before or during adsorption, but not after penetration into the host cell),<sup>23</sup> H<sub>1</sub>N<sub>1</sub> influenza virus<sup>24</sup> and inhibits avian influenza virus H<sub>11</sub>N<sub>9</sub> in aerosol, vapor and if being captured on a fiber coating materials.<sup>7</sup> The inhibitory mechanism of EEO is based on the inactivation of hemagglutinin protein of the virus in its vapor phase.<sup>7</sup> As well, eucalyptol (1,8 cineole) and Jensenone from EEO represent potential COVID-19 main viral proteinase (Mpro/3CLpro) inhibitory effect by molecular docking studies.<sup>25, 26</sup> Inhaling an effective amount of the concentrated vapors from EEO within a period of time of 30 minutes before entering a public area reduces the risk of infection with Severe Acute Respiratory Syndrome (SARS-CoV) which is a highly pathogenic coronavirus and after entering the public area, periodically inhaling vapor mixture of 50% EEO and 50% tea tree oil (TTO) in a hand-held atomizer apparatus, whereby the period of time between successive inhalations 30-120 minutes.<sup>27</sup>

**3.4. 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*<sup>22</sup> and by inhalation prophylactic use against tuberculosis, colds, flus and opportunistic infections of the human respiratory system.<sup>27</sup> In

hospitals EEO used for controlling multidrug-resistant bacteria,<sup>28</sup> reduce microbial contamination of the endotracheal tube biofilm in ventilated patients<sup>29</sup> and showed antifungal potential against intensive care units (ICU) isolated yeast.<sup>27, 30</sup>

**3.5. 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.<sup>31, 32</sup> COVID-19 hospitalized patients developed at latter phase a syndrome of dysregulated and systemic immune overactivation described as a cytokine storm or hyperinflammatory syndrome that worsens acute respiratory distress syndrome and can lead to death.<sup>33</sup> Pretreatment with EEO markedly reduced the production of proinflammatory cytokines which indicates that EEO might have its potential to stop cytokine storm.<sup>18</sup> as well suppression of inflammatory and infection responses in human lung macrophages by EEO and its constituent 1,8-cineole was reported.<sup>34</sup>

**3.6. Other activities of EEO:** EEO decreasing patient's pain<sup>35</sup>, cough treatment,<sup>36</sup> aid in the recovery from certain respiratory diseases<sup>27</sup>, air freshener, fumigating agent<sup>37</sup> and effective in cleaning mixtures for degreasing, deodorizing and disinfection.<sup>36, 38</sup>

**3.7. Dose and safety of EEO:** The WHO monograph EEO reported doses were 12drops /150mL or 1.5% v/v solution boiling water for inhalation three times daily.<sup>39, 40</sup> The oral LD<sub>50</sub> in rats (2.5g/kg).<sup>41</sup> The major risk is oral intoxication as the lethal intoxication has been reported after the accidental ingestion of 4-5ml of EEO.<sup>3</sup> A toxicological study influenced the use of EEO with certain concentration less than (233.44 mg/kg) to avoid serious metabolic and cellular damage.<sup>42</sup> 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.<sup>43-45</sup> Because of EEO strong odor, an accidental poisoning seems to be not very likely, as intoxication occurs only via oral consumption only. Williams, 1999, page 26, further states: "Eucalyptus oil can be toxic if taken internally, but breathing the oil's fumes will likely allow its bactericidal components to knock out infections in the nasal passages, sinuses, bronchial tubes, and lungs".<sup>27</sup> There is no danger of accumulating inhaled essential oils in the body even with repeated uses as the concentration of inhaled EOs decreases to half its original value within 30-40 minutes.<sup>27</sup> 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.<sup>13</sup> Studies on 1,8-cineole confirmed that it is well absorbed from breathing air. Upon inhalation period of 20 min. (2 ml 1,8-cineole 99%) the blood serum 1,8-cineole concentration was increasing in a linear way from 4-20 min. and the distribution half-life was 2-13 min. while elimination half-life was 31-281 min.

**3.8. Clinical trials of EEO on human volunteers:** The effect of 0.25ml 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 olfactory training in improving sense of smell after radiation therapy in patients with paranasal sinus or nasopharyngeal cancer 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.<sup>37</sup> Inhalation of EEO was effective in decreasing patient's pain and blood pressure following total knee replacement.<sup>35</sup> Another clinical study had concluded that the treatment of sinusitis with 1,8-cineole in patients with acute non-purulent rhinosinusitis, is effective and safe (only mild side effects were observed in two patients as heartburn and exanthema) and can avoid antibiotic treatment.<sup>46</sup> 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.<sup>47</sup>

**3.9. 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 placenta in rodents. EEO should not be used for babies and very young children less than 12 years as the risk of reflex spasm is expected.

#### 4. 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. Researchers should start the clinical trials and in vivo studies on EEO safety and efficacy as soon as possible to confirm or reject its use. 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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