The possible role of plant derived essential oils against fatigue in post-acute sequelae COVID-19: a literature review based on evidence of essential oils on fatigue

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ABSTRACT

Persistent symptoms of COVID-19 were discovered in certain individuals even after the initial onset of the illness. Fatigue is among the issues observed in people who have Post-Acute Sequelae COVID-19 (PASC). However, available treatment choices for fatigue in PASC have been constrained so far. In several patient groups, essential oils (EO) extracted from plants have been demonstrated to lessen fatigue. This review’s objective is to provide all available data on the advantages of plant-derived EO for fatigue and their capacity to heal PASC that is related to fatigue. The application of EO derived from plants, like Lavender, Sweet Orange; a blend of Lavender, Rosemary, Juniper, and Cananga; an assortment of Ravensara, Frankincense, and Sandalwood; a combination of Peppermint leaves; Evening Primrose, Clove Bud, Black Pepper, Bergamot, and White Grapefruit, has demonstrated to reduce fatigue across various groups of patients when compared to a control group. Considering the existing evidence, EO derived from plants might play a role and offer potential benefits in alleviating fatigue in individuals with PASC.

Keywords: COVID-19, Essential Oils, Fatigue
INTRODUCTION

The COVID-19 pandemic's impact on world health has resulted in widespread morbidity and mortality (Greenhalgh et al., 2020; Aiyegbusi et al., 2021). Several studies have indicated that even after recovering from mild to severe COVID-19 symptoms, many patients who survived the severe phase continue to experience persistent effects (Greenhalgh et al., 2020). Post-Acute Sequelae of COVID-19 (PASC) is the name given to this condition (Estiri et al., 2021).

An European study tracking post-acute COVID-19 outpatients for 60 days found about 87.4% of 143 patients reported chronic symptoms, with fatigue being the most common complaint (53.1%) (Carfì et al., 2020). A study of cohorts in Wuhan, China, monitored 1,733 patients after their acute start for six months, reported that 63% of patients complained of fatigue (Huang et al., 2021). Similarly, in Indonesia, 63.5% of 463 COVID-19 patients experienced ongoing symptoms, with fatigue being predominant (30.2%) (Shah et al., 2021; Susanto, 2021).

The fatigue experienced by PASC survivors shares characteristics with chronic fatigue syndrome (CFS), which can have both viral and non-viral causes (Mantovani et al., 2021). About two-thirds of CFS cases are viral in origin, often labeled as "post-viral fatigue" after infections like Influenza, MERS and SARS. Non-viral causes encompass chronic conditions such as endocrine disorders, cancer, heart issues, kidney, allergies, depression, and anxiety (Choi and Park, 2016; Hawkins et al., 2020; Shirzadegan et al., 2020; Hassanzadeh et al., 2021; Mackay, 2021; Toogood et al., 2021).

The control of fatigue involves pharmacological and non-pharmacological approaches (Hassanzadeh et al., 2021). Non-pharmacological, including complementary medicine, are considered simpler, cost-effective, and safe compared to pharmaceutical options (Ahmady et al., 2019; Varaei et al., 2021). The use of herbal products, which constitute approximately 80% of the world's population's medical reliance, falls under this category (Majdinasab et al., 2018).

Plant-derived essential oils (EO) have a long history of use for general health and well-being. They are recognized for their antiviral, antibacterial, analgesic, and relaxing effects in managing respiratory diseases, cancer symptoms, migraines, muscle pain, arthritis and hypertension (Choi and Park, 2016; Gok Metin and Ozdemir, 2016; Asif et al., 2020; Hawkins et al., 2020). The anti SARS-Cov 2 potential of EO is explained by its lipophilic character, allowing them to pierce viral membranes and induce viral lysis. Additionally, the diverse bioactive compounds within EO can collectively target various stages of viral growth. Combining traditional and herbal approaches could potentially offer a more potent approach to combating the COVID-19 (Asif et al., 2020).

Several previous reviews have discussed the symptoms, mechanisms, complications and management of PASC (Aiyegbusi et al., 2021; Greenhalgh et al., 2020; Shah et al., 2021; Mantovani et al., 2021). To the best of our knowledge, there have been no reviews addressing the role of plant-produced EO in the treatment of PASC. Currently, whether they may be used as a therapy for PASC-induced fatigue, the review's objective is to discuss the available research on the advantages of EO produced from plants in treating fatigue. This review aims to provide the groundwork for possible clinical studies that might take place in future.
Post-Acute Sequelae COVID-19

The term Post-Acute Sequelae COVID-19 (PASC) relates to manifestations and irregularities that last longer than 12 weeks following the first signs of COVID-19, yet aren’t linked to a specific diagnostic ailment (Estiri et al., 2021). Patients grappling with PASC typically encounter a range of both physical and psychological symptoms. Physical indications encompass fatigue, migraines, breathlessness, persistent coughing, chest discomfort, skin eruptions, alterations in smell and taste, as well as muscle and joint ache. Concurrently, psychological manifestations encompass "brain fog," cognitive disruptions, sleep disturbances, and shifts in mood (Aiyegbisi et al., 2021; Mantovani et al., 2021). Various investigations have unveiled that the predominant symptom experienced by most survivors is fatigue (Carfì et al., 2020; Huang et al., 2021; Susanto, 2021).

Fatigue Pathophysiology in PASC

The fatigue experienced post-infection with diseases like SARS (2003), MERS (2012), and other viral origins typically exhibit comparable symptoms to those seen with SARS-CoV-2. Despite the distinct causative agents, each disease tends to provoke a similar inflammatory reaction at the infection site. This inflammatory response can act as common "stressors," similar to those contributing to fatigue in various causes (including emotional factors, physical or mental strain, and sleep deprivation), using neuronal and humoral pathways (Mackay, 2021).

Islam et al. (2020) also looked at several cases of post-infection fatigue and hypothesized that patients with COVID-19 had elevated levels of cytokines (including IL-6, IL-1β, TNF-α, and others) which may contribute to the development of long-lasting fatigue symptoms. This hypothesis revolves around the release of proinflammatory cytokines and neurotoxic molecules by microglia cells and astrocytes, ultimately triggering neuroinflammation within hypothalamic structures and the limbic system (Mackay, 2021). The prolonged symptoms observed in PASC could stem from the hyperinflammatory response during COVID-19 acute stages (Proal and VanElzakker, 2021).

In a cohort investigation done in Wuhan, China demonstrated that 23% of COVID-19 survivors experienced anxiety and melancholy over a span of six months following the initial stages of the disease (Huang et al., 2021). This psychological stress is typically induced by factors like self-isolation, disrupted routines, feelings of loneliness, reduced family support due to the need for distancing, job losses, and the impact of lockdown measures. This psychological stress tends to initiate a cycle that contributes to fatigue (Susanto, 2021; Vollbracht and Kraft, 2021).

Essential Oils from Plants that Act as Antivirus

A variety of viruses are susceptible to the action of EO, including influenza virus (IFV), avian flu, yellow fever virus, human immunodeficiency virus (HIV), and human herpesvirus (HSV). Due to their lipophilic character, viruses with envelopes are highly susceptible to EO, allowing them to permeate the lipid bilayer membrane and induce viral breakdown. Eucalyptus globulus and Citrus bergamia EO, containing active compounds like citronellol and eugenol, are successful in combatting IFV. Carvacrol and its thymol isomer present in oregano EO have been shown to lower cholesterol levels in the HIV-1 envelope membrane, thereby obstructing viral entry into the host system by inhibiting host cell fusion and curtailing viral infection (Asif et al., 2020).
Furthermore, carvacrol has demonstrated antiviral effects in combating HSV-1, human rotavirus (HRV) and human respiratory virus (HRSV) (Kamalabadi et al., 2018).

Potential Contribution of EO to Combat Post-Viral Fatigue

The collection of data shown in Table 1 (Supplementary Files) clearly demonstrates the potential significance of EO in the treatment of fatigue. Various EO derived from plants, including Lavender, sweet orange, and their combination (Muz and Taşcı, 2017; Hassanzadeh et al., 2018; Ahmady et al., 2019; Karadag and Samancioglu Baglama, 2019; Hassanzadeh et al., 2021; Varaei et al., 2021); as well as Lavender combined with Rosemary, Cananga, and Juniper (Gok Metin and Ozdemir, 2016); Evening Primrose (Majdinasab et al., 2018); Ravensara and Frankincense combined with Sandalwood (Choi and Park, 2016); and a blend of Peppermint leaves with Clove Bud, Black Pepper, Bergamot, and White Grapefruit (Hawkins et al., 2020) have demonstrated a reduction in fatigue levels as compared to control groups in a variety of patient demographics, including those with heart failure, acute myocardial infarction, hemodialysis, rheumatoid arthritis, hypothyroidism, chronic allergic rhinitis, and multiple sclerosis.

Lavender or *Lavandula angustifolia*, is a popular plant contains linalyl acetate and linalool, which are also found in the Cananga. The parasympathetic nerves are stimulated by these substances, which results in better sleep, lessened muscular fatigue, symptom relief, and an overall improved quality of life. EO play a role in promoting bodily homeostasis and reducing emotional stress (Ahmady et al., 2019). This suggests that inhaling aromatherapy oils can be a beneficial and safe approach to alleviate symptoms and enhance quality of life (Choi and Park, 2016). Sweet orange EO is another aromatic compound known for inducing calmness, reducing stress, and alleviating depression. Inhaling aromatherapy or receiving aromatherapy massage has been shown to significantly decrease fatigue (Varaei et al., 2021).

Certain compounds like alpha-pinene, alpha-terpineol, and 1,8-cineole found in Juniper, Frankincense, Ravensara, Lavender, and other plants that produce EO have demonstrated the ability to lower the proinflammatory mediators’ generation (Choi and Park, 2016). Evening Primrose, containing substantial amounts of γ-linolenic acid and linoleic acid, has proven to be effective at suppressing inflammatory mediators like TNF-α, IL-6 and IL-1β (Timoszuk et al., 2018). These substances capacity to restore equilibrium to the autonomic nervous system is another factor contributing to their effects. The presence of santalol in Sandalwood EO has a relaxing and sedative effect, promoting an increase in the parasympathetic nervous system. Studies have consistently indicated that EO aromatherapy, including Sandalwood, Rosemary and Lavender, increase sleep quality and lessen fatigue (Choi and Park, 2016).

Peppermint leaf-derived aromatherapy EO has been shown to improve overall sensations of alertness and vitality. Practitioners use different EO, including those from Black Pepper and Citrus plants, as well as peppermint EO, which is the most popular option in aromatherapy literature for relieving exhaustion (Hawkins et al., 2020). It should be noted that receiving the advantages of inhalation may require some time and brief exposure, with advantages possibly not immediately apparent (Varaei et al., 2021).
The Role of EO in Post-Viral Fatigue Management: The Mechanism of Action

The application of EO in aromatherapy represents a widely employed complementary therapeutic approach worldwide for addressing diverse symptoms associated with various illnesses. Aromatherapy includes applying EO obtained from plants to the skin or inhaling them to produce physiological or pharmacological effects (Gok Metin and Ozdemir, 2016).

During aromatherapy, when EO are breathed in, distinct molecules within them stimulate olfactory nerve cells, subsequently transmitting these signals through the olfactory pathway in the nose to the brain’s limbic system. Neurotransmitters including endorphins, enkephalins, serotonin, and noradrenaline are released as a result of this limbic system activation. Within the limbic system, the amygdala and hippocampus play pivotal roles in processing smell (Proal and VanElzakker, 2021). Administering EO via inhalation imparts a revitalizing impact, influencing both mental and physical stability, ultimately reducing chronic fatigue, stress and depression (Proal and VanElzakker, 2021; Vollbracht and Kraft, 2021). Because EO quickly absorb into the body, they are often used in massage (Gok Metin and Ozdemir, 2016).

The Lamiaceae family plant Lavender is known to have properties similar to those of the drug Diazepam, which reduces emotional reactivity to the outside world by promoting inhibitory neurons rich in Gamma-Aminobutyric Acid (GABA) in the Amygdala. Through interactions with the cerebral cortex, the limbic system reduces anxiety and affects critical factors including blood pressure, heart rate, hormone levels, stress, and breathing (Kamalabadi et al., 2018; Shirzadegan et al., 2020; Hassanzadeh et al., 2021).

Citrus aurantium (C. aurantium) EO has sedative and anti-anxiety properties since it contains active terpene components. After repeated oral treatment, its anti-anxiety effect may be related to the engagement of 5-HT1A receptors. According to studies, aromatherapy using C. aurantium extract can lessen preoperative anxiety to a degree equivalent to that of Diazepam. Although further evidence is required to firmly establish aromatherapy’s effectiveness in alleviating anxiety (Shirzadegan et al., 2020).

Inhalation of EO provides an invigorating effect, enhancing concentration by entering the bloodstream and lungs through the nasal route, thereby affecting mental and physical equilibrium. Smell stimulates the limbic system and hormones, intensifying emotional reactions that aid in alleviating chronic fatigue, stress and feelings of sadness (Vollbracht and Kraft, 2021). The potential mechanism by which EO counteract fatigue is depicted in Figure 1.

COVID-19 and Essential Oils
Sharma and Kaur (2020) used the molecular docking method to demonstrate the antiviral effectiveness of EO against COVID-19. In this study, they identified an active plant compound named Jensenone in Eucalyptus jensenii. The EO showed interactions with hydrophobic molecules such as, PRO52, PRO184, LEU29, TRY126, TRP207, and ALA7; hydrogen bonds with L30, V18, and T16 and M4D10; additionally to ionic interactions with ARG38, ASP34, HIS163, and LYS3. These interactions led to the formation of complexes with the Mpro protein of SARS-CoV-2. Another active constituent of Eucalyptus EO, namely 1,8-cineole/eucalyptol, exhibited the ability to bind to the Mpro protein, thereby disrupting viral replication. The Mpro-eucalyptol complex demonstrated robust hydrogen and hydrophobic interactions.
**CONCLUSION**

There have been several suggested EO mechanisms for COVID-19. As a result of their ability to interact with viral proteins, EO’s active compounds can prevent the viral replication and lessen the amount of pro-inflammatory mediators that increase dramatically in COVID-19. By stimulating the limbic system through the olfactory pathway, which creates certain neurotransmitters when EO molecules are breathed during aromatherapy use, one might positively influence on psychological stability. Considering the existing evidence, EO sourced from plants might potentially play a part and offer utility in alleviating symptoms of post-viral fatigue within the context of PASC.

**REFERENCES**


