

## The Possible Role of Plant Derived Essential Oils Against Fatigue in Post Acute Sequele Covid-19: A Literature Review Based on Evidence of Essential Oils on Fatigue

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### Abstrak

Gejala COVID-19 ditemukan menetap setelah onset akut pada beberapa orang yang selamat. Salah satu masalah Post Acute Sequele Covid-19 (PASC) adalah kelelahan. Hingga saat ini, pilihan pengobatan untuk mengatasi kelelahan pada PASC masih terbatas. Minyak esensial yang berasal dari tanaman (EO) telah terbukti mengurangi kelelahan pada beberapa populasi pasien. Tujuan dari tinjauan ini adalah untuk menyajikan semua bukti mengenai manfaat EO yang berasal dari tanaman untuk mengatasi kelelahan, apakah mereka dapat digunakan sebagai terapi untuk PASC yang berhubungan dengan kelelahan. Metode: Pencarian literatur dilakukan pada database PubMed, Science Direct, Google Scholar, dan Springer Link yang berfokus pada studi uji klinis acak (RCT) 10 tahun terakhir dengan topik pengaruh EO terhadap kelelahan dengan kata kunci 'Minyak Atsiri', 'Kelelahan', dan 'Long Covid-19'. Bukti dan informasi lain yang diperoleh kemudian dianalisis menggunakan sintesis PICO dan disajikan dalam bentuk tabel dan narasi. Hasil: Berdasarkan analisis dari 11 artikel yang diperoleh, ditemukan bahwa pemanfaatan tanaman EO seperti Lavender, Sweet Orange; Lavender campuran Cananga, Juniper, dan Rosemary; Cendana campuran Kemenyan dan Ravensara; Evening Primrose; daun Peppermint campuran Lada Hitam, Cengkeh, Jeruk Purut, dan Bergamot terbukti dapat mengurangi kelelahan pada beberapa populasi pasien dibandingkan dengan kelompok kontrol. Kesimpulan: EO yang berasal dari tanaman mungkin memiliki peran dan berguna untuk mengurangi kelelahan pada PASC.

*Kata Kunci : covid-19; minyak esensial; kelelahan; lavender; sweet orange*

### Abstract

Symptoms of COVID-19 were found to be persistent after acute onset in some survivors. One of the Post Acute Sequele Covid-19 (PASC) problems is fatigue. Until now, the treatment options for fatigue in PASC are limited. Plant derived essential oils (EO) have been shown to reduce fatigue in several patient populations. The aim of this review is to present all the evidence regarding the benefits of plant derived EO for fatigue, whether they can be used as a therapy for fatigue associated PASC. Method: Literature search was conducted on the PubMed, Science Direct, Google Scholar, and Springer Link databases focusing on the last 10 years randomized clinical trial (RCT) study on the topic of the effect of EO on fatigue with the keywords 'Essential Oils', 'Fatigue' and 'Long Covid-19'. The evidence and other information obtained is then analyzed using PICO synthesis and presented in tabular and narrative form. Results: Based on the analysis of the 11 articles obtained, it was found that the utilization of plants EO such as Lavender, Sweet Orange; Lavender mixed Cananga, Juniper, and Rosemary; Sandalwood mixed Frankincense and Ravensara; Evening Primrose; leaves of Peppermint mixed Black Pepper, Clove Bud, White Grapefruit and Bergamot have been shown to reduce fatigue in several patient populations compared to control group. Conclusion: Plant derived EO may have a role and be useful for reducing fatigue in PASC.

*Keywords: covid-19; essential oils; fatigue; lavender; sweet orange*

## Introduction

The Covid-19 pandemic is still ongoing and has caused a global health crisis with an increase in morbidity and mortality on a large scale(1,2). Several studies have reported that most of the patients who survived the acute phase of Covid-19 experienced a persistent effect even though they had recovered from mild to severe symptoms(2). This condition was reported in a previous study as Post Acute Sequele of Covid-19 (PASC) (3).

One study in Europe that followed up for 60 days from acute onset of post acute Covid-19 outpatient, as many as 87.4% of 143 patients reported persistent symptoms and most complained of fatigue (53.1%) (4). A prospective cohort study in Wuhan, China evaluated 1,733 patients 6 months from acute onset, 63% complaining of fatigue (5). As many as 63.5% of 463 patients in Indonesia experienced persistent symptoms of Covid-19 and most of them complained of fatigue (30.2%). Survivors feel that the body has not recovered as usual and these persistent and prolonged symptoms can reduce the quality of life and work productivity (6,7).

Fatigue experienced by PASC survivors has the same characteristics as the diagnosis of chronic fatigue syndrome (CFS), a multietiology diagnosis that can be caused by virals and non-virals (8). Two-thirds of the CFS etiology is viral and refers to "post-viral fatigue", where prolonged fatigue was also complained in patients post infection of SARS (2003), MERS (2012), Epstein-Barr Virus (EBV), Human Herpes Virus (HHV), HIV, Hepatitis C, Parvovirus B19 and Influenza Virus. Non-viral etiology includes chronic diseases such as cancer, kidney, heart, anxiety, depression, allergies and endocrine (9–14).

Until now, the treatment options for fatigue in PASC are limited because understanding of the mechanism of the condition is not yet fully understood (1,9). Approaches to the management of fatigue can be pharmacologically and non-pharmacologically (12). Non-pharmacologically methods are included in the category of complementary medicine, this treatment is considered to be simpler, cost effective and safe than drug methods and has fewer side effects (15,16). Complementary and alternative medicine (CAM) in recent years has been in great demand (13). The use of herbal products is increasing worldwide, and World Health Organization studies show that 80% of the world's population depends on plants for medical aspects (17).

Plant derived EO has long been used on an as-needed basis for general health and wellness and is known to have antiviral, anti-inflammatory, immunomodulatory, antiseptic, antibacterial, analgesic, antispasmodic, antitoxic, and relaxing effects for the management of the respiratory diseases, symptoms of cancer, migraine, hypertension, arthritis, and muscle-related pain (13,14,18,19). The antiviral properties of EOs against SARS CoV-2 have been proposed due to their lipophilic characteristic, suggesting that EOs penetrate viral membranes and cause viral lysis. In addition, EO contains many active phytochemicals that can act synergistically at various stages of viral replication. Some essential oils are also often used as aromatherapy for antispasmodic, relaxation or sedation (12,13). This aromatherapy effect is reported to reduce fatigue levels and increase stamina (12). Based on existing knowledge, combined chemo-herbal (EO) could be a better and more effective approach against Covid-19 pandemic (19).

The aim of this review is to present all the evidence regarding the benefits of plant-derived EO for fatigue, whether they can be used as a therapy for fatigue associated with PASC. It is hoped that this review can help build thinking as a basis for conducting clinical trial research in the near future.

## **Methods**

Literatur search was conducted on the PubMed, Science Direct, Google Scholar, and Springer Link databases on October 15-20th, 2021, focusing on the last ten years of randomized clinical trial (RCT) research on the topic of the effect of EO on fatigue with the keywords 'Essential Oils', 'Fatigue' and 'Long Covid-19'. The evidence and other information obtained is then analyzed using PICO synthesis and presented in tabular and narrative form. The analysis is based on previous studies that have investigated the effect of EO on fatigue in several patient populations

## **Results**

The literature search carried out resulted in 11 articles that matched the topic of the review. The results of the analysis can be seen in table 1.

**Table 1. List of Evidence for Essential Oils in Treating Fatigue in Various Patient Populations**

Ref.	Study Design/Population/ Location	Plant & Most Active Compound in EO	Dose of EO And Administration	Comparison	Measurement of Fatigue	Impact on Fatigue
(13)	Double blind RCT/54 perennial allergic rhinitis Adult Patient/ Seoul, South Korea	Sandalwood (Santalol), frankincense (Alpha-pinene), and Ravensara (1,8-cineole, Alpha-terpineol)	EO dissolved in almond oil at a concentration of 0.2% (v/v). Inhale for 5 minutes twice daily for 7 days.	<b>Treatment group:</b> Mixture of Sandalwood, Frankincense, Ravensara EO in Almond Oil <b>Control group:</b> almond carrier oil (placebo)	Chalder Fatigue Scale (CFS)	Fatigue (mean±SD) <b>Treatment group:</b> Pre (35.000 ± 7.000); Post (23.741 ± 4.703) <b>Control group:</b> Pre (33.481 ± 7.678); post (27.778 ± 5.938) [Treatment group improved significantly more than the placebo group (p= 0.021)]
(17)	Double-blind RCT/52 patients with Multiple Sclerosis (MS)/Jundishapur, Iran	Evening primrose/ <i>Oenothera biennis</i> (gamma-linolenic acid)	1 g oral capsule containing Evening Primrose Oil (EPO) every 12 hours for 3 months	<b>Treatment group:</b> EPO oral capsule and MS standard treatment <b>Control group:</b> Placebo and MS standard treatment	Modified Fatigue Impact Scale (MFIS).	Fatigue (Mean) <b>Treatment group:</b> Pre (32.08); Post (11.96) <b>Control Group:</b> Pre (24.42); Post (20.69) [Significant difference between the average scores on the MFIS after treatment in both control and treatment groups (P<0.001)]
(15)	RCT/90 Hemodialysis Patient/ Kermanshah, Iran	Lavender/ <i>Lavandula angustifolia</i> Miller (Linalool and Linalyl acetate) and Orange/ <i>Citrus sinensi</i> (Linalool, Linalyl acetate and Limonen)	in each of the lavender EO and orange EO groups, 5 drops of each essence were poured on a cotton ball and pinned to the patient's collar for 30 min.	<b>Treatment group:</b> 1 group EO Lavender and 1 group EO Orange <b>Control group:</b> Distilled Water	Fatigue Severity Scale (FSS)	Fatigue (Mean± SD) <b>Treatment group:</b> Lavender group Pre (47.83±14.81); Post (30.27±13.88)* Orange Group Pre (48.8±12.8) Post (33.06±14.55)* <b>Control Group:</b> Pre (37.57±16.42); Post (34.7±15.09)** *p = 0.001 **p = 0.71
(20)	RCT/105 Hemodialysis patient/ Zahedan city, Iran	Lavender/ <i>Lavandula angustifolia</i> Miller (Linalool and Linalyl acetate)	Inhaled two drops of 5% lavender essential oil inoculated in sweet almond oil was added on a cotton ball and pinned to the subject's	<b>Treatment group:</b> 1 group Relaxation (Benson muscle relaxation techniques and 1 group EO Lavender <b>Control group:</b> Received regular	Brief Fatigue Inventor y (BFI)	Fatigue (Mean± SD) <b>Treatment group:</b> EO lavender group Pre (6.49 ± 1.11); Post (3.64 ± 0.79)* Relaxation group Pre (6.8 ± 1.45) Post (5.12 ± 1.05)*

			collar for 15-20 min with normal breathing. Procedure in the dialysis ward and at home twice a day for 4 weeks.	healthcare actions		<p>*p = 0.01  <b>Control Group:</b> Pre (6.44 ± 1.27); Post (6.21 ± 1.29)**                  **p = 0.329                  ANOVA showed that the changes in the mean score of fatigue in the aromatherapy group were significantly higher than Relaxation and Control Group (p = 0.001).</p>
(21)	RCT/60 Hemodialysis patient/Turkey	Lavender/ <i>Lavandula angustifolia</i> Miller (Linalool and Linalyl acetate)	Inhaled Lavender EO in a concentration (2-mL lavender +98-mL water [2%]) intervention time (20 min), and the number of drops (2 drops). Procedure performed during the dialysis treatment for a total of 30 days (2 or 3 times a week).	<b>Treatment group:</b> EO Lavender <b>Control group:</b> No Intervention	Fatigue Severity Scale (FSS)	<p>Fatigue Mean (SD)  <b>Treatment group:</b> Pre 41.23 (8.51); Post 35.23 (5.21)*  <b>Control Group:</b> Pre 37.60 (10.12); Post 38.46 (9.12)**                  *p = 0.001                  **p = 0.208</p>
(16)	Three-group single-blind RCT/69 Hemodialysis patient/Tehran, Iran	Lavender/ <i>Lavandula angustifolia</i> and Sweet Orange	<b>Inhalation group:</b> 1 drop of lavender and sweet orange EO were poured on a 2 × 2 cm gauze and it was attached to the shirt collar of each eligible patient for 20 min (breathe gently). Procedure performed 3x/week for eight weeks <b>Massage Group:</b> Lavender and sweet orange EO were mixed in a ratio of 1:1 Then, the mixture was diluted to a concentration of 3% using sweet almond oil. 5 mL of the compound was applied to each foot and it was massaged from the toes to the ankle.	<b>Treatment group:</b> Group 1: Lavender and sweet orange inhalation EO group, Lavender and sweet orange EO massage group <b>Control group:</b> Received the routine care services	Rhoten Fatigue Scale (RFS)	<p>Fatigue Mean (SD)  <b>Treatment group:</b> Inhalation Group Pre 5.72 (2.19); Post 8 weeks 4 (1.67); Post 16 weeks 5.19 (1.71)*                  Massage Group Pre 6.22 (2.09); Post 8 weeks 2.56 (1.87); Post 16 weeks 3.94 (1.27)*  <b>Control Group:</b> Pre 5.70 (1.70); Post 8 weeks 6.22 (1.36); Post 16 weeks 7.06 (1.29)**                  *p&lt;0.05                  **p = 0.54                  [Effects of aromatherapy massage on fatigue are stronger than the effects of inhalation aromatherapy]</p>

			Massage performed 10 minutes 3x/week for eight consecutive weeks.			
(14)	Randomized, blinded, placebo-controlled clinical trial/54 Hypothyroidism Patient/US	Leaves of peppermint EO/ <i>Mentha x piperita</i> Blend with small amount of Black pepper/ <i>Piper nigrum</i> EO, Clove bud/ <i>Eugenia caryophyllus</i> EO, White grapefruit/ <i>Citrus x paradisi</i> EO, and Bergamot/ <i>Citrus Arantium bergamia</i> EO (Limonene and Eugenol)	Three drops of the blend onto the inhaler stick (keep away 1 and 2 feet of the body) and inhale the oils for exactly 15 min. Inhaled the blend daily for 14 days.	<b>Treatment group:</b> Peppermint-based essential oil blend <b>Control group:</b> Avocado vegetable oil	Multidimensional Fatigue Symptom Inventory (MFSI)	Fatigue Mean (SD) <b>Treatment group:</b> Pre 2.27 (0.95); Post 1.00 (0.69) <b>Control Group:</b> Pre 2.27 (1.16); Post 1.85 (1.56) [Significant difference was found between the aromatherapy group and the placebo group on the global scale (p = 0.019)]
(22)	RCT/62 Hemodialysis patient/Turkey	Lavender and sweet orange oils	Lavender and sweet orange oils (1:1) were dropped to a gauze bandage, which was placed 5 cm away from under the nose for 2 min. Patients asked to take deep breaths 3x after smelling the mixture was completed.	<b>Treatment group:</b> Sweet orange + lavender oil <b>Control group:</b> No Intervention of Aromatherapy	Piper Fatigue Scale (PFS)	Fatigue (Mean± SD) <b>Treatment group:</b> Sweet Orange + Lavender Oil Group: Pre 8.22 ± 1.27; Post 3.09 ± 2.01* <b>Control Group:</b> Pre 7.25 ± 1.16; Post 7.38 ± 1.33** (*p<0.001) (**P=0.320)
(18)	RCT/54 rheumatoid arthritis Patient/Ankara, Turkey	<i>Lavandula augustifolia</i> (Linalool), <i>Juniperus communis</i> (a-Pinene), <i>Cananga odorata</i> Germacren-D), and <i>Rosmarinus officinalis</i> (1,8 cineol)	5% mixture in the ratio 3:3:2:2 in 100 mL of coconut carrier oil. EO applied topically to both knees. Procedure performed during home visit	<b>Treatment group:</b> Aromatherapy massage with EO: <i>Lavandula augustifolia</i> , <i>Juniperus communis</i> , <i>Cananga odorata</i> , and <i>Rosmarinus officinalis</i> Reflexology <b>Control group:</b> Routine care no intervention	Fatigue Severity Scale (FSS)	Fatigue (Mean± SD) <b>Treatment group:</b> Aromatherapy massage Group: Pre 5.86 ± 0.71*; Post 6 weeks 2.94 ± 1.13** Reflexology group Pre 5.58 ± 0.98*; Post 6 weeks 1.88 ± 1.18** <b>Control Group:</b> Pre 5.37 ± 0.82*; Post 6 weeks 4.41 ± 1.79** (*p=0.245) (**P=0.001)
(11)	Triple blind RCT/40 Acute	<i>Citrus aurantium</i> EO (Limonene, Myrcene,	three drops of <i>C. aurantium</i> EO on absorbable patches	<b>Treatment group:</b> <i>C. aurantium</i> EO	Multidimensional	Fatigue (Mean± SD) <b>Treatment group:</b> Pre 77.12 ± 22.86;

	myocardial infarction/Helsinki, Finland	Camphene, Pinene, Ocimene and Cymene)	connected to the inside of the patient's oxygen masks and they were asked to inhale the aroma for 20 min. (twice daily (10–11 AM and 6–7 PM) on two consecutive days.	<b>Control group:</b> Sunflower oil 12%	Fatigue Inventor y (MFI-20)	Post 26.4 ± 17.85* <b>Control Group:</b> Pre 71.13 ± 8.69; Post 71.13 ± 32.42* (*P < 0.001)
(12)	Single blinded three arm-RCT/40 Heart Failure NYHA class 2 or 3/Tabriz,Iran	Lavender/ <i>Lavandula augustifolia</i> (Linalool and Linalyl acetate)	a cotton ball impregnated with 2 drops of pure (100 %) Lavender EO was pinned on the patient pillow cover at the bedtime (10:30 pm) for 15 days and was taken in the morning after the patient woke up.	<b>Treatment group:</b> Group 1: C. Lavender EO Group 2: Sedamin <b>Control group:</b> Routin Care	Fatigue Severity Scale (FSS)	Fatigue (Mean± SD) <b>Treatment group:</b> Sedamin Group Pre 5.44 ± 0.80*; Post 1 week 4.2 ± 0.96**; Post 2 weeks 3.41 ± 0.60** Lavender EO group Pre 5.16 ± 0.63*; Post 1 week 4.1 ± 0.52**; Post 2 weeks 3.40 ± 0.42** <b>Control Group:</b> Pre Pre 5.13 ± 0.64*; Post 1 week 5.04 ± 0.54**; Post 2 weeks 5.85 ± 0.39** (*p=0.215) (**P<0.0001)

## **Discussion**

### **Post Acute Sequele Covid-19**

Post Acute Sequele Covid 19 (PASC) refers to the persistence of symptoms and abnormalities for more than 12 weeks from the acute onset of Covid-19 and is not associated with a specific disease diagnosis (3). Several authors refer to the PASC conditions as "Long Covid-19", "long-haul COVID-19" and "post covid-19 syndrome" (1,2,7,8).

Patients with PASC generally experience both physical and psychological symptoms. Physical symptoms include fatigue, headache, shortness of breath, coughing, chest pain, skin rash, changes in smell and taste, muscle and joint pain. while psychological symptoms include "brain fog", cognitive disturbances, sleep disturbances, and mood changes (1,8). Several studies have shown that most survivors experience symptoms of fatigue predominantly (4–6).

### **Pathophysiology of Fatigue in PASC**

Fatigue that occurs after infection of SARS (2003), MERS (2012), Epstein-Barr Virus (EBV), and other viral causes generally display the similar manifestations as SARS-CoV-2. Although the causative pathogen is different, each disease will cause a similar inflammatory response at the site of infection. The inflammatory response can be the same "stressors" as most causes of fatigue (such as emotional, sleep deprivation, physical or mental overexertion) using both humoral and neural routes. Angus M et al. have hypothesized that stressors, both viral and non-viral, can activate stress centers in the brain (hypothalamic paraventricular nucleus) (10).

Islam et al. also reviewed various cases of post-infectious fatigue and suggested that elevated levels of cytokines (TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and others) in Covid-19 patients contributed to the development of long-term fatigue symptoms (23). It has been hypothesized that proinflammatory cytokines and neurotoxic molecules in the acute condition of Covid-19 will be released in response to microglia cells and astrocytes which then cause neuroinflammation of the hypothalamic structures and limbic system. Although this hypothesis requires confirmation of brain-focused studies in search of a brain-signature for fatigue in PASC (10).



Hyperinflammation in acute Covid-19 causes multiorgan damage. Long-term symptoms in PASC can be caused by this. Most of the evaluations performed on PASC patients after discharge from the hospital had abnormalities in the lung parenchyma, small airway disease and acute kidney injury. These biologic factors are likely to play a role in some patients. SARS Cov-2 also demonstrated the ability to persist on certain tissues after acute infection. Some infected patients were reported not to be completely clear of the virus over a long period, with the discovery of inert RNA that should have been successfully eliminated by the body's immune system. Inert RNA deposited in certain tissues is suggested to trigger the reactivation of SARS CoV-2 (24).

A cohort study in Wuhan, China showed that over a period of 6 months from acute onset, 23% of COVID-19 survivors also complained of anxiety and depression (5). This psychological stress is generally caused by self-isolation, broken routines, loneliness, lack of family support (maintaining distance to prevent virus transmission), job loss, and due to lockdown. Psychological stress then becomes a circle that triggers fatigue (6,25).

### **Plant Derived-Essential Oils as Antivirus**

Essential oils (EO) consist of a complex mixture of volatile phytochemicals from a diverse class including monoterpenes, phenylpropanoids and sesquiterpenes. EO is active against various viruses, such as human herpesvirus (HSV), influenza virus (IFV), yellow fever virus, human immunodeficiency virus (HIV), and bird flu. Viruses with envelopes generally respond sensitively to EO because of their lipophilic characteristic, so they can penetrate the lipid bilayer membrane and cause viral lysis. The EO obtained from Citrus bergamia, Eucalyptus globulus, with its active compounds such as eugenol and citronellol are capable against IFV. Carvacrol and its thymol isomer contained in oregano can suppress viral host cell fusion through by depletion of HIV-1 envelope membrane cholesterol, thereby blocking viral entry into the host system (19). In addition, carvacrol was able to reduce alveolar enlargement, trigger macrophage recruitment, and production of IL-1 $\beta$ , IL-6, IL-8, and IL-17 in bronchoalveolar lavage fluid. In addition, carvacrol has also been reported to have antiviral activity against human respiratory virus (HRSV), human rotavirus (HRV), and HSV-1 (26).

The active component 1,8-cineole from various plants has been proposed to have the ability to inactivate free influenza A viruses and disrupt the structure of the viral

envelope. 1,8-cineole has also been shown to protect mice from the HSV-2 virus. Eugenol has been shown to have antiviral activity against HSV-1 and HSV-2. also found to inhibit leukocyte recruitment into the lung and downregulate the expression of pro-inflammatory cytokines (IL-6 and TNF-). EO have long been known to have antiviral activities and proposed to be able to fight SARC-CoV-2. In general, the antiviral activity of EO is by direct mechanism of action on free virus, interfere various phases including attachment, penetration, intracellular replication, and release from host cells (19).

### **Possible Role of EO against Post Viral Fatigue**

Previous studies in Table 1 have shown that aromatherapy can effectively control symptoms such as fatigue, anxiety, stress and insomnia. Various plant derived essential oils such as Lavender, Sweet Orange and a mixture of both (12,15,16,20–22); Lavender mixed with Cananga, Juniper, and Rosemary (18); Sandalwood mixed with Frankincense and Ravensara (13); Evening Primrose (17); leaves of Peppermint mixed with Black Pepper, Clove Bud, White Grapefruit and Bergamot (14) have been shown to reduce fatigue levels compared to control group in several patient populations, including perennial allergic rhinitis, multiple sclerosis, hemodialysis, hypothyroidism, rheumatoid arthritis, acute myocardial infarction, heart failure.

*Lavandula angustifolia* known as lavender contains linalool and linalyl acetate, the same as in the *Cananga* plant which stimulate the parasympathetic nerves and can improve sleep, reduce muscle fatigue, improve symptoms and improve quality of life. EO plays a role in modifying mental stress and helping the body maintain its homeostasis (15). These findings suggest that inhalation of aromatherapy oils can be used as effective and safe treatment to reduce symptoms and improve quality of life (13). Another aromatic substance is sweet orange EO which is known to produce calm and reduce depression and stress. Inhaled aromatherapy and aromatherapy massage significantly reduce fatigue (16).

The compound of 1,8-cineole, alpha-terpineol and alpha-pinene from Lavender, Frankincense, Ravensara, Juniper and other EO-producing plants has been shown to reduce the production of proinflammatory mediators (13). Evening Primrose is also known to contain a lot of linoleic acid and  $\gamma$ -linolenic acid which has been shown to

suppress inflammation mediators such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (27). The effects of aromatherapy oils can also be explained by their role in correcting imbalances in the autonomic nervous system. Santalol contained in Sandalwood EO is associated with an increase in the parasympathetic nervous system for its relaxing and sedative effects. Numerous studies have also shown that aromatherapy EO including lavender, rosemary, and sandalwood help improve sleep and reduce fatigue (13).

Inhaled aromatherapy EO distilled from the leaves of *Mentha plus Piperita* (Peppermint EO) has been found to reduce fatigue and increase stamina in the general population. Peppermint EO dominates the literature on aromatherapy for fatigue, aromatherapists also use other EO, such as those from the Citrus plant and Black Pepper, as a traditional approach to reducing fatigue (14). The benefits that come from inhalation may not be immediately apparent, but require some short-term exposure over a period of time (16).

### **The Mechanism of Action of EO in the Management of Post Viral Fatigue**

The use of EO as aromatherapy is one of the complementary therapeutic modalities that is widely used throughout the world to manage various disease symptoms. Aromatherapy is a type of therapy that utilizes EO produced by plants to provide pharmacological or physiological effects through the inhalation or skin absorption (18).

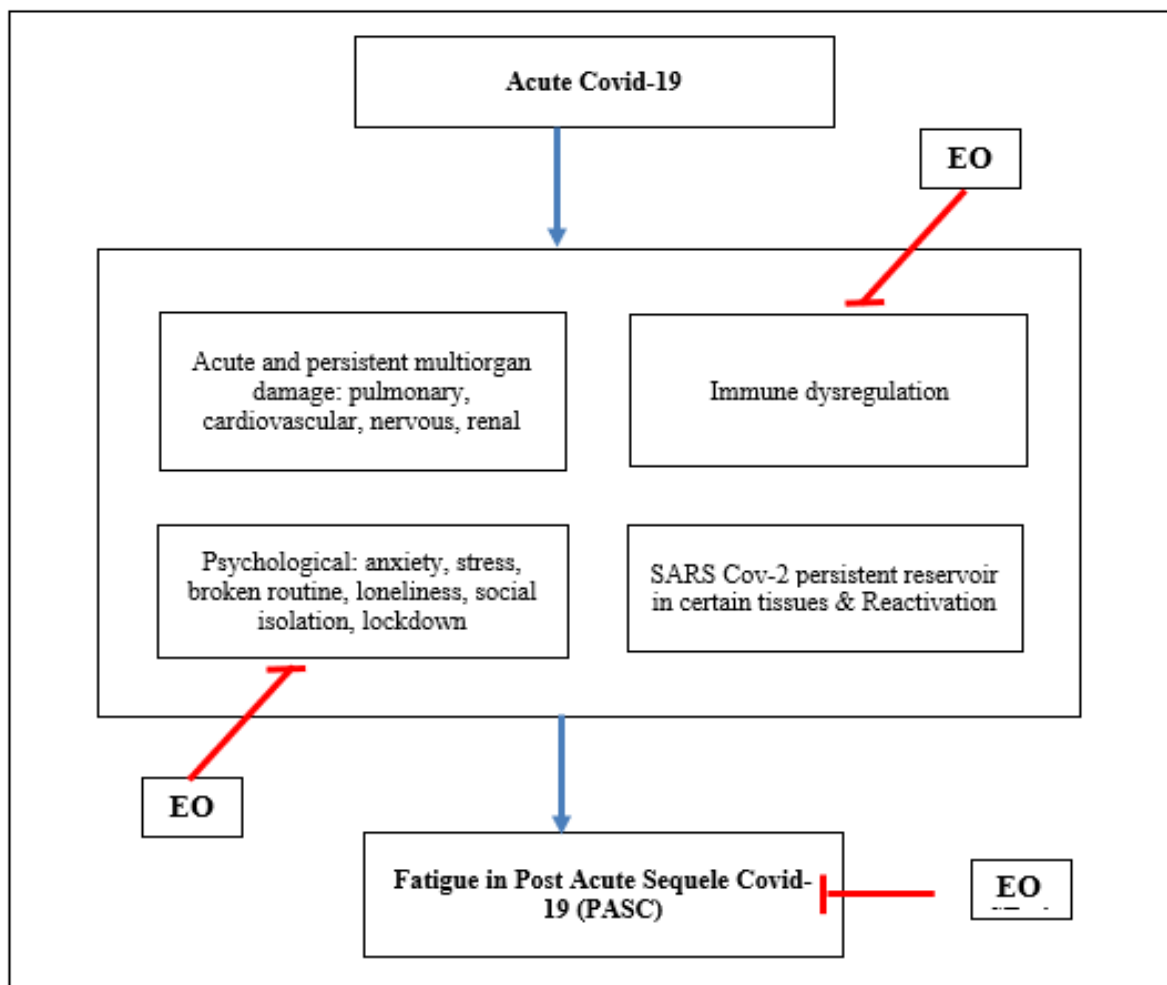
When the EO used in aromatherapy are inhaled, several different molecules contained in EO stimulate the olfactory nerve cells and are then transferred to the limbic system in the brain via the olfactory route in the nose. The limbic system is then activated and triggers the release of neurotransmitters such as endorphins, enkephalins, serotonin and noradrenaline. The amygdala and hippocampus areas of the limbic system are the most important areas for processing scent (24). Administration of EO by inhalation has a refreshing effect, this will affect mental and physical stability so that it can reduce depression, stress, and chronic fatigue (24,25). EO have also been used in massage because of their rapid absorption into the body (18).

Lavender belonging to the *Lamiaceae* family is considered to have the same effect as diazepam. Diazepam is known to decrease external emotional excitability by increasing inhibitory neurons containing aminobutyric acid in the amygdala. The limbic system provides sedative and relaxing effects and reduces anxiety by interacting with the cerebral cortex and influencing heart rate, breathing, blood pressure, stress, and hormone levels (11,12,26).

*Citrus aurantium* (*C. aurantium*) EO contains active terpene compounds that provide sedative and anti-anxiety effects. Its mechanism of action as an anti-anxiety agent is probably

mediated by the involvement of 5-HT1A receptors after repeated oral administration. Previous research concluded that aromatherapy with *C. aurantium* extract was as effective as diazepam in reducing preoperative anxiety. Although more evidence is needed to come to a firm conclusion about the efficacy of aromatherapy in reducing anxiety (11).

Inhalation has an invigorating effect and improves concentration by being absorbed in the blood and lungs through the nose and affecting mental and physical stability. The sense of smell activates the limbic system and hormones, which can reduce depression, stress, and chronic fatigue by increasing emotional responses (25). The suggested mechanism of EO against Fatigue can be seen in Figure. 1.



**Figure 1. Schematic of the Potential Role of EO in the Management of Fatigue in PASC (6,13,16,20–22,26).**

### Essentials Oils and Covid-19

The antiviral effect of EO against Covid-19 has been reported by Sharma AD et al. by the molecular docking method. Jensenone an active phytochemical that was isolated from *Eucalyptus jensenii* EO showed the formation of complexes with the Mpro SARS CoV 2 protein by molecular docking through hydrophobic interactions with PRO52, ALA7, TRP207, LEU29, PRO184, and TRY126; hydrogen interactions with, L30, V18, and T16, M4D10; and ionic interactions with, HIS163, ARG38, ASP34, and LYS3. Another active componen of *Eucalyptus* EO (1,8-cineole/eucalyptol) showed that it could bind to Mpro protein resulting in disturb viral reproduction. The Mpro-eucalyptol complex was shown to form strong hydrogen and hydrophobic interactions (28).

### Conclusion

Based on the available evidence, plant-derived EO may have a role and be useful for reducing post viral fatigue symptoms in PASC.

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