Inflammopharmacology
https://doi.org/10.1007/s10787-020-00744-0

REVIEW

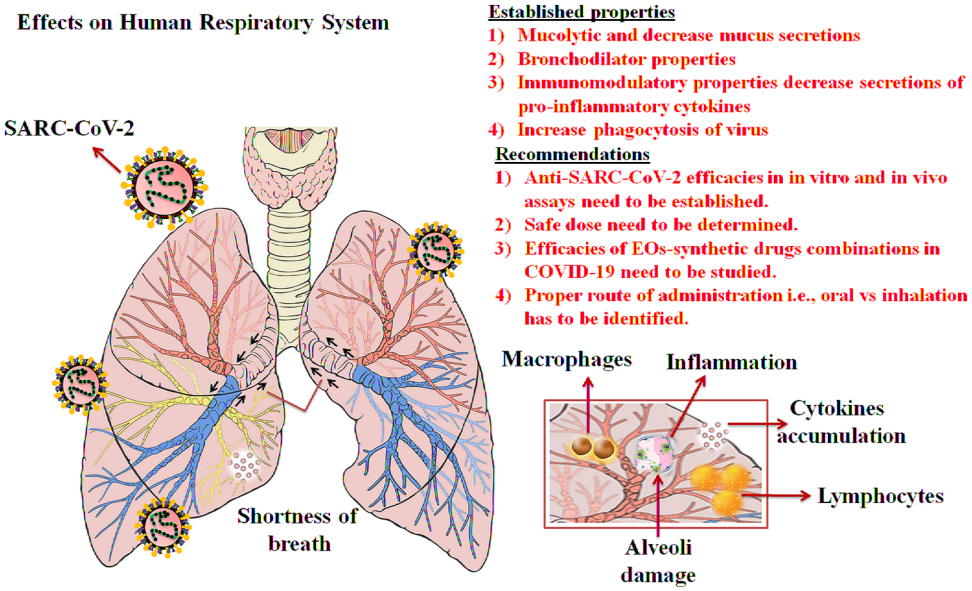
COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties

Muhammad Asif[1] · Mohammad Saleem[2] · Malik Saadullah[3] · Hafiza Sidra Yaseen[3] · Raghdaa Al Zarzour[4]

Received: 19 June 2020 / Accepted: 31 July 2020

Abstract

Coronavirus disease of 2019 (COVID-19) has emerged as a global health threat. Unfortunately, there are very limited approved drugs available with established efficacy against the SARs-CoV-2 virus and its inflammatory complications. Vaccine development is actively being researched, but it may take over a year to become available to general public. Certain medications, for example, dexamethasone, antimalarials (chloroquine/hydroxychloroquine), antiviral (remdesivir), and IL-6 receptor blocking monoclonal antibodies (tocilizumab), are used in various combinations as off-label medications to treat COVID-19. Essential oils (EOs) have long been known to have anti-inflammatory, immunomodulatory, bronchodilatory, and antiviral properties and are being proposed to have activity against SARC-CoV-2 virus. Owing to their lipophilic nature, EOs are advocated to penetrate viral membranes easily leading to membrane disruption. Moreover, EOs contain multiple active phytochemicals that can act synergistically on multiple stages of viral replication and also induce positive effects on host respiratory system including bronchodilation and mucus lysis. At present, only computer-aided docking and few in vitro studies are available which show anti-SARC-CoV-2 activities of EOs. In this review, role of EOs in the prevention and treatment of COVID-19 is discussed. A discussion on possible side effects associated with EOs as well as anti-corona virus claims made by EOs manufacturers are also highlighted. Based on the current knowledge a chemo-herbal (EOs) combination of the drugs could be a more feasible and effective approach to combat this viral pandemic.



Keywords Essential oils · SARC-CoV-2 · Immunomodulatory · Docking studies

Extended author information available on the last page of the article

Published online: 14 August 2020

Introduction

The 2019 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged as a new respiratory pathogen and is responsible for large-scale morbidities and mortalities around the globe. It is caused by a single positive-stranded RNA virus from the coronavirus (CoV) family of *Coronaviridae* (Ludwig and Zarbock 2020). This family is composed of four genera out of which α- and β-CoV can infect mammals including humans (Ludwig and Zarbock 2020). These two strains are reported to be originated from *Rousettus leschenaultia*, i.e. a bat species (Lau et al. 2010; Valencia 2020). SARS-CoV-2 is identified as β-CoV (Valencia 2020) and is responsible for coronavirus disease 2019 (COVID-19). These viruses are wrapped in host cells-derived lipid membranes in which viral surface proteins are embedded. One of these surface proteins known as spike [S] protein protrudes out of membranes and give a characteristic crown/halo-like appearance to the virus when observed under the electron microscope hence, named coronavirus (Latin word meaning: garland/crown) (Ludwig and Zarbock 2020). Once the virus gains entry into the respiratory tract, SARS-CoV-2 causes damage to epithelial cells of the airways making lungs unable to clear dirt and mucus which can lead to pneumonia. Clinical symptoms of COVID-19 include fever (approx. 99% of cases), chills, dry cough (observed in approx. 59% cases), sputum production (observed in approx. 27% cases), fatigue (observed in approx. 70% of cases), lethargy, arthralgia, myalgia (observed in approx. 35% cases), headache, dyspnoea (approx. in 31% of cases), nausea, vomiting, anorexia (approx. 40% cases), and diarrhoea (approx. 2% cases) (Yang et al. 2020). In the extreme cases, patients experience a dramatic increase in the levels of pro-inflammatory chemokines and cytokines including IL-6 and TNF-α, a condition known as "cytokine storm". This leads to the development of acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and even death (Yang et al. 2020). There is no clear, unified, and effective treatment plan for COVID-19 but various approaches are being tried depending upon various sign and symptoms of individual patients. Inhibition of virus entry into the host cell via affecting glycosylation of ACE2 receptors in pulmonary cells as well as through inhibition of S protein priming and endocytosis (Gao et al. 2020a; Hoffmann et al. 2020), blockage of RNA-dependent RNA polymerase thus halting viral replication (Gao et al. 2020b), and increasing pH of pulmonary cells (alkalinisation) and endosomes thus disrupting viral replication as well as endosomes functions are among the few mechanisms through which currently studied drugs are known to act against SARS-CoV-2 (Valencia 2020). Use of convalescent plasma and IL-6R blocker tocilizumab (a recombinant humanized anti-human IL-6 receptor monoclonal antibody) either alone or in combination with different classes of drugs are also under clinical trials and have shown clinical improvements (Girija et al. 2020; Rothan and Byrareddy 2020; Yang et al. 2020). Currently, there is no vaccine available for SARS-CoV-2, but clinical trials are on the way to test the efficacies of multiple newly formulated vaccines; however, this will take some time to develop.

An in vitro study conducted by Hoffmann and colleagues revealed that SARC-CoV-2 depends on cellular serine protease (TMPRSS2) for S proteins priming which are known to interact with human ACE2 receptors in the lungs and facilitate entry into the cells. Data of this study showed that blockage of TMPRSS2 by camostat mesylate inhibited infection of cells in in vitro assays. Moreover, it was also found that SARC-CoV-2 viruses also utilize endosomal cysteine proteases, cathepsin B and L (CatB/L), for S protein priming (Hoffmann et al. 2020). Wang and colleagues used clinical isolates of SARC-CoV-2 (2019-nCoV) to evaluate the anti-SARC-CoV-2 efficacy of five FDA-approved drugs, i.e. ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705). African green monkey kidney cells (Vero E6) were exposed to SARC-CoV-2 in the presence of different concentrations of these drugs. RT-PCR techniques were used to quantify viral load by copy number estimation in the cell supernatants. Among these drugs, remdesivir, an adenosine analogue and chloroquine, were found to be highly effective in blocking the infection of African green monkey kidney cells (Vero E6, both drugs) and human lung cancer cells (Huh-7, remdesivir only) by SARC-CoV-2 (Wang et al. 2020). Chloroquine (CQ) and hydroxychloroquine (HCQ) have been shown to block the release of the viral genome by inhibiting the transport of SARS-CoV-2 from early endosomes (EEs) to endolysosomes (ELs). Moreover, CQ has been known to elevate the pH of the endosomes, thus halting endosomal maturation and ultimately failure in the transport and release of SARC-CoV-2. HCQ has also been proposed to halt the production of pro-inflammatory cytokines in COVID-19 patients (Liu et al. 2020).

Essential oils (EOs) are comprised of a complex mixture of volatile phytochemicals from diverse classes including monoterpenes, sesquiterpenes, and phenylpropanoids. Numerous researchers have studied the antibacterial, antifungal, antioxidant, and antiviral properties of EOs. These EOs are found to be active against a wide variety of viruses, such as influenza virus (IFV), human herpesviruses (HSV), human immunodeficiency virus (HIV), yellow fever virus, and avian influenza (Ma and Yao 2020). HSV (-1 and -2) are known to cause many life-threatening diseases in humans and are one of the major reasons for mortality in immunocompromised patients. HSV-1 is majorly responsible

for HSV-induced lesions in the oral cavity and epidermis, while HSV-2 causes genital herpes, a sexually transmitted disease. An in vitro study conducted by Schnitzler and colleagues showed that lemon balm oil inhibited plague formation of HSV-1 and HSV-2 viruses in a dose-dependent fashion. Moreover, at higher concentrations it abolished the viral infectivity almost completely (Schnitzler et al. 2008). Pre-treatment with EOs obtained from *illicium verum, Melaleuca alternifolia*, *Leptospermum scoparium*, and *Matricaria recutita* was found to inhibit the infective ability of acyclovir-sensitive and -resistant HSV stains, indicating the immense antiviral potential of EOs (Schnitzler et al. 2010). Anti-IFV properties of liquid and vapour forms of EOs obtained from various plant species were studied using in vitro techniques. Vapours of EOs obtained from *Citrus bergamia*, *Eucalyptus globulus*, and their isolated compounds, i.e. citronellol and eugenol showed rapid anti-IFV actions. While in liquid form, EOs obtained from *Cinnamomum zeylanicum*, *Citrus bergamia*, *Cymbopogon flexuosus*, and *Thymus vulgaris* showed better anti-IFV properties i.e. 100% inhibitory activity at 3.1 µL/mL as compared with others. Vapour form of EOs was also found to be safe against monolayers of epithelial cells. The study concluded that EOs in vapour form could benefit people suffering from influenza (Vimalanathan and Hudson 2014). Carvacrol and its isomer thymol obtained from oregano have been shown to inhibit viral host cell fusion via depletion of viral cholesterol from the HIV-1 envelope membranes, thus blocking the entry of the virus into the host system (Mediouni et al. 2020).

Owing to the lipophilic nature of EOs, these have the potential to intercalate into the lipid double layer of the viral envelope. Subsequently, the fluidity of the membranes is changed and, at a higher concentration, the membranes are even ruptured (Wink 2020). Major mechanisms through which EOs induce antiviral actions are, direct actions on free viruses, inhibition of steps involved in virus attachment, penetration, intracellular replication, and release from host cells and inhibition of vital viral enzymes (Ma and Yao 2020; Schnitzler et al. 2010). Keeping in view the diverse antiviral actions of EOs, various claims were made by the EOs manufacturers/suppliers as an effective therapy against COVID-19. In this regard, research activities were conducted to check the anti-SARC-CoV-2 efficacies of EOs. The current review compiles available scientific information about the possible beneficial effects of EOs in COVID-19.

Search methodology

Selection criteria for studies

The current review provides precise and comprehensive information on the essential oils and their possible contribution in the prevention and treatment of COVID-19. All available information was collected via an electronic search of different scientific sources including PubMed (https://www.pubmed.ncbi.nlm.nih.gov), ScienceDirect (https://www.sciencedirect.com), Google Scholar (https://www.googlescholar.com), Scientific Electronic Library Online (SciELO) (https://www.scielo.org), Cochrane library (https://www.cochranelibrary.com/), and clinical trials database (https://www.clinicaltrials.gov). The study database encompassed articles of peer-reviewed journals, books, thesis, dissertations, various patents, and supplementary reports covering anti-SARC-CoV-2 properties of traditionally used essential oils. The authors opted the following keywords to find relevant studies: "essential oils", "antiviral", "COVID-19", "SARC-CoV-2", "bronchodilation", "immunomodulatory'', "anti-inflammatory'', "corona virus''. These terms were used alone or in combination using Boolean operators ("and", "or", "not"). Essential oils having scientifically established antiviral activities against SARC-CoV-2 in in vitro, docking models, or in clinical settings were selected for reporting. Essential oils having antiviral activities against other viruses and lacking any scientific evidence against SARC-CoV-2 were excluded.

Results and discussion

Enveloped viruses are known to respond sensitively to essential oils (Schnitzler et al. 2010) which formed the basis of this work.

Eucalyptus oil

Essential oils obtained from eucalyptus (*Eucalyptus globulus*) are traditionally used to treat various respiratory ailments including pharyngitis, bronchitis, and sinusitis. Eucalyptus oil and its active constituent, 1,8-cineole have been shown to exhibit muscle relaxant effects by decreasing smooth muscle contractions of airways induced by different agents (Bastos et al. 2009; Coelho-de-Souza et al. 2006). Moreover, clinical studies have indicated that inhalation of cineole (extracted from eucalyptus) exerted anti-inflammatory (by blocking cytokines release) and analgesic effects; hence, it can be effectively used in COPD and asthmatic patients (Juergens et al. 2020). Eucalyptus oil is reported to have in vitro antiviral activities against various strains of viruses including enveloped mumps viruses (MV) and herpes simplex viruses (HSV-1 and HSV-2) (Lau et al. 2010). Brochot and colleagues also reported the antiviral activities of eucalyptus oil and its active constituent, i.e. 1,8-cineole (eucalyptol) against influenza A (H1N1) virus in in vitro assays. Both essential oil and 1,8-cineole were proposed to inactivate free influenza A virus and disrupt

the envelope structures of virus (Brochot et al. 2017). 1,8-cineole is also shown to protect mice against the HSV-2 virus (Bourne et al. 1999). Having established the antiviral activity of eucalyptus oil and eucalyptol against respiratory viruses, multiple researchers have attempted to explore the antiviral efficacy of eucalyptus oil and its active ingredients against SARC-CoV-2 using in vitro assays and molecular docking techniques. Sharma and colleagues used molecular docking techniques to study the effects of jensenone, one of the active constituents of eucalyptus oil, on viral proteinase (Mpro/3CLpro). Data obtained showed that jensenone formed complex with Mpro via hydrophobic interactions with ALA7, PRO52, TRP207, LEU29, TRY126, and PRO184; hydrogen bond interactions with M4, V18, L30, D10, and T16; and ionic interactions with LYS3, ASP34, ARG38, and HIS163 (Sharma and Kaur 2020a). Sharma and colleagues also predicted (preprints) the anti-proteinase efficacy of 1,8-cineole (eucalyptol), another active constituent of eucalyptus oil, using molecular docking techniques. Data obtained showed that 1,8-cineole can bind with Mpro and thus can inhibit viral reproduction. Mpro/eucalyptol complexes were shown to form hydrophobic interactions, hydrogen bond interactions, and strong ionic interactions, respectively (Sharma and Kaur 2020b). However, in vitro enzymes assays, and animal models are suggested to confirm the efficacy of jensenone/ 1,8-cineole against SARC-CoV-2 proteinase. Among these two compounds, 1,8-cineole is more extensively studied for its pharmacological potentials against various respiratory ailments (Juergens et al. 2003). 1,8-cineole (eucalyptol) is one of the components of Vicks VapoRub™ which is known to have nasal decongestant effects when applied to nose or inhaled as vapours in warm water. Juergens and colleagues conducted a double-blind clinical trial to check the efficacy of 1,8-cineole in steroid-dependent bronchial asthma patients. Data of long-term studies showed 36% reduction of steroid dose in asthma patients receiving 1,8-cineole than placebo control group. 1,8-cineole was suggested to have profound bronchial anti-inflammatory activity in severe asthmatic patients (Juergens et al. 2003). A recent review highlighted the favourable safety and efficacy profile of eucalyptol (1,8-cinoele) in numerous multi-centre, double-blinded, and randomized clinical trials conducted in Germany in patients having acute and chronic respiratory conditions including rhinosinusitis, bronchitis, COPD, and asthma, respectively (Juergens et al. 2020).

A study conducted by Merad and colleagues showed that almost all COVID-19 positive patients have lung abnormalities. Abnormal and overactive inflammatory responses to SARS-CoV-2 are proposed to be the major causes of disease severity and death in COVID-19 patients. This hyper-inflammatory state is associated with increased levels of circulating cytokines, profound lymphopaenia, and substantial mononuclear cell infiltration in the lungs and other organs including heart, spleen, lymph nodes, and kidneys. The systemic cytokine profiles observed in patients showed increased production of cytokines such as IL-6, IL-7, and tumour necrosis factor (TNF) and many other pro-inflammatory cytokines (Merad and Martin 2020). Various in vitro and ex vivo studies were conducted to study the effects of eucalyptus oils and eucalyptol treatments on monocytes and macrophage recruitment in response to lung inflammation and infections. Data of these studies demonstrate marked immunomodulatory properties of both eucalyptus oil and its active ingredient, i.e. eucalyptol. Both treatments reduced the release of pro-inflammatory cytokines from monocytes and macrophages, but their phagocytic properties were not halted (Juergens et al. 2020; Sadlon and Lamson 2010). Eucalyptol is also known to have mucolytic and bronchodilatory properties (Juergens et al. 2020). Interestingly, eucalyptus oil has also been shown to have disinfection properties and inhibited the growth of viruses on various utensils and filter devices (Usachev et al. 2013). Taken together, data from both preclinical and clinical trials point towards the promising therapeutic potential that resides in eucalyptus oil and its active constituent, i.e. eucalyptol in the prevention and treatment of COVID-19. Therefore, further studies are urgently warranted in this regard.

Garlic oil

Garlic has been used as a medication to treat common cold, influenza, and other kinds of infections for centuries. Garlic oil was chemically analysed by the GC–MS method and 18 compounds were identified, out of which allyl disulphide (28.4%), allyl trisulphide (22.8%), allyl (*E*)-1-propenyl disulphide (8.2%), allyl methyl trisulphide (6.7%), and diallyl tetrasulphide (6.5%) were identified as the main constituents of garlic essential oil. 17 compounds were studied for their activities against ACE2 protein and viral main protease (Mpro/6LU7) of SARC-CoV-2. ACE2 is involved in the viral invasion of host cells, while Mpro is involved in viral replication. All the 17 compounds studied showed interactions with host protein (ACE2) as well as with viral proteases, indicating that garlic oil has great potential to treat COVID-19 patients (Thuy et al. 2020). Virus-induced oxidative stress plays a critical role in the viral life cycle as well as in the pathogenesis of viral diseases. This leads to the activation of host antioxidant pathways including nuclear factor erythroid 2p45-related factor 2 (Nrf2) (Lee 2018). Nrf2 transcription factor is known to control the expression of various genes involved in antiviral actions (McCord et al. 2020). A study conducted by McCord and colleagues showed that potent Nrf2 activation by PB125® compound

downregulated ACE2 and TMPRSS2 mRNA expression in human liver-derived HepG2 cells. Both of these proteins are recognized to play a major role in the entry of SARS-CoV-2 into host cells. Furthermore, treatment of primary human pulmonary artery endothelial cells with PB125® downregulated 36 genes controlling the expression of majority of cytokines identified in the "cytokine storm" during COVID-19 severe cases. The authors suggested that Nrf2 activation may significantly decrease the intensity of the cytokine storm in COVID-19 patients (McCord et al. 2020). Diallyl sulphide (DAS), one of the active constituents of garlic, has been shown to induce Nrf2 activation in lung MRC-5 cells. Activated Nrf2 after translocation into nuclei triggered p38/ERK-signalling pathways and is thus suggested to prevent oxidative stress-induced lung injury (Ho et al. 2012; Patel et al. 2018). Thus, on the basis of these docking and in vitro studies, it is proposed that garlic essential oils and their isolated constituents, especially DAS, have potential to prevent the entry of virus into host cells as well as to activate molecular antioxidant pathways that decrease the secretions of culprit pro-inflammatory cytokines.

(*E*,*E*)-α-farnesene, (*E*)-β-farnesene, and (*E*,*E*)-farnesol

A study conducted by Silva and colleagues screened the potencies of 171 essential oil components against different SARC-CoV-2 proteins including main viral proteases (Mpro), endoribonuclease (SARS-CoV-2 Nsp15/NendoU), ADP-ribose-1-phosphatase (SARS-CoV-2 ADRP), RNA-dependent RNA polymerase (SARS-CoV-2 RdRp), spike proteins (SARS-CoV-2 rS), and human angiotensin-converting enzyme (hACE2) protein using molecular docking techniques (Silva et al. 2020). Among the 171 screened compounds, (*E*,*E*)-α-farnesene, (*E*,*E*)-farnesol, and (*E*)-nerolidol showed better binding with SARS-CoV-2 Mpro, indicating that these essential oil components when given alone and in a mixture can inhibit viral replication. Non-structural protein 15 (Nsp15), an endoribonuclease of SARS-CoV, is required for successful viral infection (Bhardwaj et al. 2006). (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, (*E*,*E*)-farnesol, and (*E*)-nerolidol showed best binding scores; with Nsp15. RNA replication is catalysed by RNA-dependent RNA polymerase (RdRp) in RNA viruses and is crucial step for viral replication; thus, making it a viable target for antiviral chemotherapy (Shuai et al. 2006). The best docking scores against RdRp were obtained for (*E*,*E*)-farnesol. The SARS-CoV-2 spike protein helps in the attachment of the viral cell to human cell via interaction with angiotensin-converting enzyme 2 (ACE2) proteins present on host cells, making this interface a promising target to prevent binding of SARS-CoV-2 rS to human respiratory cells (Zhang et al. 2020). Best binding with human ACE2 was observed with α-bulnesene, eremanthin, (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, (*E*,*E*)-farnesol, (*E*)-nerolidol, β-sesquiphellandrene, and (Z)-spiroether, respectively. In case of SARS-CoV-2 spike proteins, comparatively better binding was observed with (*E*)-cinnamyl acetate, eremanthin, (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, (*E*,*E*)-farnesol, and geranyl formate, respectively. Overall, (*E*,*E*)-α-farnesene, (*E*)-β-farnesene, and (*E*,*E*)-farnesol showed better binding potentials with target proteins. These phytochemicals are present in variable quantities in essential oils obtained from different plants which can be used used to treat COVID-19 but data from well-established preclinical and clinical studies is required.

Anethole, cinnamaldehyde, carvacrol, geraniol, cinnamyl acetate, L-4-terpineol, thymol, and pulegone

An in silico study conducted by Kulkarni and colleagues evaluated the efficacy of a variety of EOs present in diverse plant families to block the S1 (also called receptor binding domain, RBD) subunit of spike (S) proteins of SARC-CoV-2. S1 protein is known to be involved in the interaction with host ACE2 receptors. In silico study findings revealed that among the evaluated EOs, anethole, cinnamaldehyde, carvacrol, geraniol, cinnamyl acetate, L-4-terpineol, thymol, and pulegone showed better potential to inhibit S1 subunit of S proteins. Cinnamaldehyde was found to have more favourable binding properties as compared with other compounds (Kulkarni et al. 2020). Another molecular docking study conducted by Elfiky evaluated the activity of cinnamaldehyde and thymoquinone against COVID-19 and SARS CoV RNA-dependent RNA polymerases (RdRps). Data obtained showed that both compounds have low binding affinities with RdRps (Elfiky 2020). Taken together, it is proposed that cinnamaldehyde may block the attachment of SARC-CoV-2. Further in vitro and in vivo studies, however, are required to establish this. The protective effects of cinnamaldehyde in lipopolysaccharide (LPS)-induced acute lung injury (ALI) mice model were evaluated by Huang and colleagues. Treatment with cinnamaldehyde was shown to markedly reduce lung wet/dry ratio and pulmonary oedema in mice. Cinnamaldehyde also significantly inhibited neutrophils, macrophages, and total cell number in the bronchoalveolar lavage fluid. Treatment with cinnamaldehyde decreased the levels of inflammatory cytokines such as TNF-α, IL-6, IL-13 and IL-1β, respectively (Huang and Wang 2017). This data along with findings of the above in silico studies give a clue about the possible beneficial role of cinnamaldehyde in COVID-19, but detailed in vitro and in vivo studies are required to establish its efficacy.

Eugenol, menthol, and carvacrol

Silva and colleagues used molecular docking techniques to screen the anti-SARC-CoV-2 efficacies of eugenol, menthol, and carvacrol, major components of EOs, against various proteins targets of SARC-CoV-2. Docking scores revealed that these compounds have binding affinities towards SARC-CoV-2 spike protein, main protease (Mpro), RNA dependent RNA polymerase and human ACE-2 proteins, respectively (Silva et al. 2020). Another in silico study conducted by Kumar and colleagues evaluated the binding potential of carvacrol against SARC-CoV-2 main protease (Mpro) and showed that it has the potential to inhibit Mpro and thus can halt viral replication (Kumar et al. 2020).

Plant extracts rich in menthol have been used in traditional medicine in Asia for the treatment of respiratory ailments since centuries. Menthol has been reported to provide symptomatic relief from nasal congestion associated with rhinitis and the sensation of dyspnoea associated with chronic obstructive pulmonary disease by its specific interaction with a cold-menthol-sensitive receptor (CMR1) located on trigeminal nerve endings (Eccles 2003). Menthol has also been shown to have gastroprotective, anti-inflammatory, and immunomodulatory properties in rat models. Treatment with menthol was found to significantly reduce the levels of pro-inflammatory cytokines, i.e. interleukin-1, interleukin-23, and tumour necrosis factor-α (TNF-α) in the treated rats (Bastaki et al. 2018; Rozza et al. 2014).

Eugenol has been shown to have antiviral activities against HSV-1 and HSV-2, respectively (Benencia and Courrèges 2000). Besides, it has anti-inflammatory properties and has been shown to protect the lungs against lipopolysaccharide- (LPS) induced acute injury. Treatment with eugenol was also found to inhibit the recruitment of leukocytes into the lung and downregulated the expression of pro-inflammatory cytokines (IL-6 and TNF-α) (Barboza et al. 2018).

An in vivo study conducted by Games and colleagues evaluated the effects of three compounds including carvacrol in an elastase-induced pulmonary emphysema mice model (Games et al. 2016). Results of the study showed that treatment with carvacrol reduced enlargement of alveoli, macrophages recruitment, and the levels of IL-1β, IL-6, IL-8, and IL-17 in the bronchoalveolar lavage fluid. The lung inflammation and emphysema were significantly less in the carvacrol-treated mice as compared with the disease control group. Moreover, carvacrol has also been reported to have antiviral activities against HSV-1, acyclovir-resistant herpes simplex virus type 1, human respiratory syncytial virus (HRSV), and human rotavirus (RV) (Kamalabadi et al. 2018; Pilau et al. 2011). In summary, data of in silico and in vivo animal models give a clue about the potential role of **e**ugenol, menthol, and carvacrol in the treatment of COVID-19 but further studies desinged to evaluate the anti-SARC-CoV-2 efficacies of these EOs are required. Figure 1 depicts the effects of these discussed EOs on the host respiratory system as well as on viral and hosts' pulmonary cells.

Essential oils manufacturers/sellers claims and limitations of current studies

After the emergence of shreds of preliminary scientific evidences about anti-SARC-CoV-2 potentials of essential oils and their active components, various essential oils selling and extraction companies claimed about efficacy of their essential oils bearing products against COVID-19. These claims were immediately noticed by the Food and Drug Administration (FDA) authority of USA and other

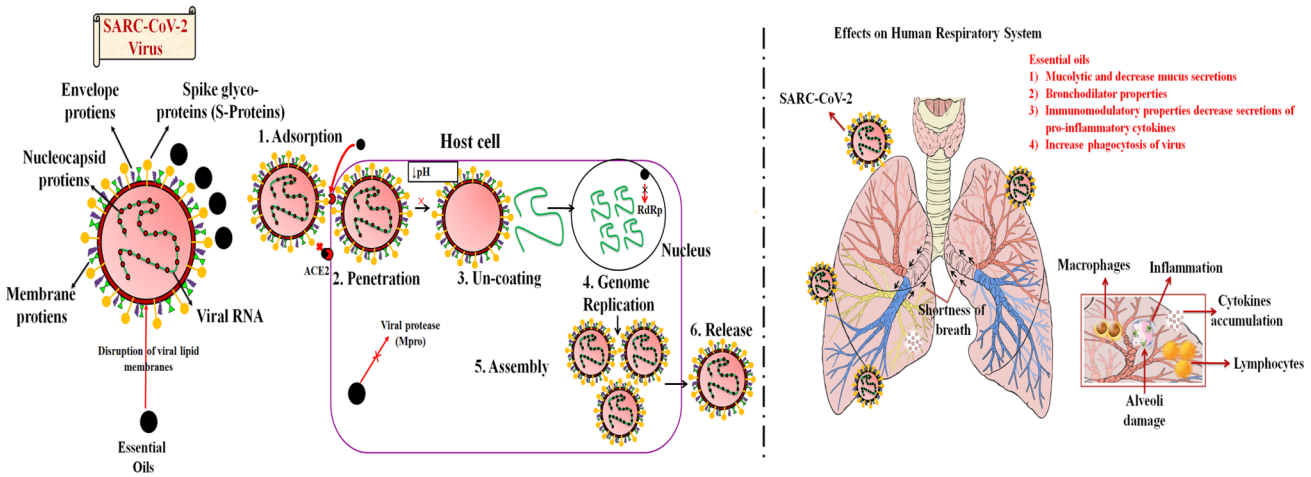


Fig. 1 The proposed anti-SARC-CoV-2 actions of essential oils and their complementary effects on the human respiratory tract

authorities, and warning letters were issued to the companies selling essential oils with these claims. A warning letter (MARCS-CMS 605752) was issued to a company by the Center for Drug Evaluation and Research, USA and was asked to withdraw the material about anti-corona efficacy of essential oils obtained from *Eucalyptus* species, cinnamon, clove, frankincense, ginger, grapefruit, lemongrass, rosemary, tea tree, and lavender. Another warning letter (MARCS-CMS 607753) was issued to a company claiming about immune-boosting and antiviral including anti-corona properties of a product named 'Nobel laurel'. In addition to these sellers, FDA has issued letters to various companies making false claims about their diagnostic products and other such materials (https://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products). Another issue associated with the use of essential oils is hypersensitivity reactions. Essential oils containing pinene and linalool are known to cause wide variety of respiratory complications including seasonal asthma and rhinitis in allergic patients (Gibbs 2019). Moreover, some individuals are sensitive/allergic to specific components of EOs and upon exposure may develop a wide range of allergic reactions including contact dermatitis (Burfield 2000).

Conclusion and future recommendations

COVID-19 has emerged as a very serious threat to global health. Unfortunately, very few medications have been clinically shown to have efficacies against SARC-CoV-2 and its inflammatory complications. Drugs having different labelled uses are currently being tried in various combinations as supportive treatments. Essential oils have long been known to have anti-inflammatory, antioxidant, immunomodulatory, and antiviral properties and are being proposed to have activity against SARC-CoV-2. However, the existing information about these essential oils is very preliminary and the majority of claims are based on data obtained from computer-aided docking and preliminary in vitro studies. In this regard, well-planned in vitro and in vivo studies are warranted to establish the safe dose and clinical efficacy of essential oils against SARC-CoV-2. Moreover, keeping in view the multiple pharmacological attributes of essential oils, a combination approach whereby essential oils with established pharmacokinetic and pharmacodynamic properties are administered with synthetic drugs is suggested to combat this viral disorder and its associated complications.

Funding This research received no external funding.

Compliance with ethical standards

Conflict of interest Essential oil suppliers'/sellers' names mentioned in the manuscript were taken from FDA letters and we do not intend to harm or damage their business repute. This review is purely for academic purposes. The authors declare no conflict of interest in the current work.

References

Barboza JN, da Silva Maia Bezerra Filho C, Silva RO, Medeiros JVR, de Sousa DP (2018) An overview on the anti-inflammatory potential and antioxidant profile of eugenol. Oxid Med Cell Longev 2018:3957262. https://doi.org/10.1155/2018/3957262

Bastaki SM, Adeghate E, Amir N, Ojha S, Oz M (2018) Menthol inhibits oxidative stress and inflammation in acetic acid-induced colitis in rat colonic mucosa. Am J Transl Res 10:4210–4222

Bastos VP et al (2009) Inhibitory effect of 1,8-cineole on guinea-pig airway challenged with ovalbumin involves a preferential action on electromechanical coupling. Clin Exp Pharmacol Physiol 36:1120–1126. https://doi.org/10.1111/j.1440-1681.2009.05189.x

Benencia F, Courrèges MC (2000) In vitro and in vivo activity of eugenol on human herpesvirus. Phytotherapy Res PTR 14:495–500. https://doi.org/10.1002/1099-1573(200011)14:7<495:aid-ptr650>3.0.co;2-8

Bhardwaj K, Sun J, Holzenburg A, Guarino LA, Kao CC (2006) RNA recognition and cleavage by the SARS coronavirus endoribonuclease. J Mol Biol 361:243–256. https://doi.org/10.1016/j.jmb.2006.06.021

Bourne KZ, Bourne N, Reising SF, Stanberry LR (1999) Plant products as topical microbicide candidates: assessment of in vitro and in vivo activity against herpes simplex virus type 2. Antiviral Res 42:219–226. https://doi.org/10.1016/s0166-3542(99)00020-0

Brochot A, Guilbot A, Haddioui L, Roques C (2017) Antibacterial, antifungal, and antiviral effects of three essential oil blends. MicrobiologyOpen 6:e00459. https://doi.org/10.1002/mbo3.459

Burfield T (2000) Safety of essential oils. Int J Aromather 10:16–29

Coelho-de-Souza L, Leal-Cardoso J, Matos F, Saad L, Magalhães P (2006) Relaxant effects of the essential oil of *Eucalyptus tereticornis* and its main constituent 1,8-cineole on guinea-pig tracheal smooth muscle. Planta medica 71:1173–1175. https://doi.org/10.1055/s-2005-873173

Eccles R (2003) Menthol: effects on nasal sensation of airflow and the drive to breathe. Curr Allergy Asthma Rep 3:210–214. https://doi.org/10.1007/s11882-003-0041-6

Elfiky AA (2020) SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: an in silico perspective. J Biomol Struct Dyn. https://doi.org/10.1080/07391102.2020.1761882

Games E et al (2016) Structurally related monoterpenes p-cymene, carvacrol and thymol isolated from essential oil from leaves of *Lippia sidoides* Cham. (Verbenaceae) protect mice against elastase-induced emphysema. Molecules (Basel, Switzerland) 21:1390. https://doi.org/10.3390/molecules21101390

Gao J, Tian Z, Yang X (2020a) Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 14:72–73. https://doi.org/10.5582/bst.2020.01047

Gao Y et al (2020b) Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science 368:779–782. https://doi.org/10.1126/science.abb7498

Gibbs JEM (2019) Essential oils, asthma, thunderstorms, and plant gases: a prospective study of respiratory response to ambient biogenic volatile organic compounds (BVOCs). J Asthma Allergy 12:169–182
Girija ASS, Shankar EM, Larsson M (2020) Could SARS-CoV-2-induced hyperinflammation magnify the severity of coronavirus disease (CoViD-19) leading to acute respiratory distress syndrome? Front Immunol. https://doi.org/10.3389/fimmu.2020.01206
Ho CY, Cheng YT, Chau CF, Yen GC (2012) Effect of diallyl sulfide on in vitro and in vivo Nrf2-mediated pulmonic antioxidant enzyme expression via activation ERK/p38 signaling pathway. J Agric Food Chem 60:100–107. https://doi.org/10.1021/jf203800d
Hoffmann M et al (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181:271–280.e278. https://doi.org/10.1016/j.cell.2020.02.052
Huang H, Wang Y (2017) The protective effect of cinnamaldehyde on lipopolysaccharide induced acute lung injury in mice. Cell Mol Biol (Noisy-le-Grand, France) 63:58–63. https://doi.org/10.14715/cmb/2017.63.8.13
Juergens UR, Dethlefsen U, Steinkamp G, Gillissen A, Repges R, Vetter H (2003) Anti-inflammatory activity of 1.8-cineol (eucalyptol) in bronchial asthma: a double-blind placebo-controlled trial. Respir Med 97:250–256. https://doi.org/10.1053/rmed.2003.1432
Juergens LJ, Worth H, Juergens UR (2020) New perspectives for mucolytic, anti-inflammatory and adjunctive therapy with 1,8-cineole in COPD and asthma: review on the new therapeutic approach. Adv Therapy 37:1737–1753. https://doi.org/10.1007/s12325-020-01279-0
Kamalabadi M, Astani A, Nemati F (2018) Anti-viral effect and mechanism of carvacrol on herpes simplex virus type 1. Int J Med Lab 5:113–122
Kulkarni SA, Nagarajan SK, Ramesh V, Palaniyandi V, Selvam SP, Madhavan T (2020) Computational evaluation of major components from plant essential oils as potent inhibitors of SARS-CoV-2 spike protein. J Molec Struct 1221:128823. https://doi.org/10.1016/j.molstruc.2020.128823
Kumar A, Choudhir G, Shukla SK, Sharma M, Tyagi P, Bhushan A, Rathore M (2020) Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches. J Biomol Struct Dyn. https://doi.org/10.1080/07391102.2020.1772112
Lau SKP et al (2010) Coexistence of different genotypes in the same bat and serological characterization of *Rousettus* bat coronavirus HKU9 belonging to a novel *Betacoronavirus* subgroup. J Virol 84:11385–11394. https://doi.org/10.1128/jvi.01121-10
Lee C (2018) Therapeutic modulation of virus-induced oxidative stress via the Nrf2-dependent antioxidative pathway. Oxid Med Cell Longev 2018:6208067–6208067. https://doi.org/10.1155/2018/6208067
Liu J et al (2020) Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 6:16–16. https://doi.org/10.1038/s41421-020-0156-0
Ludwig S, Zarbock A (2020) Coronaviruses and SARS-CoV-2: a brief overview. Anesth Analg. https://doi.org/10.1213/ANE.0000000000000484510.1213/ANE.0000000000004845
Ma L, Yao L (2020) Antiviral effects of plant-derived essential oils and their components: an updated review. Molecules 25:2627
McCord JM, Hybertson BM, Cota-Gomez A, Gao B (2020) Nrf2 activator PB125® as a potential therapeutic agent against COVID-19. bioRxiv:2020.2005.2016.099788. https://doi.org/10.1101/2020.05.16.099788
Mediouni S et al (2020) Oregano oil and its principal component carvacrol inhibit HIV-1 fusion into target cells. J Virol. https://doi.org/10.1128/jvi.00147-20
Merad M, Martin JC (2020) Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol 20:355–362. https://doi.org/10.1038/s41577-020-0331-4
Patel VJ, Biswas Roy S, Mehta HJ, Joo M, Sadikot RT (2018) Alternative and natural therapies for acute lung injury and acute respiratory distress syndrome. Biomed Res Int 2018:2476824. https://doi.org/10.1155/2018/2476824
Pilau M, Alves SH, Weiblen R, Arenhart S, Cueto A, Lovato L (2011) Antiviral activity of the *Lippia graveolens* (Mexican oregano) essential oil and its main compound carvacrol against human and animal viruses. Braz J Microbiol. https://doi.org/10.1590/S1517-83822011000400049
Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 109:102433. https://doi.org/10.1016/j.jaut.2020.102433
Rozza AL, Meira de Faria F, Souza Brito AR, Pellizzon CH (2014) The gastroprotective effect of menthol: involvement of anti-apoptotic, antioxidant and anti-inflammatory activities. PLoS ONE 9:e86686. https://doi.org/10.1371/journal.pone.0086686
Sadlon AE, Lamson DW (2010) Immune-modifying and antimicrobial effects of eucalyptus oil and simple inhalation devices. Altern Med Rev J Clin Ther 15:33–47
Schnitzler P, Schuhmacher A, Astani A, Reichling J (2008) Melissa officinalis oil affects infectivity of enveloped herpesviruses. Phytomed Int J Phytotherapy Phytopharmacol 15:734–740. https://doi.org/10.1016/j.phymed.2008.04.018
Schnitzler P, Astani A, Reichling J (2010) Antiviral effects of plant-derived essential oils and pure oil components. Lipids Essent Oils Antimicrob Agents. https://doi.org/10.1002/9780470976623.ch10
Sharma AD, Kaur I (2020a) Jensenone from eucalyptus essential oil as a potential inhibitor of COVID 19 corona virus infection. Res Rev Biotech Biosci 7:59–66
Sharma AD, Kaur I (2020b) Eucalyptol (1,8 cineole) from eucalyptus essential oil a potential inhibitor of COVID 19 corona virus infection by molecular docking studies. Preprints: 2020030455
Shuai C et al (2006) An overall picture of SARS coronavirus (SARS-CoV) genome-encoded major proteins: structures, functions and drug development. Curr Pharm Design 12:4539–4553. https://doi.org/10.2174/138161206779010459
Silva J, Figueiredo P, Byler K, Setzer W (2020) Essential oils as antiviral agents. Potential of essential oils to treat SARS-CoV-2 infection: an in-silico investigation. Int J Mol Sci 21:3426. https://doi.org/10.3390/ijms21103426
Thuy BTP et al (2020) Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil. ACS Omega 5:8312–8320. https://doi.org/10.1021/acsomega.0c00772
Usachev EV, Pyankov OV, Usacheva OV, Agranovski IE (2013) Antiviral activity of tea tree and eucalyptus oil aerosol and vapour. J Aerosol Sci 59:22–30. https://doi.org/10.1016/j.jaerosci.2013.01.004
Valencia DN (2020) Brief review on COVID-19: the 2020 pandemic caused by SARS-CoV-2. Cureus 12:e7386
Vimalanathan S, Hudson J (2014) Anti-influenza virus activity of essential oils and vapors. Am J Essent Oils Nat Prod 2:47–53
Wang M et al (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 30:269–271. https://doi.org/10.1038/s41422-020-0282-0
Wink M (2020) Potential of DNA intercalating alkaloids and other plant secondary metabolites against SARS-CoV-2 causing COVID-19. Diversity 12:175
Yang Y et al (2020) The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J Autoimmun 109:102434. https://doi.org/10.1016/j.jaut.2020.102434
Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS (2020) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intens Care Med 46:586–590. https://doi.org/10.1007/s00134-020-05985-9

Affiliations

Muhammad Asif[1] · Mohammad Saleem[2] · Malik Saadullah[3] · Hafiza Sidra Yaseen[3] · Raghdaa Al Zarzour[4]

✉ Muhammad Asif
asif_pharmacist45@yahoo.com; drmasif@iub.edu.pk

Mohammad Saleem
saleem2978@hotmail.com

Malik Saadullah
maliksaadullah@gcuf.edu.pk

Hafiza Sidra Yaseen
drhsidrarph@gmail.com

Raghdaa Al Zarzour
raghdaa@usm.my

[1] Department of Pharmacology, Faculty of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

[2] Punjab University College of Pharmacy, University of the Punjab, Lahore, Pakistan

[3] Faculty of Pharmaceutical Sciences, Government College University Faisalabad, Faisalabad, Pakistan

[4] Discipline of Pharmacology, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden Penang, Malaysia