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# Essential Oils for SARS-CoV-2 prevention and treatment: Systematic Review

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**Abstract.** A viral disease caused by a new severe acute respiratory syndrome (SARS-CoV-2), is a new strain that was discovered in December 2019 in China, which has quickly resulted in a pandemic. The antiviral properties of aromatic plants and essential oils can justify their use against COVID-19. Our purpose in this article is to review the use of essential oils during the pandemic for the treatment, prevention and reduction of symptoms due to COVID-19. A literature search was executed using Google Scholar, PubMed, ScienceDirect and SpringerLink databases to search for suitable keywords such as 2019-nCoV, essential oil, symptoms, prevention for relevant publications up to 5.5.2020. The present systematic review was performed based on PRISMA protocol, the results of the search and based on the inclusions and exclusions criteria, 14 articles were included in the final review. The result of this study shows that several essential oils could prove beneficial for COVID-19 patients and also could reduce the severe symptoms caused by SARS-CoV-2. The essential oils of Eucalyptus globulus, Corymbia citriodora, Pelargonium graveolens, Citrus limon, Allium sativum and Syzygium aromaticum can be used as a potential agents for SARS-CoV-2 prevention.

**Keywords:** Essential oil, 2019-nCoV, symptoms, prevention, in Silico

## 1 Introduction

Corona viruses are a family of viruses, some of which can infect humans, most often causing mild cold-like symptoms. Nevertheless, three deadly epidemics have already occurred in the 21st century, including the current one. They involve emerging corona viruses harbored by animals and suddenly transmitted to humans: SARS-CoV and MERS-CoV. In December 2019, a new coronavirus epidemic called the new coronavirus disease (COVID-19) was identified in the Wuhan City of Hubei Province of China [1]. The COVID-19 pandemic is spreading as rapidly as uncontrolled bushfires. The World Health Organization (WHO)

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declares pandemic on March 11th, 2020, Today, 28 July 2021, the World Health Organization reported 195 266 156 confirmed cases, including 4 180 161 deaths [2].

Through the COVID-19 pandemic, all populations used traditional natural products for prevention and reduction of symptoms. Essential oils are considered as a remarkable source of bioactive metabolites, EOs are well recognized for their strong antiviral, anti-inflammatory and immunomodulatory activities [3, 4]. EOs and their components disturb viral replication and also avail the host respiratory system via mucus lysis and bronchodilation. Their activity is related to their lipophilic nature, which permits them to disrupt or interfere with viral membrane proteins involved in host cell attachment [5] but their precise mode of action is due to the biochemical structure related with functional groupings of active molecules activities [6, 7]. The essential oil of Laurus nobilis consists of -ocimene and 1,8- cineole (eucalyptol) as major constituents, has been mentioned to possess a strong antiviral activity against SARS-CoV-1, 96% of the same genetic background as SARS-CoV-2, with a selective index and IC50 values of 4.6 and 120 mg/mL, respectively [8]. Many studies have reported the possible effect of several essential oils against SARS-CoV-1. The aim of the present article is to review the use of essential oils during the pandemic for the treatment, prevention and reduction of symptoms due to COVID-19.

## 2 Methods

This systematic review was represented based on PRISMA protocol [9] (Table 1).

### 2.1 Search strategy and selection criteria

Among the 56 records that were identified through electronic search using Google Scholar, PubMed, ScienceDirect and SpringerLink databases to search for the proper keywords such as: 2019-nCoV, essential oil, symptoms, prevention for publications published until 05.05.2021. The reviewers independently extracted the data of interest to detect potentially related articles. All reviewers independently evaluated the titles and abstracts. The full texts of articles that seemed confusing were estimated to decide their appropriateness for inclusion.

### 2.2 Included studies

In this article studies about essential oils used against 2019-nCoV treatment, prevention and reduction of symptoms were considered, in Silico studies were also retained.

### 2.3 Excluded studies

The articles with only abstract were eliminated from this review. Studies about possible effects of essential oil against SARS-CoV-1 were also excluded. Some

other articles were also excluded because they were about antiviral activity of essential oil, but not specific to SARS-CoV-2.

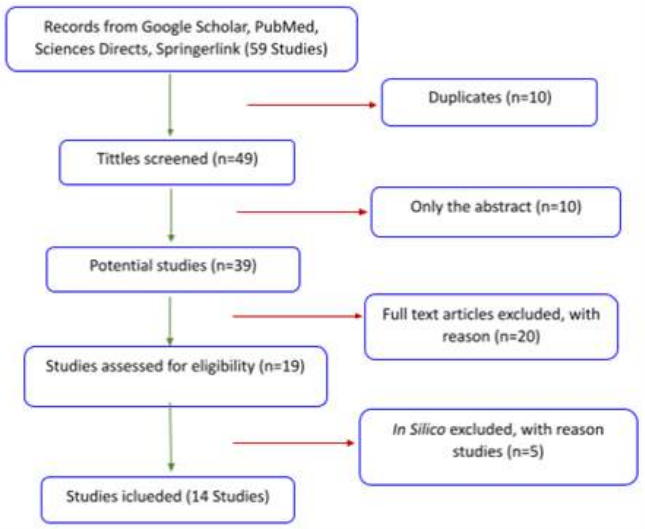


**Fig. 1.** Flowchart of the studies selection.

### 2.4 Statistical analysis

It was not possible to conduct a meta-analysis, because there were not enough proper research studies on this subject.

## 3 Results

### 3.1 Study selection

We retrieved a total of 59 potentially eligible studies from initial database searches, 10 articles were excluded because of being duplicate. 10 articles were also excluded because their full text was not accessible, 20 studies were also eliminated for the reason that they were about antiviral activity of essential oil but not specific to SARS-CoV-2. Therefore, a total of 14 articles were included in final analysis (Fig. 1).

### 3.2 Study characteristics (Eligibility criteria)

Among the 14 studies comprising the qualitative synthesis, 5 were clinical trials, 2 were in vivo studies, the rest were in Silico studies. Only articles in English

language were selected. We used Endnote library (version X6, Thomson Reuters) to import Citations from all databases. All authors review the remainder search results by eliminating trivial studies.

According to the extracted data in table 1 and table 2, all researches on essential oils efficiency against SARS-CoV-2, have been done in vitro and through clinical trials for their use to prevent and reduce symptoms. Efficiency of EOs for treatment were not conclusive, only In silico research have addressed this topic extensively.

**Table 1:** Main characteristics of including studies concerning reducing symptoms, prevention and treatment of COVID-19.

| Essential oils | Major compounds | Usage size | Study type | Ref |
|---|---|---|---|---|
| Mixture of EOs (Thymbra capitata Salvia fruticosa and Origanum dictamnus) | Carvacrol (53%), Eucalyptol (13%), -Caryophyllène (3%) | Treatment: Calculated EC50 through a logistic fit was estimated as 1/60 of the proposed dose for viral growth, and 1/250 for cell phenotype. | Clinical trials | [10] |
| Eucalyptus globulus | Eucalyptol 52.47%, *α — Pinene*17.00%, *o – Cymene*5.06%, *d – Limonene*4.49% | Treatment: Eucalyptol reduces the production of inflammatory mediators (TNF-, IL-6, and IL-8) by inducing modifications at an epigenetic level in white blood cells. | Clinical trials | [11] |
| Eucalyptus globulus | Eucalyptol 52.47%, *α – Pinene*17.00%, o-Cymene 5.06%, d-Limonene 4.49% | Reduction of symptoms: Inhalation of EEO (Eucalyptus globulus Esssential Oil) provides the ability to reduce COVID-19 patients symptoms and morbidity risk factors. | Clinical trials | [12] |
| 1% PVP-I essential oils (Listerine® Original) | Eucalyptol, Menthol Thymol. | Prevention: Gargling with 1% PVP-I shows great potential to be part of the treatment of Stage 1 COVID-19. | Clinical trials | [13] |
| Geranium essential oil | Citronellol (27.1%), Geraniol (21.4%) and Nerylacetate (10.5%), | Treatment: ACE2 inhibitory effects in epithelial cells | In vitro | [14] |
| Citron essential oil | Limonene, 73.0%, Terpinene (9.2%) *β – Pinene*(8.6%) | Treatment: ACE2 inhibitory effects in epithelial cells | In vitro | [14] |

(Continued)

| Essential oils | Major compounds | Usage size | Study type | Ref |
|---|---|---|---|---|
| Thymus vulgaris | Thymol (23%–60%), *γ − Terpinene*(18%–50%), p-Cymene (8%–44%), Carvacrol (2%–8%). | Treatment: EO reduce the severity of symptoms (fever, cough, dyspnea, muscular pain and weakness,) | Clinical trial | [15] |
| Syzygium aromaticum | Eugenol 52.53% Caryophyllene 37.25% Eugenyl acetate 4.05% | Treatment: On the 4th day of treatment, 10 patients who were symptomatic testified having recovered all their olfactory and gustatory faculties. | Clinical trial | [16] |

**Table2:** Main characteristics of including *In Silico* studies (docking)

| Essential oils | Major compounds | Docking molecular | Ref |
|---|---|---|---|
| Eucalyptus globulus | Eucalyptol 52.47%, *α − Pinene*17.00%, o- Cymene 5.06%, d-Limonene 4.49%, | Eucalyptol docked (AutoDock) with the Mpro (PDB : 6LU7) has shown the best Binding Score Energy of -5.86 kcal/mol and The interaction residues were 11 hydrophobic bonds with MET49, MET165, HIS164, ARG188, and PRO52 ; one pi-sigma interaction with HIS 41; and four van der Waals forces with ASP187, GLN189, TYR54, and PHE181 residues. The most powerful anti-SARS-CoV-2 activity was expressed in the order: Eucalyptol > -pinene¿ d-Limonene > o-Cymene. | [17] [18] |
| Corymbia citriodora | Citronellol (59.31%), Eucalyptol(13.54%), 3-Carene (5.39%), | Citronellol was docked (AutoDock) with the Mpro (PDB : 6LU7) has shown a Binding Score Energy of -4.94 kcal/mol and five hydrophobic bonds formed with HIS41, MET165 and MET49; and seven van der Waals forces with TYR54, ASP187, HIS164, ARG188, GLN189, GLN192, and THR190 residues. The most powerful anti-SARS-CoV-2 activity was expressed in the order : Eucalyptol > 3-carene > citronellol. | [18] |
| Nigella sativa | p-Cymene (18.46-52.64%) *α — Thujene*(4.5 − 10.23%) *α—Terpineol*(5.11 − 9.72%) Thymoquinone (0.14-9.2%) Ongifolene (3.07-8.34%) | Thymoquinone docked (AutoDock Vina) with the Mpro (PDB: 6LU7) has shown a Binding Score Energy of -5.1 kcal/mol. The interaction residue was HIS164, and heat shock protein A5 active sites with a score less than hydroxychloroquine in 6LU7. | [21] |

(Continued)

| Essential oils | Major compounds | Docking molecular | Ref |
|---|---|---|---|
| Allium sativum | Allyl disulphide 28.4%<br>Allyltrisulphide 22.8%<br>Allyl (E)-1- propenyl disulphide 8.2%<br>Allyl methyl trisulphide 6.7%<br>Diallyl tetrasulphide, 6.5% | Majority compounds were docked (MOE 2015.10) with the Mpro (PDB: 6LU7) Allyl disulphide has shown the best Binding Score Energy of –15.32 kcal/mol. The Mpro/Allyl interaction residues were PRO 565, GLN 102, GLU 208, ASN 210, GLY 205, GLN 98, TRP 566, LYS 94, VAL 209, GLN 101, ASP 206, ASN 103, SER 563, ALA 396, and LYS 562.<br>Diallyl tetrasulphide docked with the ACE2 has shown the best Binding Score Energy of -14.06 kcal/mol and the ACE2/ Diallyl tetrasulphide interaction residues were PRO 565, TRP 566, ALA 396, GLN 102, GLN 101, GLU 208, GLY 205, GLN 98, ASN 210, LYS 94, LYS 562, VAL 209. The most powerful anti-SARS-CoV-2 activity was expressed in the order: Allyl disulphide = Allyltrisulphide > Diallyl tetrasulphide > Allyl methyl trisulphide > Allyl (E)-1- propenyl disulphide. | [19]<br>[20] |
| Melaleuca cajuputi | Terpineol 10.7%<br>Guaiol 6.5%<br>Cineol 31.6%<br>*β − Selinenol*6.8%<br>*α − Eudesmol*6.7%<br>*γ − Eudesmol*4.3% | Terpineol and Guaiol were docked (MOE 2015.10) with the Mpro (PDB: 6LU7) have shown the same Binding Score Energy of –10.9 kcal/mol and The Mpro/Terpineol interaction residues were HIS 163, LEU 141, MET 165, PHE 140, GLU 166, HIS 164, ASN 142, SER 144, CYS 145, GLY143, HIS 41. Guaiol docked with the ACE2 has shown the best Binding Score Energy of –11.1 kcal/mol and the ACE2/Guaiol interaction residues were ASN 103, GLN 101, LEU 85, AN 194, HIS 195, TYR 196, GLN 102. The most powerful anti-SARS-CoV-2 activity was expressed in the order: Terpineol = Guaiol > Cineol > β -Selinenol > α -Eudesmol > γ -Eudesmol. | [22] |

(Continued)

| Essential oils | Major compounds | Docking molecular | Ref |
|---|---|---|---|
| Lantana camara | Allo-aromadendrene epoxide azulenol, germacrene A, Guaia-6,9-diene, humulene epoxide II, -calacorene , -muurolene | 14-hydroxy--muurolene docked (AutoDock Vina) with the Mpro (PDB: 6Y2F) have shown the best Binding Score Energy -6.6 kcal/mol compared with -6.4 kcal/mol. The most powerful anti-SARS-CoV2 activity was expressed in the order: 14-hydroxy α-muurolene>α - amorphene> α -calacorene > germacrene A, = aristolochene=-cadinene ¿azulenol=hedycaryol >guaia-6,9-diene >allo-aromadendrene epoxide = humulene epoxide II= -muurolene. | [23] |
| Lippia alba | 14-Hydroxy--muurolene, allo-aromadendrene epoxide, germacrene A, hedycaryol, -amorphene, -muurolene. | | |
| Lippia origanoides | Aristolochene, humulene epoxide II, -amorphene, –cadinene -calacorene , -muurolene. | | |

## 4 Discussion

Essential oils and their chemical components have been reported of targeting various potential bimolecular ways in different viruses including coronaviruses, a mixture of essential oils of three Cretan aromatic plants Thymbra capitata, Salvia fruticosa and Origanum dictamnus, possesses a potent antiviral activity, against SARS-CoV-2, in which it also possesses a prophylactic activity and can reduces general and local symptoms [10]. A preliminary study showed that usual gargling with 1% PVP-I and essential oils formula have the potential for achieving early SARS-CoV-2 viral clearance among stage 1 SARS-CoV-2 patients. Thus, eucalyptol or essential oils rich in eucalyptol can be utilized in patients with uncomplicated infections caused by SARS-CoV-2 [11-13].

Recently, ACE2, was found as one of the first targets to reduce the infection. Pelargonium graveolens and Citrus limon essential oils and their major composites, could decrease ACE2 expression in epithelial cells and block virus entry into host cells, and in the end prevent viral infection [14].

The outcomes one week after taking Thymus vulgaris essential oils revealed the reduction of the severity of symptoms (fever, cough, dyspnea, dizziness, headache, muscular pain, weakness and chest pain) [15].

The released volatile active principles of a decoction vapor are inhaled by patients during 5 min. The preparation of decoction consists of boiling 5 cloves, ginger, eucalyptus, mint, lemongrass leaves in water for 15 min. On the 4th day of treatment, 10 patients having received this treatment recovered all their olfactory and gustatory faculties. [16].

Table 2 shows a selection of essential oils with an important computational anti-SARS-CoV-2 activity, in addition to a resume of the docking studies re-lated to the most active molecules among each essential oil was noted : theused program, the target protein, the complex interaction residues and the score energy trends. It was found that for Eucalyptus globulus, the main compound eucalyptol was the most important inhibitor with -5.86 kcal/mol. Clinical trial for Eucalyptus globulus, concluded that it prevents lung damage in the ”cytokine release syndrome”. which is one of the consequences of COVID-19 [11]. However citronellol, the majority compound of Corymbia citriodora, was found less inhibitor than eucalyptol with -4.94 kcal/mol. Therefore the essential oil of Eucalyptus and Corymbia species, mainly eucalyptol, can be used as a potential inhibitor against SARS-CoV-2. The anti-SARS-CoV-2 activity of the Allium sativum essential oil into the PDB6LU7 protein of SARS-CoV-2 was expressed by the highest content in the garlic essential oil, allyl disulphide and allyl trisulphide (51.2%). Nigella sativa as a potential phytotherapy candidate in the treatment of SARS-CoV-2. In the literature review, it was found at least 8 in silico studies about the effects of N. sativa compounds on SARS-CoV-2 [21]. Thymoquinone docked (AutoDock Vina) with the Mpro (PDB: 6LU7) has shown a Binding Score Energy of -5.1 kcal/mol. For Melaleuca cajuputi, terpineol and guaiol have the strongest inhibitory effects on ACE2 and PDB6LU7. It is considered as a valuable resource for preventing SARS-CoV-2 invasion into the human body.

The molecular docking results propose that these three essential oils (Lantana camara, Lippia alba and Lippia origanoides) would have potential to inhibit SARS-CoV-2 and they may be indicated for future in vitro trial studies.

## 5 Conclusion

In conclusion, the literature survey on antiviral effects of essential oils and their chemical constituents show that they could demonstrate as leads in drug development against SARS-CoV-2. Essential oils can easily penetrate the membrane's virus thereby causing membrane disruption. Essential oils also have an extraordinary potential of inhibiting virus attachment (by inhibition of ACE-2) and replication (by inhibition of Mpro). Due to these activities of essential oils, it is believed that they could prove beneficial for COVID-19 patients and also could reduce the severe symptoms caused by SARS-CoV-2. The result of this study shows that although very few in vivo studies and clinical trials have been done on essential oil efficiency, many In silico studies have addressed this topic extensively and have proved their efficiency [24]. Researchers have established a large library of essential oils constituents, showing favorable binding affinity with validated targets aided [25, 26] with computational chemistry and virtual screening, but the efficacy and toxicity of those lead compounds need further testing in both preclinical models and human subjects.

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