IJPSR (2020), Volume 11, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 21 April 2020; received in revised form, 07 August 2020; accepted, 13 August 2020; published 01 September 2020

INHALATION OF ESSENTIAL OILS: COULD BE ADJUVANT THERAPEUTIC STRATEGY FOR COVID-19

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Keywords:

SARS-CoV-1, Covid-19, SARS-CoV-2, Essential oils, Treatment

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ABSTRACT: The current pandemic of the novel coronavirus (SARS-CoV-2) termed as COVID-19 is the third recorded blowback of an animal coronavirus to a human being in the last twenty years. The pandemic is originated from China and currently impacted more than 205 countries worldwide (as on dated 2nd April 2020). This pandemic is not only affecting human life but also has questioned the worldwide status of healthcare facilities and resulted in a slowdown of the economy. But the fact is the SARS-CoV-2 virus, which causes Covid-19, has less virulence but a high infection rate than SARS-CoV-1, which caused an outbreak of SARS in 2003. The disease is mainly transmitted either through close contact with an infected person via respiratory droplets or by touching a contaminated surface. Treatment involves a combination of certain potent antiviral drugs. SARS-CoV-1 and SARS-CoV-2 share 80 to 90 percent genetic similarity; thus, the treatments which are effective against SARS-CoV-1 can be adjuvant therapeutic strategy against SARS-CoV-2. Some of the essential oils with certain active compounds show strong anti-viral activity against SARS CoV. Therefore, the essential oils like *T. orientalis, J. oxycedrus, L. nobilis,* Rosemary, Ravensara, Ravintsara, Tea Tree, Bergamot, Eucalyptus, Lemon balm, Thyme, Oregano, Fennel, Peppermint, Cinnamon, Clove with active compounds such as β-ocimene, 1,8-cineole, α-pinene, and β-pinene, rosmarinic acid, carnosic acid may be helpful against Covid-19. Conclusively, inhalation of mentioned essential oils could be an adjuvant therapeutic strategy for Covid-19. Also, several ayurvedic herbs can be used as an immunity booster.

INTRODUCTION: Coronaviruses is an established family of the virus, invading humans and animals. The several coronavirus strain strikes with respiratory infections with common symptoms as Common cold and fever but can lead to severe illness Such as MERS (Middle East Respiratory Syndrome) and SARS (Severe Acute Respiratory Syndrome) [1].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(9).4095-03

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(9).4095-03

The SARS epidemic in 2003 was manifested by the virus strain SARS-CoV-1, which is believed to be transmitted from animal sources (Civet cats, a farmed wild animal). Equivalently the SARS-CoV-2 has crossed the species horizon and infected humans. The virus concluded to have an intermediate host, which is again accredited to an animal species handled by a human being like a feral animal or household animal.

The first human case of Covid-19 came in light in December 2019 in Wuhan City, China. But with the outbreak being witnessed, it is unfeasible to know the initially contaminated human with SARS-CoV-2 [2]. WHO sanctioned the outbreak of Covid-19 as Pandemic on 11th march 2020 and

promulgated. World leaders to scale up their efforts in Diagnosing and fighting the virus [3]. In a 'Situation Report- 190' dated July 28th, 2020. WHO reported global effects of Covid-19 disease [4]. Some highlighting points of these reports included; this deadly disease affects more than 205 countries; situations are different in every state, countries like the USA, Brazil, India, Russia, Africa, Mexico, Peru, UK, Iran, Spain, *etc*. Covid-19 becomes a threat to them, while several countries like New Zealand, China, Thailand, North Korea, *etc*. have tackled this pandemic successfully.

TABLE 1: REPORTED FIGURES OF STRONGLY IMPACTED COUNTRIES (AS PER 'SITUATION REPORT- 190' DATED JULY 28, 2020) [4]:

Reporting Country	Total Confirmed Cases	Total Deaths
USA	4209509	146331
Brazil	2419091	87004
Russia	823515	13504
Africa	726105	12257
Mexico	390516	43680
Peru	384797	18229
UK	300115	45759
Iran	293606	15912
Spain	278782	28434
Pakistan	275225	5865
Colombia	248976	8525
Italy	246286	35112
Turkey	227019	5630
Germany	206242	9112

According to the Ministry of Health & Family Welfare (MoHFW), Situation Update in India is as follows: [3] A total of 1336861 Confirmed COVID-19 cases were registered in 29 States/union territories as of 26 July 2020 (8:00 PM). Those include 467882 active cases, 885576 cured / discharged cases, 1 migratory and 32063 deaths. Hospital isolation of all confirmed cases, tracing and home quarantine of the contacts is ongoing. Proper management of Covid-19 disease is necessary otherwise it could have a major effect on human lives.

Why it is known as Novel: Naming the novel virus is work of the International Committee on Taxonomy of Viruses (ICTV). Number of Virologist and Scientist community are involved in naming process. Based on virus genome the naming is done. The main purpose behind naming any novel virus is to provide it with a universally accepted identity [2].

Coronaviruses are known to cause severe illness in humans [5]. The current pandemic of the corona virus is the third blowback in the last twenty years [6]. On 11 February 2020, ICTV assigned a unique identity to the novel coronavirus as "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)." The name was selected on the basis of genetic similarities between novel coronavirus and SARS-CoV-1 virus responsible for the epidemic of SARS in 2003. Though the name is assigned to the virus, it's not necessary that the disease will have same name. Generally, the virus and the disease they cause have different names. World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO) have set guidelines to name novel disease.

Following the recommendations of the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO), WHO named the developing pandemic as Covid-19. For the sake of simplicity, SARS-CoV-2 also known as Covid-19 Virus [2].

Classifying the Virus: Coronaviruses (CoV) are mainly classified into four classes, namely α-CoV, β-CoV, γ CoV, δ-CoV. Class α- and β-CoV are effective against mammals; Class γ- and δ-CoV appear to infect birds. Six CoVs have been identified so far as a human-susceptible virus, which includes α-CoVs, namely HCoV-NL63, HCoV-229E, and β-CoVs, namely HCoV-HKU1, HCoV-OC43 with minimum ability to infect, cause mild respiratory signs like a common cold, Flu, *etc*. Remaining β-CoVs, SARS-CoV and MERS-CoV, are known to cause severe respiratory tract infections [7].

Transmission: The current pandemic of deadly coronavirus (SARS-CoV-2) termed as (COVID-19) is the third recorded blowback of an animal coronavirus to a human being in the past several years that has led to massive widespread [6].

Animal to Human Transmission: Depending on the findings of viral genomics, bat was believed to be a primary host of coronavirus origin, and SARS-CoV-2 could be spread from bats by unknown intermediate carriers into humans and cause disease. Now, it's confirmed that SARS may have used Angiotensin-Converting -Enzyme-2, the

receptor which was used by SARS-CoV-1 to cause disease in human beings [8].

Human to Human Transmission: SARS-CoV-2 viruses mainly spread via direct interaction with an infected person. The easiest way of transmission, when the infected person coughs or sneezes, the produced microdroplets are believed to be carriers of virus [9]. These droplets will quickly settle down on surfaces due to their large size and weight. Viruses can enter the human body through breathing if any person is surrounded by 1 meter of an infected person who has COVID-19 or by having contact with a contaminated surface. If proper hygiene is not maintained and one touches the eyes, nose, and mouth without cleaning it, then the rate of transmission drastically increases[1].

WHO Describes the Contact in Following Way: [10] A contacts is a person who has undergone one of the preceding exposures 2 days prior to and 14 days after a suspected or confirmed patient symptom.

1. Person to Person / Close contact within a distance of 1 meter and for more than 15 min with a suspected or confirmed patient.
2. Touch or physical contact with a suspected or confirmed COVID-19 patient.
3. Close interaction while taking care of suspected or confirmed COVID-19 patient without using suggested personal protective suit as per guidelines.
4. Several other conditions, as the regional risk evaluations suggest.

Mode of Transmissions:

Latest Findings of WHO on Routes of Transmission from COVID-19 Patients are as follow: [4]

Symptomatic Transmission: Symptomatic transmission is spread while a person is experiencing symptoms. Epidemiology and Virology studies claim that the pandemic Covid-19 has been transmitted primarily through breathing droplets from symptomatic people. Direct interaction with an infected person and touching of contaminated surfaces has also been a source of widespread. All these studies and reports have been aided by Health Ministries and the number of experts, professionals working with WHO. Samples collected by professionals from patients affirm that Covid-19 at an early stage (3 days from the onset of symptoms) has the maximum widespread effect with the SARS-CoV-2 virus attacking the upper respiratory tract (nose and throat). Preceding studies propound that the infected person spreads the virus at an alarming rate in the early-stage disease.

Pre symptomatic Transmission: Incubation period, better known as 'pre-symptomatic' period of Covid-19, is proclaimed to be 5-6 days but can extend up to 14 days. Virus transmission is possible in the pre-symptomatic case as the infected person can transmit the virus to a healthy person. Pre symptomatic transmission eventuates and spread through contagious droplets or contaminated objects. There have been cases where people are tested positive for COVID-19 at an early stage (1-3 days) even before showcasing any symptoms.

Asymptomatic Transmission: A person with absolutely no signs and symptoms of Covid-19 can spread the virus as well. Asymptomatic transmission excerpt to this spread of the virus. Several laboratories confirmed cases are actually asymptomatic, but no asymptomatic transmission has been diagnosed till date. In countries like China and South Korea, asymptomatic cases were brought into light through contact tracing.

Symptoms: Fever, dry cough, and weakness are some regular signs and symptoms of COVID-19. Many infected persons develop aches, pains, nasal congestion, runny nose, sore throat, diarrhea, and pneumonia. The symptoms are generally mild which develops gradually. Many infected cases are asymptomatic and show no signs. 1 out of every 6 patients who suffer from COVID-19 develops a severe illness and breathing complications. SARS-CoV-2 virus seriously impacts newborns, elderly persons and persons with previously existing health problems (hypertension, cardiovascular disease, lung disease or COPD, cancer, or diabetes). A person with weak immunity is more prone to get infected with COVID-19. Proper medical care is needed for patients with fever, sore throat, cough, and difficulty in breathing symptoms. Most of the infected person (around 80%) cured of the illness on the eve of their strong immunity, without demanding any special medical treatment [1].

Treatment: The SARS CoV-2 virus that develops COVID-19 and the SARS-CoV-1virus that caused the epidemic of SARS in 2003 are closely linked to one another; however, the illnesses developed are very distinct and have their own characteristics. SARS was less contagious but more fatal than COVID-19. No, any additional case was reported additionally from 2003 [1]. Currently, there is no accepted or internationally recognized treatment for SARS and Covid-19. SARS-CoV-2 (Covid-19 virus) resembles 80% to 90% in its genetic makeup with the SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavirus 1) [1], hence active constitutes effective against Cov-1 can be effective against Cov-2. Both the virus shares some similar morphology, spherical protein capsule having a strip of ribonucleic acid, and the capsule is totally enclosed in spikes. The spikes lock up receptors on the cell surface, lining the human lung in both cases and the same kind of receptor to release the virus in the cell. Once the virus is able to make its way to the cell, inside the cell, the cell's reproductive process is manipulated to produce more copies of it, until it bursts out of the cell [11]. In recent years, a number of synthetic antiviral formulations with specific molecular targets and a range of phytochemicals have been identified to control infections caused by various deadly viruses [5].

TABLE 2: ESSENTIAL OILS USED IN THE TREATMENT OF SARS-COV-1

S. no.	Essential oils
1	*L. nobilis* oil
2	*J. oxycedrus* oil
3	*T. orientalis* oil

***Laurus nobilis* Oil:** *L. nobilis* oil exhibited an effective action against the SARS-CoV-1 virus with an IC50 value of 120 mg/ml and a selectivity index of 4.16 [9]. *L. nobilis* oil contains b-ocimene, 1, 8-cineole, α-pinene, and β-pinene as the major constituents.

***Juniperus oxycedrus* Oil:** Overall, 48 compounds (82.39% of the total oil) were identified in oxycedrus berry oil. The major constituents were α-Pinene (27.4%) and β-myrcene (18.9%). Other recognized compounds were α-phellandrene (7.1%), limonene (6.7%), epibicycloses-quiphellandren (2.3%) and δ-cadinene (2.2%). All the Phyto-constituents have inhibitory action against SARS-CoV-1 virus [9].

***Theileria orientalis* Oil:** *T. orientalis* oil contains total 43 components (which comprises 86.68% of the total oil) in which the major compounds were α-pinene (35.72%), δ-3-carene (9.48%) and α-cedrol (9.55%) All the active compounds exhibit inhibitory action against SARS-CoV-1 virus [9].

Adjuvant Therapeutic Strategy of SARS-CoV-2: [9] *L. nobilis* oil exhibited an effective action against SARS Cov - 1 virus with an IC50 value of 120 mg/ml and a selectivity index of 4.16. *L. nobilis* oil contains β-ocimene, 1, 8-cineole, α-pinene, and β-pinene as the major constituents. Therefore, essential oils that are rich in β-ocimene, 1, 8-cineole, α-pinene, and β-pinene possess strong antiviral properties that can be effective in treatment against SARS-CoV-2 [12]. Oils that are the source of Monoterpenes (a-pineneand b-pinene), 1, 8 cineole, b-ocimene, Terpineol, which beliefs to show anti-viral activity against SARS-CoV-1. The substance which has the ability to stop the replication of SARS-CoV-1 can be helpful against Covid-19 because of similarity in their genetic material [1]. Also, other constituents of volatile oils (like thymol, Rosemarinic acid, carnosic acid, limonene) have antiviral properties, so the following essential oils can be effective against SARS and Covid-19 [9].

TABLE 3: ESSENTIAL OILS WHICH CAN BE USED AS ADJUVANT THERAPEUTIC STRATEGY OF SARS-COV-2

S. no.	Essential Oils
1.	*L. nobilis*
2.	*J. oxycedrus*
3.	Rosemary
4.	Ravensara
5.	Ravintsara
6.	Tea Tree
7.	Bergamot
8.	Eucalyptus
9.	Lemon Balm
10.	Thyme
11.	Oregano
12.	Fennel
13.	Peppermint
14.	Cinnamon
15.	Clove

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Rosemary Oil: The principal components of oils were found to be 1,8-cineol (33.08-37.75 %), camphor (13.55-18.13 %), α-pinene (8.58-9.32 %), α-terpineol (6.79- 8.17 %), camphene (5.07-5.58 %), borneol (4.08-5.48 %), limonene (3.19-3.04 %) and p-cymene (2.42-3.11 %) [13]. Rosemary oil is rich in 1, 8- Cineole, rosemarinic acid [14], carnosic acid [15], α- pinene, which shows strong anti-viral effects. Rosemary extract has demonstrated antiviral effects against herpes viruses and hepatitis A, which affects the liver [16, 17].

Rosemary essential oil can be effective against COVID-19, assuming the activity of its chief chemical constituents like 1, 8- Cineole, α-pinene, β-pinene, *etc.* [9].

Ravensara Oil: This oil mainly contains methyl chavicol (79.7%), methyl eugenol (8.5%) and limonene (3.1%) [18]. Therefore, based on its chemical composition, it is expected to show strong anti-viral activity against Covid-19.

Ravintsara Oil: The principal chemical components are oxides (with at least 45% to 55% 1, 8-cineole), monoterpenes (sabinene 15%, alpha-pinene, and beta-pinene), sesquiterpenes (beta-carophyllene), monoterpenic alcohols (alpha-terpineol 7% and terpineol) and esters (terpenyl acetate) and a number of trace compounds. Ravintsara is considered as essential oil with anti-viral activity against a broad range of viruses. Thus, it may show inhibitory activity against Covid-19 [9].

Tea Tree Oil: Tea tree oil comprises of various monoterpenes and sesquiterpenes as well as other aromatic compounds. The monoterpenes terpinen-4-ol, α-terpinene, α-terpinene, 1, 8-cineole, p-cymene, α-terpineol, α-pinene, terpinolenes, limo-nene, and sabinene account for 80-90% of the oil [19]. Tea tree oil can help to get rid of the herpes simplex virus, which causes cold sores, as well as viruses that cause the common cold and the flu. Monoterpenes combination in Tea tree oil shows synergetic anti-viral actions. Active components of tea tree oil show strong anti-viral activity [12]. All these properties suggest the probability of the effectiveness of tea tree oil against Covid-19.

Bergamot Oil: The main volatile compounds in the oil are limonene (37.2 %), linalyl acetate (30.1%), linalool (8.8%), γ-terpinene (6.8%) and β-pinene (2.8%) and in smaller quantities geranial and β-bisabolene [20]. Bergamot oil and its chief active compound citronellal show inhibitory action against influenza virus [21]. So, it may show inhibitory action against the SARS-CoV-2 virus.

Eucalyptus Oil: In total, 26 compounds were identified with the predominance of oxygenated monoterpenes (78.6%) *i.e.*, 1, 8-Cineole (55.3%), Spathulenol (7.4%) and α-Terpineol (5.5%) being the main components [22]. Eucalyptus oil shows considerable inhibitory action against a number of viruses, particularly the swine flu (H1N1) virus and herpes type-1 (HSV1) virus [23]. In vapor phase, Eucalyptus oil and its main compound eugenol are effective against influenza virus [21]. *Eucalyptus* oil can affect the innate cell-mediated immune response. *Essential* Oil is able to stimulate MDMs, which triggers phagocytic response [24]. Just similar to Rosemary Oil, eucalyptus oil also contains 1, 8-cineol abundantly. Therefore, it is believed to show strong anti-viral activity against the Covid-19 virus.

Lemon Balm Oil: The main active constituents of *M. officinalis* are volatile compounds (*e.g.*, geranial, neral, citronellal, and geraniol), triterpenes (*e.g.*, ursolic acid and oleanolic acid), and phenolics (*e.g.*, cis-and trans-RAisomers, caffeic acid derivatives, luteolin, naringin, and hesperidin) [25]. Lemon balm essential oil shows inhibitory activity against the influenza virus. Active constituents present in Lemon balm oil can arrest the replication cycle of influenza virus [26]. Because of its anti-viral activity, it can be used in treatment against Covid-19.

Thyme Oil: The active constituents thymol (40.5%), *p*-cymene (23.6%), carvacol (3.2%), linalool (5.4%), β-caryophyllene (2.6%) and terpinen-4-ol (0.7%) are present in thyme oil [27]. Essential oils from eucalyptus, tea tree, and thyme and their major monoterpene compounds α-

terpinene, γ -terpinene, α-pinene, p-cymene, terpinen-4-ol, α-terpineol, thymol, citral, and 1,8-cineole are examined for *in-vitro* antiviral activity against herpes simplex virus type 1 (HSV-1). These essential oils are able to reduce viral infectivity by >96%; the monoterpenes inhibited HSV by about >80% [12].

Among the investigated compounds, monoterpene hydrocarbons are with predominant antiviral properties. Alpha-pinene and alpha-terpineol reported with the highest selectivity index [12]. Presence of monoterpenes, α-terpineol, α-pinene, terpinen-4-ol, 1, 8-cineole reported showing strong inhibitory activity against Covid-19 [9].

Oregano Oil: The primary compounds are carvacrol and thymol, ranging to over 80%, while less abundant compounds include p-cymene, γ-terpinene, caryophyllene, spathulenol, germacrene-D, β-fenchyl alcohol, and δ-terpineol [28].

Oregano oil and carvacole exhibit antiviral activity against HSV-1 rotavirus, a common causative agent of diarrhea in newborns and children. Also, effective action against Respiratory Syncytial Virus (RSV), which causes respiratory infections [29, 30]. Thus, it may show anti-viral activity against the SARS-CoV-2 virus.

Fennel Oil: Phenylpropanoid compounds (52.1%-57.7%) and monoterpenes (39.2%-45.3%) characterize the majority of the fennel essential oils. Trans-anethole, estragole, limonene, fenchone, α-pinene, y-terpinene, and myrcene are the chief constituents [31]. The main component of fennel essential oil trans-anethole has demonstrated a strong antiviral effect against herpes viruses [32]. Because of its anti-viral activity, it can be used in treatment against COVID-19.

Peppermint Oil: The main chemical compounds are menthol (7-48%), menthone (20-46%), menthyl acetate (3-10%), menthofuran (1-17%) and 1, 8-cineol (3–6%). Peppermint oil also contains limonene, pulegone, caryophyllene and pinene in trace amounts. *In-vitro*, peppermint has noteworthy antimicrobial and antiviral action [33].

Cinnamon Oil: Cinnamaldehyde (65-80%) and eugenol (5-10%) is principally present in the oil. Other abundant constituents are the cinnamyl group such as cinnamic acid and cinnamyl acetate, compounds containing endocyclic double bond as α-thujene, α-terpineol, α-cubebene, unconjugated exocyclic double bond eugenol, β-caryophyllene, terpinolene, and hydroxyl-substituted aliphatic compounds [34].

Cinnamon oil with eucalyptus and rosemary essential oils shows synergism against flu viruses. Its active components show strong anti-viral activity [35].

Clove Oil: The major constituents of the clove oil are m-Eugenol (69.4%), Eugenol acetate (10.8%), Tyranton (7.8%) Caryophyllene (6.8%), 1, 4, 7-Cycloundecatriene, 1, 5, 9, 9-tetramethyl-, and trace amounts (<1%) of other constituents [36].

A blend of clove oil, wild orange oil, and cinnamon oil exhibited noteworthy antiviral activity with a 90 percent reduction in viral particles. The oil blend also decreased viral infection [37].

A literature survey shows the activity of enlisted essential oils against various viruses. Thus enlisted oils can be used to get rid of deadly coronavirus. Whether all these enlisted oils are effective against coronavirus or not, will need clinical trials.

But all these mentioned oils definitely can be used to stop the further growth and to get some relief from deadly virus. All essential oils can be administered via nebulizer or inhaler.

Inhalation Therapy as a Treatment:

- Use of essential oil diffuser or Nebulizer.
- Inhale vapors of Essential Oil.
- Active constituents will reach the blood via Lungs.
- (Active constituents Like 1, 8-Cineole, α-β pinene, β-Ocimene.
- Rosmarinic acid, Carnosic acid, sabinene) will show their action.
- Desired Effect (Anti-viral action against Covid-19).

Though all the mentioned oils can be used as adjuvant therapy, Ayurvedic ocean suggests some

herbals which can be used as a preventive measure:

TABLE 4: LIST OF HERBALS USED AS IMMUNO-MODULATOR

S. no.	Essential Oils
1.	Ginger
2.	Garlic
3.	Mushrooms
4.	Turmeric
5.	Cardamon
6.	Black Pepper
7.	Nutmeg
8.	Saffron
9.	Asafetida
10.	Chili
11.	Coriander
12.	Cumin

Turmeric: Turmeric is a common spice in India with extensive medicinal applications for ages. Curcumin, one of the major active compounds of turmeric, has the immune-boosting ability. Literature supported that curcumin helps to activate various defense mechanism cells of the body and suppresses pro-inflammatory cytokines. Curcumin can enhance an antibody response and regulates gut microbiome [38].

Ginger: This spicy plant is acclaimed for its aid in nausea. Ginger contains several active chemical constituents which are effective against a common cold-causing virus [39].

Black Pepper: Pepper reported to has considerable antimicrobial properties, hence effective against the common cold. Including it in your daily diet will help to improve immunity and aids in getting rid of various respiratory illnesses [40].

Cumin: Cumin is a rich source of iron. It is full of antioxidants, and has been shown to exhibit anti-microbial and anti-inflammatory activity. Studies revealed that cumin helps with digestion and prevent food-borne infections [41].

Garlic: Garlic can be used effectively for prevention and treatment of different diseases. Active compounds in garlic are believed to reduce the risk of cardiovascular diseases. Also, garlic possesses anti-microbial action and keeps a check on high blood glucose level [42].

CONCLUSION: Covid-19 has become a concern worldwide, claiming thousands of lives on a daily basis. Yet no full-proof treatment is approved globally for this pandemic.

All the treatments available are mainly supportive. However, some of the essential oils are reported to have anti-viral activity against SARS-CoV-1. Based on the genetic resemblance between SARS-CoV-1 and SARS-CoV-2, these essential oils can be effective against Covid-19. Therefore, use of simple essential oils diffuser or nebulizer for inhalation of essential oils such as *T. orientalis, J. oxycedrus, L. nobilis*, Rosemary, Ravensara, Ravintsara, Tea Tree, Bergamot, Eucalyptus, Lemon balm, Thyme, Oregano, Fennel, Peppermint, Cinnamon, Clove can be supportive treatment strategic tool against deadly Covid-19 disease. But further effectiveness of these essential oils against Covid-19 needs clinical trials. Apart from the essential oils therapy, immunity-boosting herbs can be included in daily diet.

ACKNOWLEDGEMENT: Authors doesn't want to acknowledge to anyone. This piece of review work is compiled by three authors.

CONFLICTS OF INTEREST: None

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How to cite this article:
Patne T, Mahore J and Tokmurke P: Inhalation of essential oils: could be adjuvant therapeutic strategy for Covid-19. Int J Pharm Sci & Res 2020; 11(9): 4095-03. doi: 10.13040/IJPSR.0975-8232.11(9).4095-03.