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Essential Oils of Allium Sativum and Eucalyptus Globulus as Antagonists for Sars-Cov-2 Infection: A Review

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ABSTRACT

The COVID-19 (2019 Coronavirus) has recently turned into a significant matter of concern on a worldwide scale, posing a substantial risk to human health. Consequently, only a few FDA-approved drugs are effective to defend against the virus, that considered being accountable for the viral condition. Immunotherapy research is ongoing, but it may be many years before these treatments are accessible to the general population. In some cases, specific drugs, such as antimalarial drugs (chloroquine/hydroxychloroquine), dexamethasone, Interleukin-6 binding site preventing mabs (tocilizumab), and antiviral drugs (remdesivir), have been used in conjunction with other drugs for treating COVID-19, that the Food and Drug Administration doesn't approve. Due to their aqueous solubility, essential oils can rapidly permeate virus walls, causing parturition to occur.

Essential oils also include several active compounds which have been shown to work collaboratively on numerous stages of viral entry and to have favorable impacts on the host airways, including mucus lysis and bronchodilation. However, at a juncture, just a few in vitro tests and a few machine docking research have been undertaken to show the essential oil's properties which is to combat viruses such as the SARS-CoV-2. Essential oils get a huge part to play in the reduction of risk and treatment of COVID-19, and hence the article examines their role in these mechanisms. The chemical constituents of essential oils and the possible negative consequences are discussed in depth. We also detail the anti-corona virus promises made by the critical oil sources. According to present understanding, it is probable that such essential oils combination of the treatments would be a more practical and effective method of countering the viral outbreak than individual medications.

The primary goal of this review is to determine whether or not Garlic and eucalyptus essential oils are effective against SARS-CoV-2 infections. Moreover, the objectives are; (1) to identify the potential role of essential oils on SARS-CoV-2 prevention and therapy; (2) to describe the test on the anti-virus performance of essential oils' major components; and (3) to discover the most suitable technique for determining the essential oils' standard dosage and therapeutic application towards the virus named SARS-CoV-2, as well as the most effective approach for its assessment.

Introduction

The severe acute respiratory syndrome coronavirus 2, a pathogen, which attacks the lungs, was found in 2019 but has given rise to a new respiratory disease implicated in extensive morbidity and mortality around the globe. It is the CoV (Coronavirus), which is a lone-stranded positive ribonucleic virus pertaining to that same Coronaviridae classification, that is responsible for the condition. The group consists of multiple species that are capable of infecting mammals, especially humankind [1]. Both of these strains, according to the findings, are derived from the bat species Rousettus leschenaultia, which translates as "small bat" [2].

Conditions of coronavirus produced by the virus of COVID-19 have already been considered a major cause of coronavirus sickness in 2019 [3], and they are predicted to become more prevalent. Also, it is believed that recipient particle walls wrap around viruses, encasing virus antigens on the surface and enabling these viruses to proliferate in the infected cells' habitat. When the pathogen is observed under a microscope, a surface protein on the virus known as the spike protein or S protein can be seen emerging from the walls, giving the virus a characteristic crown appearance. As a result, the viral pathogen was given the name Coronavirus, which is a Latin word that means crown or garland. As eventually, as the pathogen enters through the airways, SARS-CoV-2 begins to cause severe damage towards the respiratory epithelium, especially the airways, hampering the potential of the respiratory system to expel mucus and debris, which may result in pneumonia. Among the symptomatology of COVID-19 are dry cough (62%), shivers, fatigue (70%), flu (98%), sputum development (27%), arthralgia, headache, lethargy, myalgia (35%), dyspnea (31%), anorexia (40%), vomiting, and nausea. The most severe cases of a cytokine storm are characterized by a significant upregulation of inflammatory molecules in the blood, including il6 together with TNF-a in the circulation. Acute Respiratory Distress Syndrome, known as ARDS, can occur under severe circumstances, with associated consequences including septicemia, electrolyte imbalance, clotting failure, and even mortality [4]. For the time being, it seems that there is no well-defined, coordinated, and successful curative therapy for the virus of COVID-19.

Other strategies, however, have now been examined in a variety of individuals based on their individual indications, feelings, and overall health, such as modifying the pH of alveolar cells and endosomes, which has the effect of interfering with viral proliferation and endocytosis [5]. Remedies to long-term care serum and interleukin-6 antagonist tocilizumab, a reverse transcriptase humanized anti-human mab, have been explored in medical studies. Early findings suggest that they have been efficient [6]. Even though there is currently no vaccine available to guard against the said virus, academic studies are being conducted to examine the efficiency of several freshly formed vaccines; regrettably, this one will take a while to establish.

Essential oils have the capacity to penetrate the cell wall phospholipid bilayer of the viral membrane, where they have the potential to cause infection. This is due to the general lipophilicity of the essential oils. Consequently, the liquidity of the barriers was changed, and at higher amounts, they were ripped, causing the membranes to lose their ability to perform their role. Deliberate actions on unrestricted pathogens, inhibition of segments required for pathogen adhesion, infiltration, subcellular procreation, and discharge from infected cells, and suppression of indispensable proteinases, as depicted in Figure "1", are the most considerable mechanisms by which essential oils exert antiviral influences [7]. The various antiretroviral capabilities of EOs have led to various assertions by distributors of essential oils that their products are a viable therapy for the condition. The severe acute respiratory syndrome was already studied to this area, and the effectiveness of essential oils against it has been shown. It is the target on this prevailing exploration to consolidate all various verifiable basis regarding the possible essential oils' therapeutic effects towards combating the COVID-19 virus, hence reducing the public health threat that the virus poses to the public.

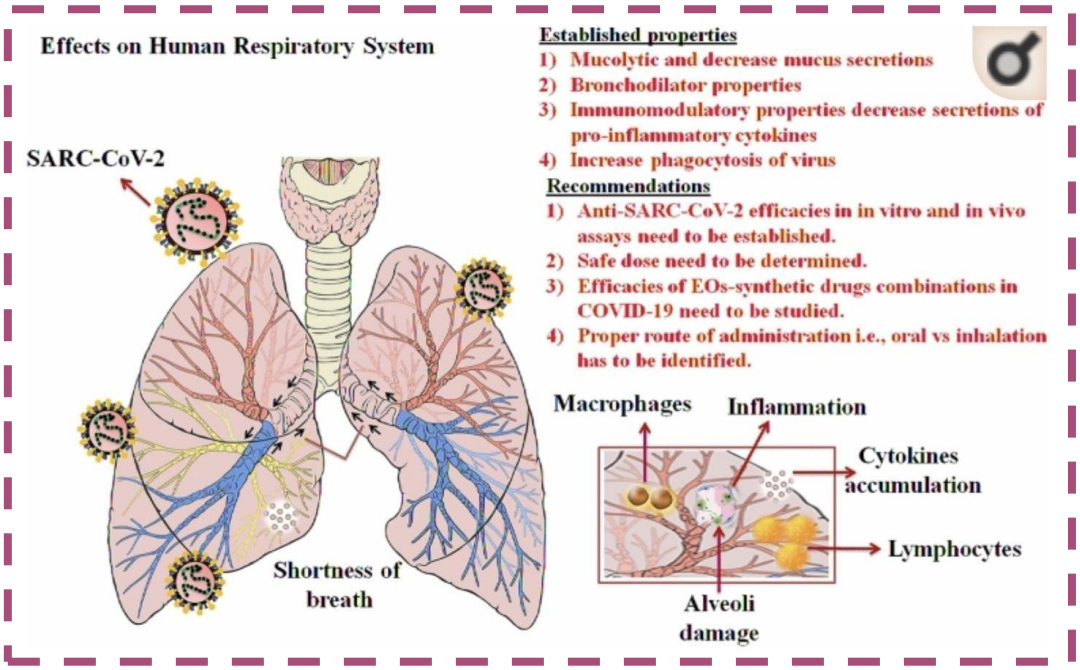

Figure 1: Various influences that COVID-19 virus impacts on the Respiratory System of a Human [23].

Established properties are the effects of the EOs on the hosts' respiratory system which are backed up by studies that were conducted and the recommendation represents the studies to be ventured more to prove that essential oils can be a useful strategy in combating the whole pandemic. It is said that Eucalyptol has mucolytic, bronchodilatory, and immunomodulator properties and menthol has been shown to prevent inflammation, which also has properties that protect the gastrointestinal tract in rodent experiments. This study is required to show the essential oils' appropriate dosage and therapeutic performance which combats SARS-CoV-2.

Methods

Eligibility Criteria

The current research gives exact and reliable information on essential oils, as well as its viable involvement of its treatment along with prevention of Coronavirus 2. Publicly accessible material were assembled utilizing the internet database with diverse research-based sources, such as Google Scholar, PubMed, and ScienceDirect. The prominent journal has also included other sources such as Clinical Trials Database, Scientific Electronic Library Online (SciELO), and Cochrane Library. The review database comprised peer-reviewed journals, papers, books, and other studies regarding the regular use of essential oils that provides anti-SARS-CoV-2 properties. The terms "antiviral," "COVID-19," "essential oils," "immunomodulatory," "SARS-CoV-2," and "anti-inflammatory" was used to search for related studies which were used alone or in conjunction with Boolean operators ("and,"and ", "or," "not,"and not"). It has long been recognized as the effects of essential oils which are immunomodulatory, antiviral, and anti-inflammatory. Several

studies have looked into and shown essential oils to be powerful antiviral agents against viral infections of the respiratory system, making them a strong contender to fight the Coronavirus.

Mechanism of SARs-CoV-2 Infection

The SARs-CoV-2 depends on intracellular proteinases for spike protein stimulation that was observed by Hoffmann, with his associates, which would be recognized to engage with human angiotensin which converts enzyme 2 receptors in its airway system that makes it easier for cells to enter. According to the findings of this research, Camostat Mesylate, a potent serine protease inhibitor, reduced infection of cells through in vitro experiments by suppressing the transmembrane serine protease 2 protein, which has been found to be the root of the infection. In addition to the proteases listed above, it has been shown that the said pathogens utilize endocytic cysteine proteolytic enzymes and also proteinase B and L, for spike protein amplification in contrast to the proteases previously discussed [8]. It also has been looked at the anti-virus potency of the following food and drug administration-approved medications, which include nafamostat, penciclovir, ribavirin, nitazoxanide, chloroquine, as well as the multiple common antiviral, wide treatments that includes favipiravir and remdesivir. The researchers employed SARS-CoV-2 strains isolated from the year 2019 forward. A study was conducted to determine the response of African wild monkey hepatocytes to multiple doses of medicines in the presence of SARS-CoV-2 to determine how they might behave. The percentage of viral replicas was determined using reverse transcription polymerase chain reaction techniques embedded in the cell homogenates, and this was utilized to determine the rate of infection. As an example, remdesivir, a nucleoside analog, and chloroquine have both demonstrated to be particularly successful over stopping the spread in the SARs-CoV-2 virus in African wild monkey cells and human respiratory cells especially the animal models in vitro and in vivo [9]. Hydroxychloroquine and chloroquine, known to be antiviral drugs, have been proven to block the liberation of the viral DNA by preventing the transition of the virus endolysosomes from endosomes. Further research has shown that chloroquine may cause endosomes to become acidic. This can prevent endocytic development from occurring and ultimately result in the inability of the said virus to be delivered and discharged from the membrane. It has also been proposed that hydrochloroquine acts as a therapy for patients on COVID-19 to inhibit pro-inflammatory cytokine production, which are known to cause aggregation [10].

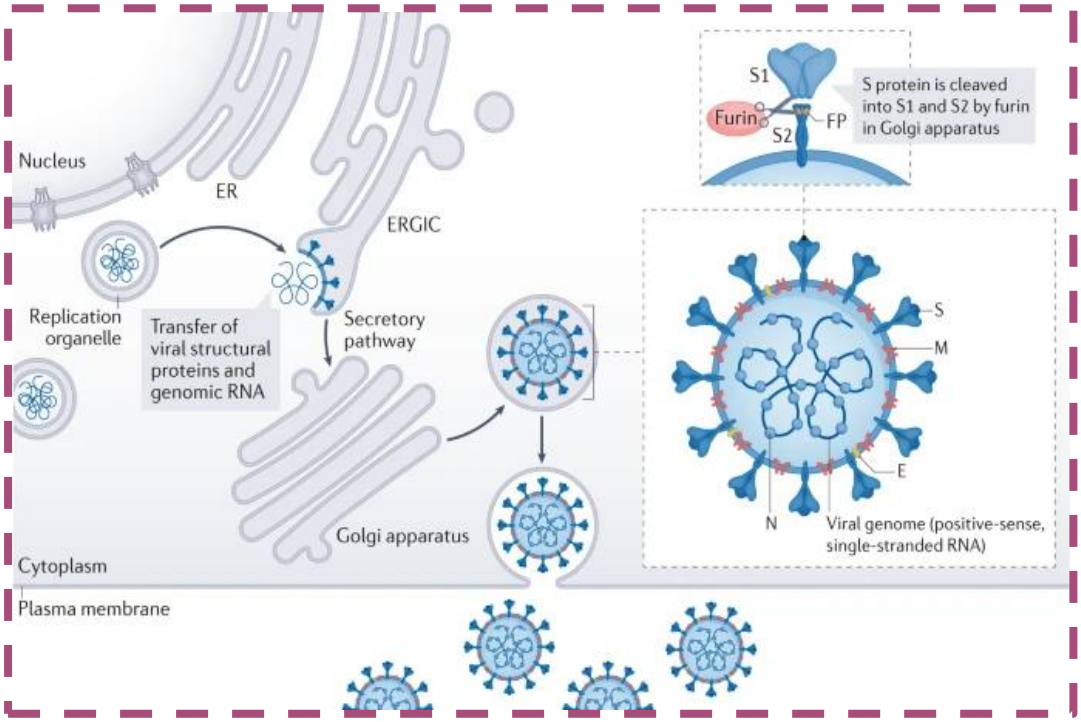

Figure 2: The structure and maturation of the coronavirus [11].

A coronavirus infection causes the new membrane structures of varying sizes and forms are formed in the perinuclear region, which are collectively called "replication organelles." [11] They are typically surrounded by double membranes and seen in cells infected with respiratory syndrome coronavirus in Middle East, acute respiratory syndrome coronavirus, or hepatitis virus of mice, using electron microscopy are assumed to come out-of the endoplasmic reticulum and store the virus replication complexes. In addition to that, it helps in keeping them safe from cellular innate defense molecules. The viral structural proteins and genomic RNA produced at the replication site are then transported to the ER–Golgi intermediate compartment, in which the virus assembly and budding happen, by an unknown process [12]. The envelope, membrane, spike, and nucleocapsid proteins are the only ones integrated into the virion. The structure of proteins S, E, and M are integrated into the virion membrane while the N protein coupled to the viral genomic RNA is packed inside the virion. Major entrance processes, such as receptor binding and membrane fusion, are intervened by the S protein, which is organized on being a trimer, yielding the image of a crown (corona). Furin or furin-like proprotein convertase in the Golgi apparatus cleaves the S protein into the S1 and S2 subunits all through synthesis and maturation in the infected cell [13]. The virus's S Protein is made up of two non-covalently related subunits with distinct functions: the S1 subunit coheres the receptor in the new target cell, while the S2 subunit fixes

the S protein to the virion membrane and promotes membrane fusion. Through interactions with other viral proteins, the E and M proteins aid in virus assembly and budding [14]. Viruses that have been assembled reach the ERGIC lumen and travel down the secretory route to the plasma membrane, when virus-containing vesicles fuse to the plasma membrane, they are discharged onto an extracellular environment. FP stands for Fusion Peptide.

Moreover, oils extracted from plants, known as EOs, which includes a complex combination of volatile phytoconstituents from different classes, such as terpenoids, triterpenes, and phenylpropanoids. A substantial amount of study has been done on essential oils for their benefits such as having antifungal, antibacterial, antiviral, and antioxidant effects by a large number of researchers. A variety of viruses, including herpesviruses, viral influenza, yellow fever virus, avian influenza, and human immunodeficiency virus, were proven to be resistant to these essential oils' antiviral effects. The viral mutant simplex of herpes which can be classified as types 1 and 2 are famous for generating a multitude of existing infections in humans and for being one of the major causes of death from immunosuppressed patients. Specifically, Histoplasma herpes simplex virus, which is classified as type 1, is the pathogen that causes sores in the mouth passage, icluding dermis; as well as its type 2 induces genital warts, which is a condition that is acquired via sexual intercourse. Schnitzler and colleagues revealed that oils from the lemon balm suppressed the development of plague in both types 1 and 2 of the Histoplasma herpes simplex viruses in an amount of the drug manner in a subsequent in-vitro investigation.

Additionally, it was able to practically eradicate the virus's ability to infect other cells. There seems to be substantiation that which was before with essential oils acquired from the Melaleuca alternifolia, illicium verum, Matricaria recutita, and Leptospermum scoparium can impede the pathogenic potential of herpes simplex virus strains that were acyclovir-sensitive and resistant, implying the tremendous antiviral prospects of essential oils [15]. The anti-viral activities of EOs obtained from several plant genuses were examined using in vitro techniques in both vapor and liquid states. Essential oils that are derived from Eucalyptus globulus Citrus bergamia, along with their isolated constituents Eugenol and citronellol, have just been proved to possess antiviral activity when emissions of these essential oils were inhaled. Comparatively, once examined in fluid states, the essential oils procured from Citrus bergamia, Cinnamomum zeylanicum, hymus Vulgaris, and Cymbopogon flexuosus demonstrated outstanding anti-viral attributes, exemplifying 100 percent inhibitory activity against the virus at 3.1 nanograms per milliliter when especially in comparison to the other essential oils studied. When administered to nanosheets of epithelium, the utilization of essential oils in their vapor state has therefore been shown to be safe (see Figure 1). Studies have identified that inhalation of essential oils in the gaseous phase may be therapeutic for those who are struggling with viral infection [16]. According to the findings of scientists, carvacrol together with its isomer called the thymol, which may have been synthesized from oregano, can block viral replication adhesion by withdrawing viral lipoprotein from the type 1 human immunodeficiency virus envelope walls, therefore preventing the virus from infiltrating the host [17].

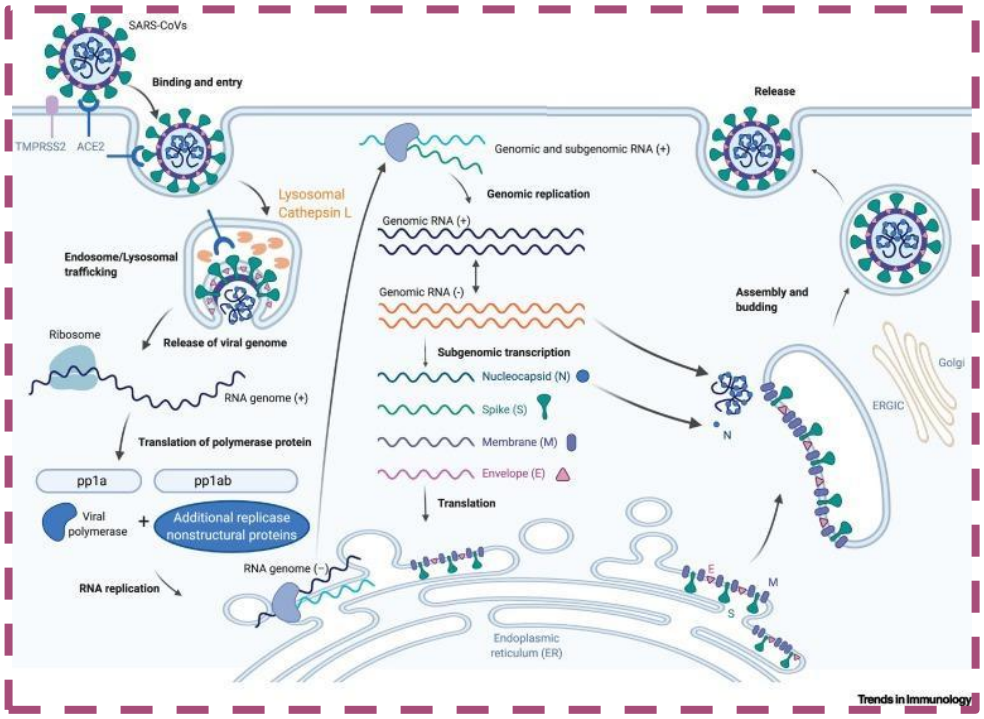

Figure 3: The Life Process of the SARs-CoV-2 Virus [17].

The lifecycle of SARS-related coronaviruses like SARS-CoV and SARS-CoV-2 starts by the binding of the envelope Spike protein to its cognate receptor, angiotensin-converting enzyme 2. Well-ordered host cell entry then depends on two things; (I) the cleavage of S1/S2 site by the surface of the transmembrane protease serine 2 and/or (II) endolysosomal cathepsin L, which mediates the virus-cell membrane fusion at the cell surface and endosomal compartments, respectively. Through either of the entry mechanisms, the RNA genome is released into the cytosol wherein it is translated into the replicase proteins. The polyproteins (pp1a and pp1b) are cleaved by a virus-encoded protease into individual replicase complex nonstructural proteins (including the RNA-dependent RNA polymerase: RdRp). Replication begins in virus-induced double-membrane vesicles which are derived from the endoplasmic reticulum which combines to form elaborate webs of convoluted membranes. The incoming positive-strand genome here then

serves as a model for full-length negative-strand RNA and subgenomic RNA. Structural and accessory proteins (represented in the figure as E, N, S, and M) are the sgRNA translation results that are inserted into the ER-Golgi intermediate compartment for virion assembly. The last step is that the subsequent positive-sense RNA genomes are then absorbed into newly synthesized virions which are secreted from the plasma membrane.

Eucalyptus Oil

Eucalyptol is an organic chemical that occurs naturally in many eucalyptus species, primarily Eucalyptus globulus, and makes up the bulk of EO extracted in distinction to these species. When it is discovered in its natural form, eucalyptol is colorless and aromatic, and it possesses mucolytic and bronchodilatory capabilities [18]. Attributed to its propensity to attach into viral proteinase, eucalyptol is conceivably a probable inhibitor of SARs-CoV-2, according to new Molecular Docking research is directly accessible as an introductory report (Sharma and Kaur, 2020). To add it up, it's a colorless liquid with a pleasant fragrance in its natural state and it's composed of both a monoterpene which is 1,8-cineole, and a cyclic ether as well [19]. It's been hypothesized regarding eucalyptol that it can serve as an antibacterial as well as an antiphlogistic agent, which reduces production of inflammatory mediators, for example, TNF-, IL-8, IL-6, and causing epigenetic alterations in white blood cells [20].
According to Zhang et al. (2020), more study is needed on eucalyptol since its probable mechanism of action might contribute significantly in the pathophysiology of lung damage and the beginning of the so-called "cytokine release syndrome," which has been associated to poor clinical outcomes in COVID-19 patients [21]. Eucalyptol, a chemical molecule made up of cyclic ether and a monoterpene which is 1,8-cineole, is a colorless liquid with a pleasant aroma when found in its natural state. In vitro studies carried out by Brochot and associates (2017) disclosed that EEO and its functional ingredient, 1,8-cineole in eucalyptol, showed antiviral activity against the influenza A virus, which had previously been reported. Both 1,8-cineole and essential oil have been postulated as potential agents for inactivating and altering the envelope structures of the free viral influenza A [22].

Garlic Oil

A lengthy history of anti-infective usage in both food and medicine may be traced back to the plant Allium sativum, which is generally known as Garlic. These assertions are backed up by in vitro evidence of fresh and freeze-dried garlic extracts' antibacterial effectiveness countering an extensive amount of viruses, fungus, and bacterias. According to pharmacological studies, essential garlic oil is a good fount of natural sulfur-containing components, which have potent antioxidants, antibacterials, antifungals, antitumor, and antiviral activities [23]. Hypoglycemia, prebiotic disorders, immunomodulatory, hypotension, and antithrombotic can all benefit from the oil. According to a recent study, garlic has lately been presented as a feasible choice for preserving immune system homeostasis. DADS suppressed the replication of the human cytomegalovirus (HCMV) as well as immediate-early virus gene expression. It works by boosting the activity of natural killer cells, which are responsible for killing virus-infected cells. In a mouse leukemic monocyte/macrophage cell line, DADS drastically lowers NO generation, protein expression, and pro-inflammatory-inflammatory cytokines. As a result, garlic components may serve as immunomodulatory agents on macrophage responses [24]. Garlic's antiviral activities are attributed to the action of its features. When fed to mice in vivo, allicin demonstrated antiviral efficacy to counter influenza viruses by escalating the generation of neutralizing antibodies. Oxidative stress caused by viruses is essential in both the life cycle of a virus and the development of virus infection [25]. According to Lee 2018, this activates host antioxidant pathways such as nuclear factor erythroid 2p45-related factor 2 [26]. Several genes involved in the antiviral activity are regulated by the Nrf2 transcription factor. Diallyl sulfide, one of Garlic's active ingredients, has been reported to activate Nrf2 in lung MRC-5 cells. Garlic essential oils and their separated components, specifically DAS, can block virus entrance into host cells while also activating molecular antioxidant pathways that lower the secretions of culprit pro-inflammatory-inflammatory cytokines, according to Asif et al. (2020). The research found that beginning Nrf2 reduced the severity of the cytokine storm in COVID-19 patients significantly [27].

Phytochemical Constituents of Essential Oils: It's Benefit on Covid-19 Infection

α-farnesene, β-farnesene, and farnesol

The antiviral qualities concerning essential oils have been demonstrated against a variety of harmful viruses. Significant protein targets of the 2019 Severe Acute Respiratory Syndrome Coronavirus 2, or SARS-CoV-2, may react to essential oil components. According to Silva et al. (2020), there were 171 elements of essential oil that were tested for antiviral efficacy against a variety of SARS-CoV-2 proteins, that includes the main viral proteases, endoribonuclease, RNA-dependent RNA polymerase ADP-ribose-1-phosphate, and RNA-dependent RNA polymerase [28]. To Mpro of SARS-CoV-2, the sesquiterpene hydrocarbon (E)—farnesene has the highest normalized docking score. The best docking ligands for SARS-CoV Nsp15/NendoU were alpha-farnesene, farnesol, and beta-farnesene. Farnesol docked in the most exothermic manner to SARS-CoV-2 ADRP. As a result, either used alone or in combination, they can all reduce viral replication. Docked poses of farnesol, farnesene and farnesene with Coronavirus 2 Mpro, Nsp15, ADRP are shown in Figure 4.

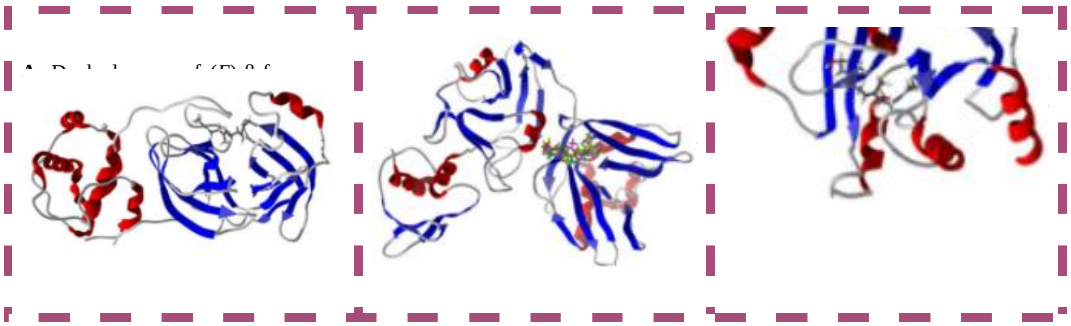

Figure 4: Docked poses of various antiviral agents [29].

Furthermore, unstructured protein 15, that is an endoribonuclease that prefers to cleave at uridine residues, is responsible for the emerging spread of SARS disease, according to Bhardwaj et al. (2006). SARs is caused due to a new Coronavirus that develops a number of atypical RNA-processing enzymes, including non-structural protein 15, an endoribonuclease that tends to cleave to uridine residues. When coupled with Nsp15, only the molecules (E,E)-farnesol, (E)-nerolidol (E,E)-farnesene, and (E)-farnesene obtained the highest binding scores [29].

A protein called RNA-dependent DNA polymerase catalyzes a virus's capacity to duplicate its RNA, which is a crucial stage in viral replication. As a result, it's a good candidate for antiviral therapy, according to Shuai et al., (2006) [30]. (E,E)-farnesol obtained the best docking scores against RdRp of all the drugs examined. Zhang et al. (2020) discovered that the ACE2 proteins on host cells interact on the spike protein for SARs-CoV-2, enhancing the viral cell's attachment to the human cell. The spike proteins of SARs-CoV-2 and SARS-CoV have nearly identical 3-D structures in the receptor-binding domain, which is responsible for maintaining van der Waals forces, according to researchers from the University of Hong Kong. Based upon the biochemical interactions and the crystal structure study, the spike protein of SARs-CoV has a strong affinity for the ACE2 protein of the human. As a result, this interface may be a desirable target for decreasing SARs-CoV-2 rS binding to human pulmonary cells [31].

The SARS-CoV-2 virus spike protein is in charge of binding to the human cell's angiotensin-converting enzyme 2 before invasion according to Silva and her colleagues, 2020 [28]. At their interface, SARs-CoV-2 rS as well as human ACE2 interact, which could be a good target for inhibiting SARs-CoV-2 rS from adhering onto the human ACE2. Several of the most effective docking ligands for human ACE2, defined as those with normalized docking scores less than -100 kJ/mol (-bulnesene, eremanthin, (E,E)- nerolidol, (E)- nerolidol, alpha - farnesene, beta - farnesene, (E,E)- farnesol, (Z)- spiroether, and In the case of SARS-CoV-2 spike proteins, (E)- cinnamyl acetate, eremanthin, (E,E)— farnesene, (E)- farnesene, (E,E)- farnesol, and geranyl formate were found to have much higher binding potentials than eremanthin, (E,E)- farnesene, (E)- cinnamyl acetate [26]. These phytochemicals, which are found in various plant concentrations in essential oils and can be used as a treatment for COVID-19, are found in various plant concentrations in essential oils and can be used to treat COVID-19. Before this can be done, information from entrenched preclinical and clinical studies is required.

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

Anthocyanins are found in essential oils, especially geraniol, thymol, anethole, cinnamaldehyde, cinnamyl acetate, L-4- terpineol, and *p*-Menth-4(8)-en-3-one block on the binding of the receptor on domain subunit of S proteins of COVID-19. Although anethole did not demonstrate any substantial anti-inflammatory effect, several of anethole's derivatives did show modest anti-inflammation activities. The anti-inflammation activities of anethole may have been enhanced and activated through adding hydroxyl groups into the conjugated double bond of the compound [32].

COVID - 19 has the potential to cause pulmonary hyperinflammation. Cinnamaldehyde, another active ingredient with anti-inflammatory effects, is also present. This chemical component is responsible for the odor and taste of cinnamon, and it is also the source of a large amount of the essential oils that are extracted from it. Cinnamaldehyde inhibits the activation of the nuclear factor-B, which leads to an attenuation of TNF-induced inflammation. It can also prevent endotoxin-mediated hyperexpression of TLR4 and NOD- [33]. Cinnamaldehyde also exhibited inhibition to the development of the influenza PR8 virus in MDCK cells [34].

Carvacrol could be a possible constituent on tackling SARs-CoV-2 through its antiviral, anti-inflammatory, and immunomodulation. Carvacrol, which is produced from oregano oil, has been investigated for its antiviral properties against rotavirus, murine norovirus, bovine diarrhea and respiratory syncytial virus. Results showed that the viruses had been deactivated within 1 hour of exposure to Carvacrol. Moreover, plants containing significant amounts of Carvacrol and Carvacrol's derivatives showcase inhibition to inflammatory mediators, pro-inflammatory-inflammatory cytokines, and CD18 frequency on human lymphocytes. This component's ability in immunomodulation could greatly aid in limiting the adverse immune-inflammatory effects of COVID - 19 [35]. Patients who have a non-infectious obstructive respiratory disease secondary to being exposed for a prolonged time to sulfur mustard from a study in 2019 yielded enhancements and positive results from their respiratory strength tests after the treatment with Carvacrol. It was stated that inflammatory cells and oxidative biomarkers were lessened after the introduction of this component [36].

A study focused on and evaluated the immunomodulatory and anti-inflammatory effects of geraniol stated that geraniol exhibits an increase of interleukin-10 by human monocytes. Interleukin-10 is noted for being an essential anti-inflammatory cytokine. The study concluded that the immunomodulatory activities shown in human monocytes were the monoterpene geraniol's responsibility [37].

Carvacrol, Eugenol, and Menthol

Silva et al. have used molecular docking methods upon investigating the anti-Coronavirus 2 efficacy of carvacrol, eugenol, and menthol, three key elements of essential oils, countering diverse proteins known to be SARs-CoV-2 targets. According to the results, these medications displayed strong binding affinities for the spike protein of SARC-CoV-2, the main proteinase, the RNA-dependent RNA polymerase, and the ACE2 proteins of humans [38].

Traditional Asian medicine has traditionally employed natural menthol-rich plant extracts to treat and prevent respiratory problems. Menthol has been shown to give therapeutic benefit from sinus problems caused by sinusitis, as well as the impression of dyspnea caused by airway obstruction, by interacting from a menthol cold sensitive receptor found on the trigeminal nerve endings [39]. In rat illness models, menthol have been found to have anti-inflammation, immunomodulatory, and gastroprotective activities. Menthol treatment significantly reduced pro-inflammatory cytokines such as interleukin-23, interleukin-1, as well as tumor necrosis factor-alpha in rats, according to a study [40;41].

Eugenol exhibits antiviral effects opposing the herpes simplex virus types 1 and 2 [42]. It also has the effects of anti-inflammation and appears to be protecting the lungs from the acute effects of lipopolysaccharide. Furthermore, Eugenol therapy inhibited leukocyte migration into the lungs as such as the production of pro-inflammatory-inflammatory cytokines (IL-6 and TNF-) [43].

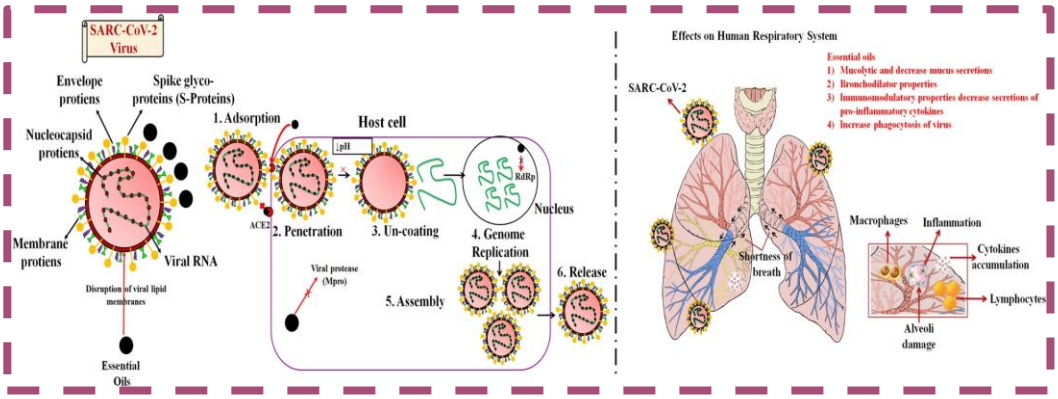

Figure 5: Essential oils' antiviral and synergistic effects [38].

Claims and Limitations of Current studies on EOs manufacturers/sellers

Several essential oil distribution and extraction businesses claimed that their oil-based products were effective against COVID-19. It happened after bits of initial scientific evidence regarding the anti-SARS-CoV-2 capacity on EOs as well as its active ingredients arose. These claims have already been noted and responded to by the United States Food and Drug Administration and its other government bodies. Companies selling essential oils that make similar claims have received warning letters from the FDA. The Drug Evaluation and Research Center in the United States issued a notice letter (MARCS-CMS 605752) to an institution. Those materials on the anti-corona effectiveness of essential oils produced from Eucalyptus species, grapefruit, rosemary, tea tree, ginger, frankincense, lavender, clove, and lemongrass were later taken down. Aside from that, a company received another warning notice saying that a product called "Nobel laurel" had immune-boosting, antiviral, and anti-corona effects. This is why the FDA has written to a number of companies that make false promises, notably in the area of diagnostic products and other materials.

Hypersensitivity responses are another concern connected with the usage of essential oils. Some EO, such as linalool and pinene, have been linked to its variety of pulmonary problems, including allergic rhinitis and allergic asthma, according to Gibbs (2019) [44]. According to Burfield (2000), specific persons have been allergic to certain compounds of Essential Oils that can develop a wide variety of adverse reactions as a result of exposure, which includes contact dermatitis [45]. Aside from that, Lakhan S. (2016) stated that EOs might cause slight irritation of the skin at the application site in some situations. Essential oils could trigger phototoxic responses if consumed in a sufficient doses, which can be fatal in rare cases [46]. According to Ackerman L (2020), there is often doubt about the efficacy of EOs among the general public and food and medicine regulators [47]. In addition, few comprehensive assessments provide evidence for EOs'EOs' overall usefulness. A definition of the exact biological processes through EOs deliver benefits to people is notably lacking in the EO literature. Finally, Lee M et al. (2017), inhaling essential oils as part of aromatherapy reduced subjective stress and depression and improved sleep quality but had no effect on physiological indicators like the stress index or immunological condition [48].

Discussion

There is a chance that COVID-19 can be the cause of pulmonary hyperinflammation. In spite of that, anethole did not present any substantial anti-inflammatory effect but a variety of anethole's derivatives exhibited modest anti-inflammatory activity. Another active ingredient with anti-inflammatory effects is Cinnamaldehyde which is a chemical component that is accountable for the odor and taste of cinnamon. Cinnamaldehyde acts as the inhibiting factor towards the nuclear factor-B activation which then results in an attenuation of TNF-induced inflammation. Essential oils have antiviral properties that were tested against numerous harmful viruses. One of the results is that the components of essential oil have the chance for reacting to significant SARC-CoV-2 protein targets. Through its natural form, eucalyptol is colorless and aromatic, and it possesses mucolytic and bronchodilatory capabilities. It is also claimed for its capacity to bind proteinase of a virus, which is also a viable blocker of the virus in notable

molecular docking research that is presently only accessible as a preliminary report. Oil from garlic contains sulfur components that are excellent antioxidants, antifungals, antitumor, antibacterial, and antiviral effects. In a similar time, docking and in vitro studies, DAS, particularly isolated constituent and garlic essential oils can prevent virus from entering the host cells reducing the production of pro-inflammatory-inflammatory-caausing cytokines through activating molecular antioxidant pathways and were suggested that starting Nrf2 would considerably reduce the severity from the cytokine outburst in COVID-19 patients. The virus's ability to replicate its RNA is catalyzed by a protein known as RNA-dependent DNA polymerase (RdDp), a critical stage in viral replication that results in a desirable target for antiviral treatment.

It was also stated that (E,E)-farnesol had the highest docking scores against RdRp. The virus' S protein shows strong attachment towards ACE2 protein of humans based on the interactions in biochemicals and crystal structural research, making this a prospective target for inhibiting the SARs-CoV-2 rS binding of human's respiratory cells. It was stated that carvacrol, which is commonly derived from oregano oil, is considerably a potential constituent on tackling SARs-CoV-2 as to its antimicrobial, anti-inflammation, and immunomodulation. Eugenol has antimicrobial effects countering the 2 types of herpes simplex virus, and it possesses anti-inflammatory characteristics and is found to help protect the airways from the immediate damage caused by LPS. In rat disease models, menthol was found having anti-inflammation, immunomodulation, and gastroprotective effects and was indicated that with the help of menthol, cytokines responsible for inflammation such as il1 and TNF-a, and interleukin-23 was dramatically decreasing.

Several essential oils were selling, and extraction companies stated that their actual oil-containing products were effective against COVID-19 which resulted in the FDA and other government agencies issuing a number of warning letters to these companies stating.

The SARS-CoV-2 Virus's Mechanism of Action

The virus' admission into a host cell, including penetration and attachment, results in the replication of genetic material and the production and discharge of additional virions [45]. The virus's infectivity will be reduced by adverse effects on related targets during the infection stage (Figure 1). The most often used technique for establishing the essential oils' molecular mechanisms including their components inhibiting viruses is to alter time-of-addition tests, a kind of kinetic experiment. One hour before virus injection, cultured cells are treated with essential oils to prime them for pre-viral infection. A negative finding shows that essential oils have no effect on viral attachment since they are unable to impede the host cell receptor's ability, resulting in the conclusion that essential oils have no effect on viral attachment. Instead, viruses are cultured with host cells for one hour prior to being prepared with essential oils, and this process is called "simultaneous viral infection". A positive discovery implies that essential oils impede free virions by changing the form of the virus envelope or masking the presence of surface replication, which are both required on infectious adherence but also penetration through into the cell wall, respectively. Additionally, depending on the virus under investigation, essential oils are supplied to infected cells during various phases of the life cycle of viral infection, with the spectrum of penetration after viral infection through progeny development. With this condition, it is feasible to detect the stage of the viral infection cycle during which essential oils are active against viruses. However, for the time being, the time-of-addition experiment remains the most often used method for examining the overall inhibitory effects of essential oils, both intercellularly and intracellularly. Taken together, essential oils and their own constituents have a strong direct influence on free viruses, which is called an intercellular mode of action. Additionally, there are several methods of action, some of which may vary according to the particular EOs.

Essential Oils During the Invasion Process

Based on a single experiment, only vague information on the mechanisms of action may be obtained. It is difficult to determine from the time-of-addition experiment, for instance, whether essential oils affect viral adsorption by killing or concealing it. Remarkably, structural alterations in the virus were seen using TEM (transmission electron microscopy) imaging. It was when the discovery of murine virus, a which doesn't have an envelope, has been subjected on essential oils, it increased in diameter from 20–35 nanometers to 40–75 nanometers, but still retained its shape [49]. A different essential oil was used to treat murine norovirus, which caused it to grow from its normal size to around 900 nanometers in diameter, leading to capsid disintegration. When a non-enveloped virus infects a host cell, the capsid shields the viral ribonucleic acid from breakdown and stimulates infection by adsorption to the host cell. Although the capsid of murine norovirus has been partly destroyed, it is possible that the virus is still infectious due to the fact that the Ribonuclease I safeguard experiment demonstrated that capsid breakdown did not result in significant viral RNA decrease. Essentially, the findings showed that essential oils inhibited viral adsorbent onto the host of the cells by obscuring or adhering to the capsid, rather than by inflicting structural damage on the virus.

The virus' HA (hemagglutinin), a transmembrane domain that is critical for viral entry and departure from the host cell [50], permits the virus to enter and leave the cell. Hemagglutination inhibition assays are often employed to determine whether or not essential oils have an impact on viral adhesion to host cells because of the fact that hemagglutinin may induce the agglutination of red blood cells. The omission of agglutination shows that hemagglutinin activity has been inhibited. Another crucial surface protein for early viral infection is NA (neuraminidase), which seems to be an aim of the synthetic medicines oseltamivir and zanamivir, which are used to treat the virus. To summarize, essential oils have a greater tendency to operate on hemagglutinin than on neuraminidase, with the amount of action varying depending on the kind of essential oil or combination.

The acidic endosomal and lysosomal conditions required by the viral uncoating stage during the infection process [51] are required throughout the infection process. An analysis of changes in the pH of both endosomes and lysosomes following the administration of essential oils may be used to monitor the influence of it on the early stages of viral replication lifespan. It has been shown that the tea tree essential oil together with its components will inhibit the virus' replication through interfering with an acid of the intralysosomal phase that is necessary to its uncoating of the virus [52]. Viral infection is known to cause intrinsic glutathione deprivation, which is related to an increase of the rate of redox alteration [53]. Piperitenone oxide, a component generated from essential oils, has been shown to block the late stage of the HSV-1 lifecycle through inhibiting the redox transcription factor [54]. Additionally, as discovered by genomic techniques, essential oils may attack genetic sequence locations [55]. Modes of action against a certain

kind of virus may be essential oil-dependent [56], presumably as a result of the essential oils' fundamental differences. To summarize, the most prevalent method of action for essential oil is direct contact with free viruses.

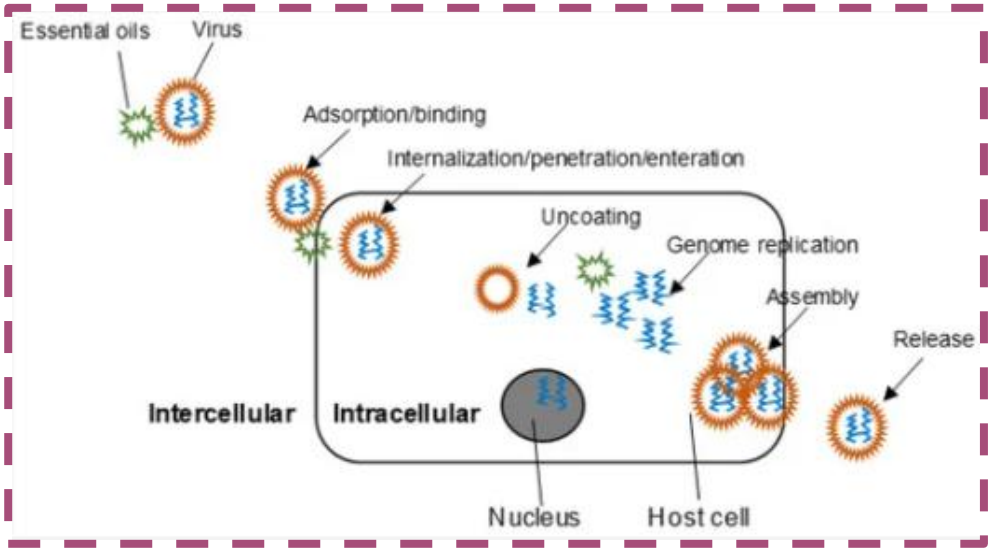

Figure 6: The virus' life phases that essential oils may be used to target [49].

Specific Components that Play to Prevent Infection

EOs have an extent of pharmacotherapeutic actions, as well as antihistamine, immunomodulation, antitumor, and anti-inflammation activities. Recent publications incorporating researches have highlighted potentiality regarding numerous natural plant oils that are ideal adjuvants with regards to the handling of viral or autoimmune disorders as an alternative to conventional medicine. Despite the fact that essential oils were shown to have therapeutic potentials, their hazardous propensity should be regarded in order to secure future usage [57]. It has been observed that essential oils may help to enhance the immune response through increasing the number of flowing neutrophils and boosting its antigen presentation, hence aiding in the eradication of bacterial infection [58].

The mammalian immune system's adaptive and innate immune systems are functionally distinct compartments. By producing an inflammatory response, infectious pathogens are removed or contained by the body's immune response, which begins fundamental defensive mechanisms. Mast cells, macrophages, dendritic cells, basophils, monocytes are all effectors of the innate immune system's cells [59]. These cells are responsible for the synthesis of cytokine, phagocytosis, and representation of antigen. When a supervised classification ligand is coupled to specific foreign constituents, including such transcriptionally active DNA or endotoxin, a component of the bacterial cell wall, the immune system identifies the presence of invading pathogens and warns it of the situation. As a result of this interaction, the cells become activated, initiating pathogenic ingestion and generating systemic responses, including the stimulation and mobilization of more adhesion molecules to the infected area via the production of cytokines and chemokines [59].

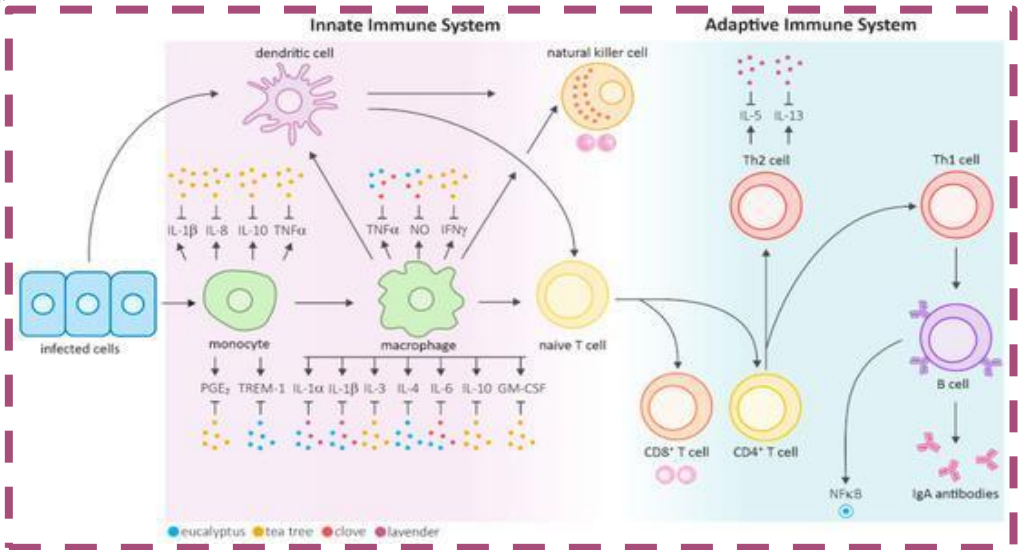

Figure 7: Certain EOs that have a regulating influence on cytokines [59]

Dendritic cells and macrophages, for example, are drawn to the infection site as antigen-presenting cells (APCs). The cytokines released cause natural killer cells to become more active and T cells to mature. The trigger towards various generic pathways will be required in the antibodies production's incitement, which is a deferred yet domain specific resistance against the particular pathologic invader [58]. As a result, since the engagement of the immunological is associated with cell loss or destruction, pathological changes are tightly controlled by a number of processes as well as when the source of the inflammation is identified and removed, the treatment is typically halted [59]. Considering their extraordinary properties, plant essential oils have the potential to be employed in natural remedies. A greater rate of patient adherence with organic products is also seen, as are fewer adverse reactions to them as compared with synthetic drugs [58].

Eucalyptus Essential Oil

Respiratory illnesses, such as cold, cough, and influenza, have all been treated with eucalyptus essential oil (EEO) for centuries. The most important element is 1,8-cineole which is also called eucalyptol, a monoterpene with a strong, harsh fragrance and medicinal value [60]. Many dental care products, including chewing gums and mouthwashes, also the chemical 1,8-cineol, which is shown that demonstrated to have analgesic and anti-inflammatory properties. EEO also contains limonene and -terpineol, which are typical components [60]. EEO and its components' immunomodulatory properties have recently received a lot of interest. Serafino et al. (2008) used confocal imaging to investigate the EEO's effects on macrophages following the addition of fluorescent beads. Human MDMs treated with EEO had significantly higher phagocytic activity than those treated with LPS, according to the findings [61]. Furthermore, Serafino et al. (2008) discovered that in vivo injection of EEO in immunosuppressed and immunocompetent rats affected the phagocytic capacities of of human leucocytes [61].
The impact of EEOs together with its major component, 1,8-cineol, upon its antigen presentation of pulmonary phagocytic cells was investigated [62]. There was a rise in alveolar macrophage phagocytic activity and intracellular pathogen elimination Once lymphocytes being exposed with 0.02 percent EEOs within 3 hours prior to bacterial infection [62].

Garlic Essential oil

Garlic compounds are classified into various categories or families. The major prelude constituents of the S-allyl cysteine sulfoxide and S-methyl cysteine sulfoxide chemical families are -glutamyl cysteine derivatives, which are produced by alliinase's enzymatic action, allicin and the thiosulfinate compound families, which serves as catalysts for a variety of organosulfur compound families. Non-organic sulfur compounds, which are seen in AGE, found in garlic preparations include fructans, glucose-linked -D-fructofuranosyl, and tetrahydro-beta-carbolines [63].
Garlic's distinct components responsible for efficient immunological activation or suppression are unknown clearly, and despite mounting evidence, various factors are most likely involved in its immunopharmacological activities. As a result, more research with garlic fructans potentially provides light on the underlying immunomodulation processes, as well as aid in the identification of prospective uses for garlic fructans in a variety of therapeutic applications [8]. The anti-inflammatory action of garlic extract in inflammatory bowel disease (IBD) is due to IL-10 dysregulation and reduced IL-12 synthesis, which inhibits interleukin-12 for attaching towards its ligand on T lymphocytes and its natural killer cells, resulting in IFN- production suppression. Garlic or its components have been shown to have a variety of immunomodulatory effects on leukocyte cytokine production. The extracts and constituents of garlic have been shown to drastically suppress the production of cytokines responsible for inflammation in Th1 cells, indicating that they may have promising clinical applications towards inflammation disorders like IBD and dengue. Garlic oil, on the other hand, has been shown to alter the Th1 and Th2 systems in favor of the Th2 type [64].

Conclusion

COVID-19 had already developed into a serious public health hazard on a worldwide scale. There have only been these few medications that have already been believed to enhance clinical testing against the virus and the inflammatory symptoms that accompany it. Supportive treatments are now being investigated using a variety of medications with a number of labeled uses in varied combinations. Given the recent discovery of essential oils' antioxidant, inhibition of inflammation, antiviral, and neuroprotective impacts on health, there have also been discussions that they might have anti-pathogenic effects on the body, such as the virus causing the COVID-19. Such essential oils, on the other hand, have very minimal proof to support them, with the bulk of assertions depending on findings from machine docking and rudimentary in vitro experiments. Through the order to assess the therapeutic dosage and medicinal effectiveness of essential oils against SARS-CoV-2, well-designed research is necessary. Aside from that, given the diverse therapeutic potential of essential oils, it is recommended that a composite approach must be used to combat this viral illness and its comorbidities, which includes the government of essential oils with pharmacological actions as well as prescription medicines.

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Disclosure of conflict of interest

No conflict of interest from the authors.

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