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Review

Exploring essential oils as prospective therapy against the ravaging Coronavirus (SARS-CoV-2)

Emmanuel Onah Ojah[a,*]

[a]*Medicinal Chemistry Research Group, Organic Chemistry Unit, Department of Chemistry, University of Ibadan, Ibadan, Nigeria*

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ABSTRACT

Introduction: Aromatic plants produce diverse chemical constituents with potential to inhibit viral infections. These plants have been utilized for the prevention and treatment of a range of infectious and non-infectious diseases. Essential oils are among the plant-derived antiviral agents that are being employed in phytomedicine, and are considered as prospective drug candidate against the ravaging Coronavirus.
Methods: Relevant articles relating to the concept were identified using a combination of manual library search as well as journal publication on the subject and critically reviewed.
Results: Essential oils in medicinal plants have extensive applications in medicinal chemistry, aromatherapy and pharmaceuticals. Essential oils have several biological properties such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, wound-healing and anti-cancer effects *in vitro* and *in vivo*. Several reports have analyzed and described essential oils as good antiviral agents against Respiratory tract viral infections hence are excellent prospective candidate against Corona virus.
Conclusions: It is hoped that efficient and effective exploration and optimization of essential oils from medicinal plants would improve the drug discovery process against the ravaging Coronavirus.

1. INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an emerging respiratory disease. The epidemic started in December 2019 in Wuhan, Hubei province, China, and has rapidly spread throughout the World thereby becoming a major global health concern. SARS-CoV-2 can be transmitted among humans and has shown a high degree of morbidity and mortality globally [1, 3]. SARS-CoV-2 belongs to a family of single-stranded RNA viruses known as *corona viridae*, a common type of virus which affects mammals, birds and reptiles. In humans, it causes mild infections, similar to common cold, and accounts for 10-30% of respiratory tract infections in adults [2, 3]. More serious infections are rare, although coronaviruses can cause enteric and neurological disease [3]. The incubation period of coronavirus varies from one individual to another but it is generally up to two weeks [6]. Previous coronavirus outbreaks include Severe Acute Respiratory Syndrome Coronavirus (SARS- CoV-1), identified in southern China in 2003 and Middle East Respiratory Syndrome (MERS), first reported in Saudi Arabia in September 2012 [3, 4]. MERS infected around

* *Corresponding author.*
E-mail address: eojah7403@stu.ui.edu.ng

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2,500 people and led to more than 850 deaths while SARS infected more than 8,000 people and resulted in nearly 800 deaths [5]. SARS-CoV-2 is a new strain of coronavirus that has not been previously identified in humans. Although the incubation period of this strain is currently unknown, the United States Centers for Disease Control and Prevention indicated that symptoms may appear in as few as 2 days or as long as 14 days after exposure. Chinese researchers have indicated that SARS-CoV-2 may be infectious during its incubation period [6]. The number of reported cases of SARS-CoV-2 infection increased geometrically from March to June 2020. On June 1, 2020 the global number of infected individuals was 6,057,853 with as many as 31,166 deaths worldwide across World Health Organization region as indicated in Figure 1 and Figure 2 [7]. A large number of laboratory confirmed cases and mortality had been recorded in the past three months in America and Europe compared to other continents in the World as expressed by the World Health Organization in Figure 2 [7].

There are currently no approved vaccines available for the prevention of the infection therefore; there is an urgent demand for potential chemotherapeutic agents to mitigate this ravaging disease. Since the start of the pandemic, there has been an urgent need to accelerate the research and development of SARS-CoV-2 candidate vaccines. Essential oils have been screened against several pathogenic viruses and other respiratory diseases caused by viral infections. Due to the activities of several essential oil components against human pathogenic viruses, essential oil components could be potentially useful antiviral agent against SARS-CoV-2.

2. WHAT ARE ESSENTIAL OILS?

Essential oils are odorous and volatile compounds found in plants and are stored in special fragile secretory structures, such as glands, secretory hairs, secretory ducts, secretory cavities or resin ducts [8-11]. The total essential oil content of plants is generally very low and rarely exceeds 1% [12], however the percentage yield of essential oils may exceed 1% for example clove (*Syzygium aromaticum*) and nutmeg (*Myristica fragrans*) exceeds 10% yield. Essential oils are hydrophobic, soluble in alcohol, non-polar or weakly polar solvents but only slightly soluble in water. They are usually colourless or pale yellow, with exception of the blue essential oil of chamomile (*Matricaria chamomilla*) and most are liquid of lower density compared to water with few exceptions of the essential oil obtained from sassafras, vetiver, cinnamon and clove [13]. Aromatherapy utilizes various essential oils that can be issued through topical application, massage, inhalation or water immersion to stimulate a desired therapeutic response. They are colorless pleasant smelling liquids with high refractive index. Essential oils are composed of saturated and unsaturated hydrocarbons, alcohol, aldehydes, esters, ethers, ketones, oxides phenols and terpenes which may produce characteristic odours. Essential oils are neither acidic nor alkaline. They have the ability to go into the body tissues and literally become free radical scavengers [14].

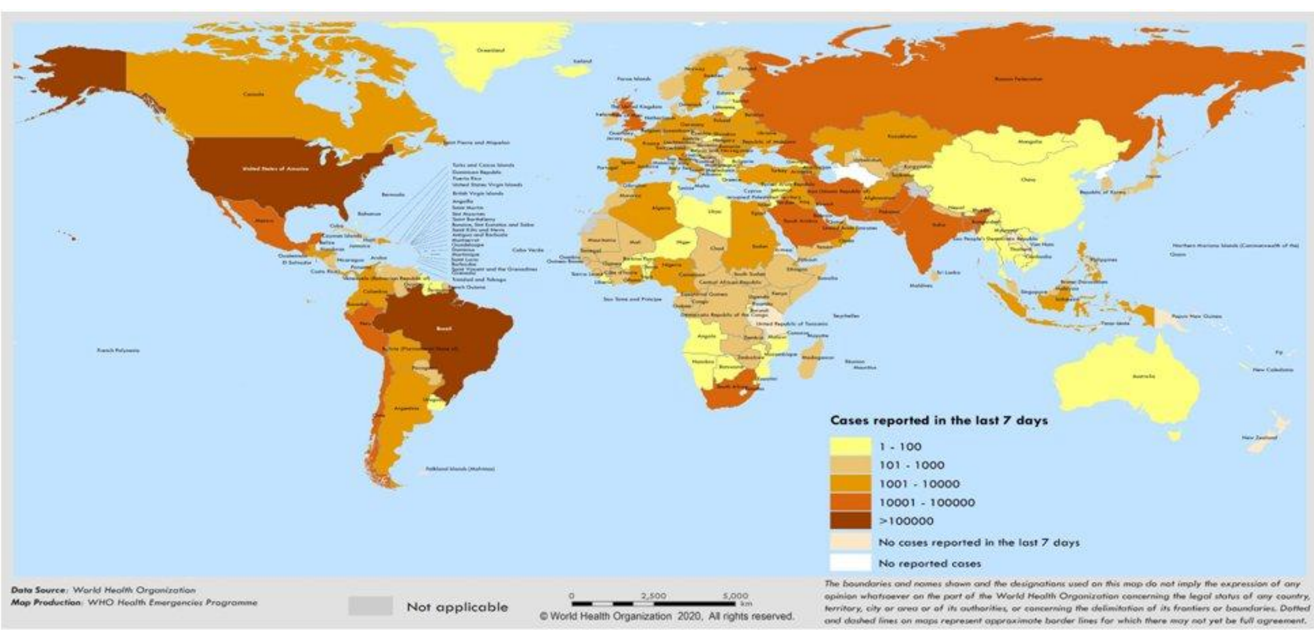

Figure 1: *World distribution of the number of confirmed cases reported as at 01, June 2020 by the World Health Organization (WHO) [7].*

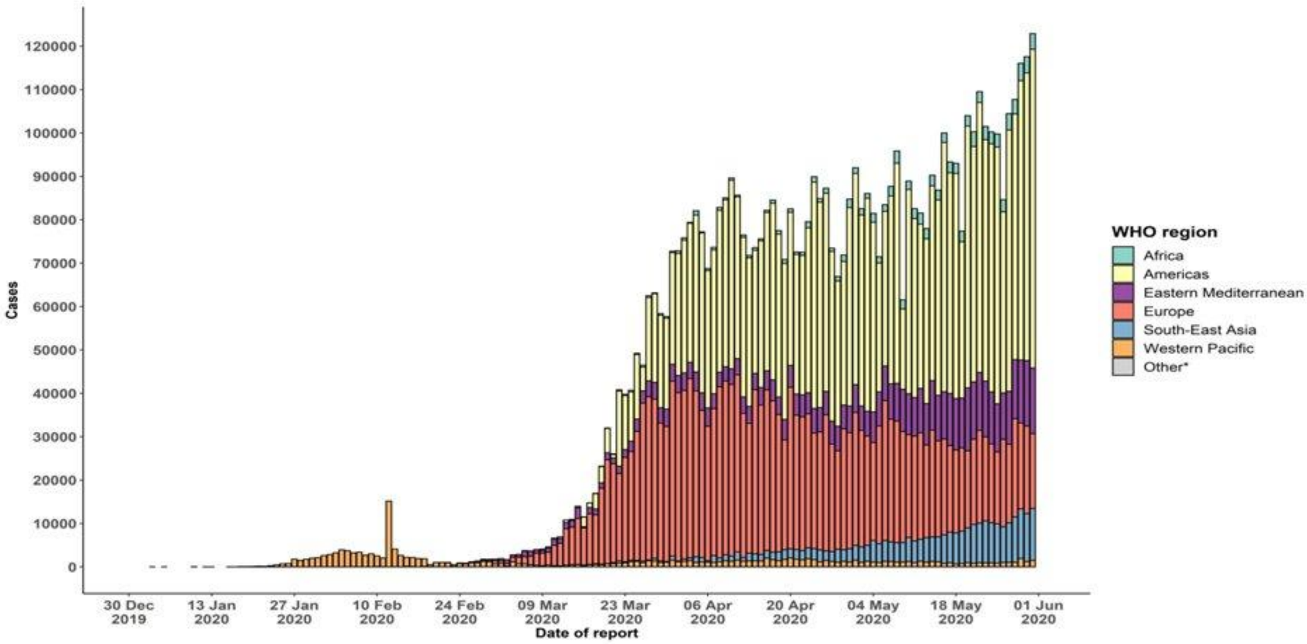

Figure 2: Number of confirmed cases, by the World Health Organization region from 30 December 2019 through 01 June, 2020 [7]. Counts reflect laboratory-confirmed cases based on WHO case definitions, unless stated otherwise and include both domestic and repatriated cases.

3. CLASESS OF ESSENTIAL OILS

Essential oils can be classified based on the number of carbon chain formed from basic isoprene units (monoterpenes: C_{10}, sesquiterpenes: C_{15}, and diterpenes: C_{20}). Essential oils contain the following classes of compounds [15, 16];

- Hydrocarbons (Examples include: Limonene, myrcene, p-menthane, α-pinene, β-pinene, α-sabinene, p-cymene, myrcene, α–phellandrene, thujane, fenchane, farnesene, azulene, cadinene and sabinene).
- Esters (Examples include: linalyl acetate, geraniol acetate,eugenol acetate and bornyl acetate).
- Oxides (Examples include: bisabolone oxide, linalool oxide, sclareol oxide and ascaridole).
- Lactones (Examples include: nepetalactone, bergaptene, costuslactone, dihydronepetalactone, alantrolactone, pinepetalactone, aesculatine, citroptene, and psoralen).
- Alcohols (Examples include: linalool, menthol, borneol, santalol, nerol, citronellol and geraniol).
- Phenols (Examples include: thymol, eugenol, carvacrol and chavicol).
- Aldehydes (Examples include: citral, myrtenal, cuminaldehyde, citronellal, cinnamaldehyde and benzaldehyde).
- Ketones (Examples include: carvone, menthone, pulegone, fenchone, camphor, thujone and verbenone)

Examples of some classes of essential oils constituents, monoterpene hydrocarbon and oxygenated monoterpenes, sesquiterpene hydrocarbon and oxygenated sesquiterpenes are indicated in Figures 3, 4 and 5, respectively [15, 16]

4. THERAPEUTIC BENEFITS OF ESSENTIAL OILS

Aromatic herbs, spices and some dietary supplements can supply the body with essential oils. There are a lot of specific dietary sources of essential oils, such as orange and citrus peel, caraway, cherry, spearmint, black pepper and lemon grass. Thus, human exposure to essential oils through diet or environment is widespread. In most cases, essential oils can be absorbed from the food matrix or as pure products and cross the blood brain barrier easily. This later property is due to the lipophilic character of volatile compounds and their small size. The action of essential oils begins by entering the human body via three possible different ways including direct absorption through inhalation, ingestion or diffusion through the skin tissue [17-20].

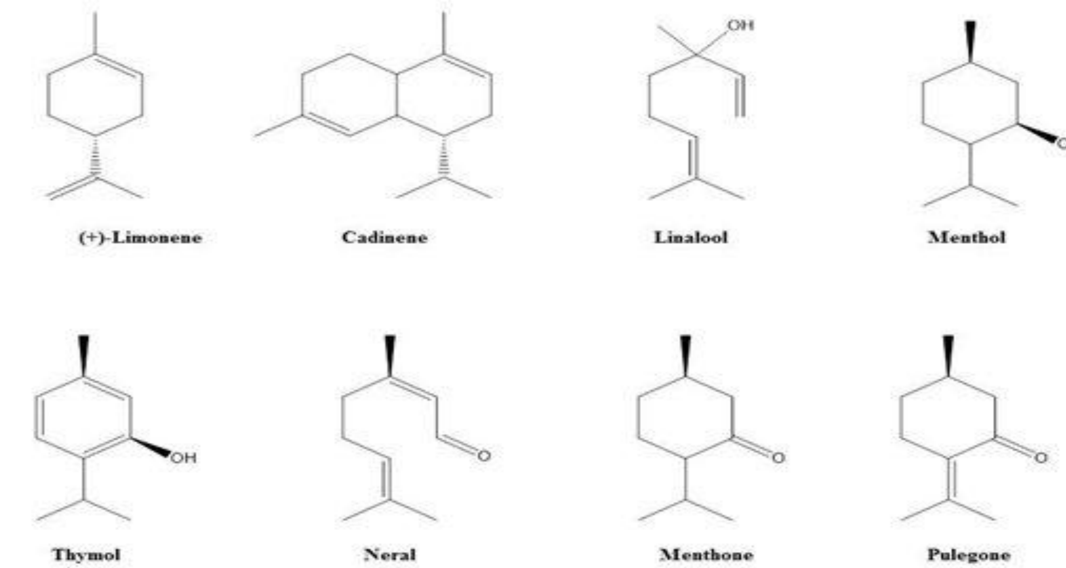

Figure 3: *Examples of essential oil constituent.*

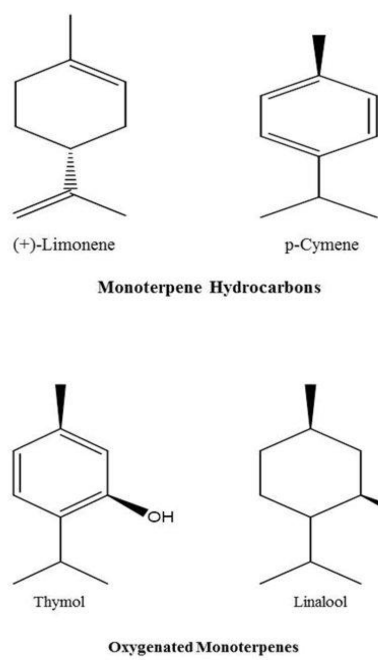

Figure 4: *Classes of essential oil (Monoterpene hydrocarbons and Oxygenated monoterpenes).*

4.1. INHALATION

Essential oils can enter the body easily by inhalation. Due to their volatility, they can be inhaled easily through the respiratory tract and lungs, which can distribute them into the bloodstream. In general, the respiratory tract offers the most rapid way of entry into the body system followed by the dermal pathway [20, 21].

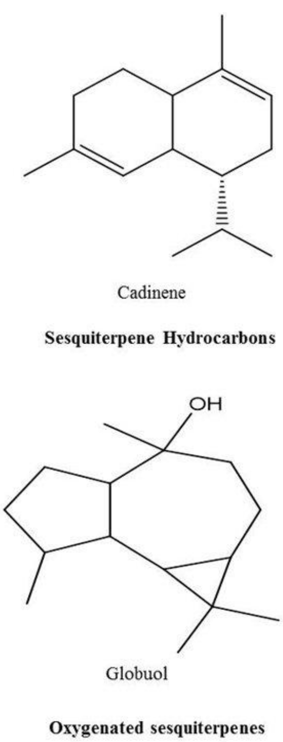

Figure 5: *Classes of essential oils (Sesquiterpene hydrocarbons and Oxygenated Sesquiterpene).*

4.2. ABSORPTION THROUGH THE SKIN

Essential oil compounds are fat soluble, thus they have the ability to permeate membranes of the skin before being captured by the micro-circulation and drained into the systemic circulation, which reaches all targets organs [22, 23].

4.3. INGESTION

Oral ingestion of essential oils needs attention due to the potential toxicity of some oils. Ingested essential oil compounds may then be absorbed and delivered to the rest of the body by the bloodstream and then distributed to parts of the body. Once essential oil molecules are in the body, they interrelate with physiological functions by three distinct modes of action which may be Biochemical (pharmacological), Physiological or Psychological. Biological activity of essential oils may be due to one of the compounds or due to the entire mixture [22-24].

5. MEDICINAL AND PHARMACOLOGICAL USES OF ESSENTIAL OILS

Essential oils are valuable natural products used as raw materials in aromatherapy, phytotherapy, perfumery, cosmetics, spices and nutrition [25]. Aromatherapy is the therapeutic use of fragrances or at least mere volatiles to treat or prevent diseases by means of inhalation [26]. Inhalation of essential oils has a significant role in controlling the central nervous system. For instance, aroma inhibition of storax pill essential oil and inhalation of *Aconus gramineus* rhizome essential oils are used in Chinese folk medicine in the treatment of epilepsy [27, 28]. The fragrance compounds, cisjasmonate, which characterized the aroma of *Jasminum grandiflorum* have a tranquilizing effect on the brain upon inhalation [29]. Cendrol, which is a major component of card-wood essential oil, shows a sedative effect and prolonged pentobarbital induced sleeping time on rats upon inhalation [30]. The vapour of lavender essential oil or one of its main component linalool may also be utilized for the treatment of menopausal disorder through inhalation [31]. Lavender essential oil demonstrated an analgesic activity, mainly relevant after inhalation at doses devoid of sedative side effects [32].
Medicinal chemists are more interested in the medicinal properties of essential oils. Many oils show antibacterial, fungicidal, relaxant, stimulating, antidepressant effect and can be very effective therapeutic agent. Essential oils are known for their therapeutic properties hence, used in the treatment of various infections caused by both pathogenic and non-pathogenic diseases. Pathogenic diseases caused by bacteria, virus, and fungi can be treated with essential oils. Strong *in vitro* evidence indicates that essential oil can act as antibacterial agent against a wide spectrum of pathogenic bacteria strains including; *Listeria monocytogenes, Linnocua, Salmonella typhimurium, Shigella dysentria, Bacillus cerus*, and *Staphylococcus aureus* [33-36]. Thyme and oregano essential oils can inhibit some pathogenic bacteria strains such as *Escherichia coli, Salmonella typhimurium, Salmonella entritidis* and *Salmonella choleraesuis* [37], with the inhibition directly correlated to the phenolic components carvacrol and thymol. Eugenol and carvocrol showed an inhibitory effect against the growth of four strains of *Escherichia coli* and *Listeria* mono-cytogens [38]. Essential oil with significant concentration of thymol and carvacrol inhibited gram positive more than gram-negative pathogenic bacteria [39].
Essential oils show bactericidal activity against oral and dental pathogenic microorganisms and can be incorporated into rinses or mouth washes for pre-procedural mouth control, general improvement of oral health, interdental hygiene and to control oral malodour [40]. Mouth rinses containing essential oils with chlorhexine gluconate are commonly used as preprocedural preparations to prevent possible disease transmission and decrease aerolization of bacteria [41]. *Croton cajucara* benth essential oil was found to be toxic to some pathogenic bacteria and fungi associated with oral cavity diseases [42].
Besides their antibacterial and antifungal activities, essential oils have also been reported to possess interesting antiviral activities. They have demonstrated virucidal properties with the advantages of low toxicity [43]; Herpes simplex virus (type III) causes some of the most common viral infections in human and can be fatal. Synthetic antiviral drugs have been used to treat Herpes infection, but not all are efficacious in treatment of genital herpes infections. Incorporation of *Artemisia arboreseens* essential oils in multi lamella liposomes greatly improved its activity against intra cellular herpes simplex virus type 1 (HSV-1) [44]. Due to the presence of Citral and citronellal in *Melissa officinalis* L. essential oil, it inhibits the replication of HSV-2 and the ability to replicate HSV-1 can be suppressed by incubation with different essential oils *in vitro* [45].
Essential oils can also be used for the treatment of non-pathogenic diseases. For instance, Garlic essential oil significantly lowered serum cholesterol and triglycerides while raising the level of high-density lipoproteins in patients with acute coronary heart diseases [46]. Intravenous administration of essential oil of basil (*Ocimum gratissium*) induced an immediate and significant hypotension. The hypotensive activity of the essential oil resulted from its vasodilator effect, acting directly upon vascular smooth muscles [47]. This effect was attributed to the suction of eugenol known about 80% [48].
Essential oils and their individual aroma components showed cancer suppressive activity when tested on a number of human cancer cells lines including glioma, tumours, breast cancer, leukaemia and others. Glioma is one of the most malignant human tumours [49, 50]. Antiangiogenic therapy is one of the most promising approaches to control cancer. Perillyl alcohol (POH) which is the hydroxlated analogue of *d*-limonene has the ability to interfere with angiogenesis [51]. Treatment of human leukaemia cells with *eucalyptus* oil showed morphological changes (fragmentation of DNA) indicating an induction of

apoptosis [52]. The essential oil of lemon balm (*mellisa oficinalis* L) was found to be effective against a series of human and a mouse cell line and that of *Artemisia annua* L. Induced apoptosis of cultured hepato-carcinoma cells [53, 54]. Essential oils from Australian tea tree (*Melaleuca alternifolia*) and its major monoterpene alcohol, terpinen-4-ol, were able to induce caspase dependent apoptosis in human melanoma cells and their drug-resistant counterparts, adriamicin-resistant [55]. There was evidence to suggest that the effect of the total oil of terpinen-4-ol was caused by their interaction within the plasma membrane and subsequent reorganization of membrane lipids. Hepatic arterial infusion with Curcuma oil had a similar positive effect in treating primary liver cancer [56]. The essential oil of *Tetraclinis articulate*, (a conifer tree) showed the hallmarks of apoptosis when tested on a number of human cancer cell lines including melanoma, breast and ovarian cancer in addition to peripheral blood lymphocytes [57].

Essential oils are reported to have insecticidal properties essentially as ovicidal, larvicidal, growth inhibitor, repellence and antifeedant [58, 59]. The influence of certain oils and their constituents on the reproduction of some insect species and on morphological changes has also been reported [60].

Essential oils are used as flavouring agents. Flavours are added to food to enhance their taste and aroma. Flavouring in vanilla, is isolated from vanilla beans and methyl salicylate, which has a characteristic minty taste and odour. Essential oils and their terpene constituents may be accepted as natural alternative to synthetic skin penetration enhancers. They are characterized by their relatively low price and promising penetration enhancing activities. The mechanism of skin penetration of terpenes was postulated due to the popularity of these essential oils [61, 62]. Cineone and menthol are reported to improve the skin permeation of hydrophilic drugs better than other terpenes [63]. Menthol and limonene produce maximum permeation of melatonin and fatty acids [64]. The combination of two penetration enhancers of two different classes such as terpenes (e.g. cineole) and fatty acids (e.g. oleic acid), synergistically enhanced transdermal flux of zidovudine in addition to reducing lag time [65]. Niaouli essential oil showed a high activity for the permeation of estradiol through hairless mouse skin *in vitro* [66].

6. ANTIVIRAL ACTIVITIES OF ESSENTIAL OILS

There are over 37 licensed antiviral drugs on the market [67], but numerous illnesses produced by viruses are not curable and several frequent problems in treatment are also of concern in search for therapeutic antiviral intervention [68]. The use of essential oils in aromatherapy and phyto-medicine is mostly due to their antiviral, antibacterial, antifungal and antioxidant effects. The exploration and search for new and promising antiviral molecules or drugs should therefore be explored and all potential approaches should be organized and employed [69]. New bio-active molecules can be screened to find novel antiviral agents capable of combating the novel coronavirus. Over 70% of therapies have a natural origin or were motivated by natural product chemistry. Natural products and medicinal plants have delivered up to 40% of the present antibacterial, antifungal, antiviral or anticancer molecules for the pharmaceutical industry, but science has studied only a minor fraction of potentially useful herbs and plants in its efforts to design more bio-active molecules extracted from natural products [70].

The pharmaceutical industry is increasingly targeting volatile constituents of medicinal plants with the aim of identifying lead compounds, focusing mainly on suitable alternative antiviral agents. In recent years there has been a growing interest in the use of medicinal plants and some queries regarding the security of synthetic molecules have motivated more detailed and comprehensive investigations of natural products [71].

Aromatic plants produce a diversity of chemical constituents with the potential to inhibit viral replication and chemical molecules from natural products. These plants have been used to treat a range of non-infectious and infectious illnesses and are considered as rich sources of innovative bioactive compounds [72]. Thus medicinal plants continue to be a main source of new lead bio-active molecules. Besides minor compounds from medicinal chemistry, medicinal plants are still key sources of beneficial agents for combating different diseases and infections [73]. Essential oils are among the plant-derived antiviral molecules that are being employed in phytomedicine. They prevent the replication of some viruses such as hepatitis B, human immunodeficiency virus, herpes simplex and severe acute human respiratory diseases [74, 75].

Essential oils extracted from medicinal plants have extensive use and application in phytomedicine and aromatherapy as well as in pharmaceutical industries [76]. Essential oils have several biological properties such as antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, wound-healing and anti-cancer effects *in vitro* and *in vivo* [77]. For many decades, results on the antiviral activities of essential oils and their major chemical compounds lagged behind those of other strains with respect to the range of Essential oils and viruses tested and description of the mechanisms of antiviral effect [78, 79]. More recently, several investigations and reports have analyzed and described the *in vitro* activity of an extensive variety of essential oils. The *in vitro* works have been done using the enveloped influenza or herpes simplex viruses 1 or 2 (HSV-1 or -2) [80-81].

Essential oils from *Origanum acutidens* [82], *Artemisia glabella* [83], *Houttuynia cordata* [84], and *Salvia limbata* [85] have been assessed against influenza viruses. Minami *et al.* tested oils from *Juniperus communis* (juniper), *Eucalyptus globulus* (eucalyptus), *Cupressus sempervirens* (cypress), *Ocimum basilicum* album (tropical basil), *M.*

piperita (peppermint), *M. alternifolia* (tea tree), *Citrus limonum* (lemon), *Cymbopogon citrates* (lemongrass), *Origanum majorana* (marjoram), *Ravensara aromatica* (ravensara), *Lavandula latifolia* (lavender), and *Rosmarinus officinalis* (rosemary) against HSV-1 [86]. Apart from the more extensively evaluated influenza virus and HSV, adenovirus and mumps virus [87], dengue virus type 2 and Junin human respiratory syncytial virus [88], Human Immune-deficiency Virus (HIV) [89], yellow fever virus [90], Herpes virus [91] and the viral agent of SARS, a novel Coronavirus [92], have also been evaluated and determined against a range of essential oils and chemical compounds. In a study conducted by Wen *et al.* [93], 221 phytochemical constituents were tested for antiviral effect against severe acute respiratory syndrome associated with coronavirus (SARS-CoV) using a cell-based assay measuring SARS-CoV-induced cytopathogenic effect on Vero E6 cells. Ten diterpenoids and two sesquiterpenoids were potent inhibitors at concentrations between 3.3 and 10μM. These phytochemical constituents of essential oils were revealed for the first time to display specific and significant anti-SARS CoV effect and thus offer a new pathway for improvement of anti-SARS-CoV drugs [94].

7. CONCLUSIONS

This review attempts to shed light on the therapeutic potential of essential oils and their aroma volatile constituents in the prevention or treatment of diseases. The results reviewed in this article are aimed at attracting the attention of those investigating the pharmaceutical diversity of essential oils as well as researchers seeking new drugs from natural products as therapeutic agent against the novel Coronavirus. The information presented provides a basis for reviving the old art of 'essential oil therapy' based on our modern scientific knowledge of their mechanism of action. Thus essential oils and their constituents can hopefully be considered in the future for more clinical assessment and possible applications in search for vaccines against the ravaging Coronavirus.

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