Chapter 16
Therapeutic Potential of Essential Oils against SARS-CoV-2 Infection

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16.1 Introduction

The present era has witnessed a tremendous global health crisis and rising mortality rates due to the ongoing coronavirus disease 2019 (COVID-19) pandemic. The SARS-CoV-2 (a new strain of coronavirus), primarily originated in China, gradually dissiminated across the world and created a major health disaster to the global economy. However, this expanding health catastrophe was effectively tackled by the high-throughput advances in medical science, via the development of various COVID-19 vaccines (Alshrari et al. 2022). In the last few years, a new variant of coronavirus has emerged and controlled with effective medications/vaccines. Moreover, another variant, B.1.167 has been currently detected in many countries including India, Canada and the United Kingdom (Sanyaolu et al. 2021). With a fast mutation and multiplication characteristics, the emergence of a more deadly and infectious viral strain (Malabadi et al. 2021) cannot be ruled out, however, with effectual healthcare and bio-based therapeutics, these challenges can be addressed and countered to a major extent.

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Herbal medicines have been traditionally used for the treatment of human diseases and are gaining recognition as effective therapeutics in the current era. Bioactive components and extracts from multiple plants have demonstrated pharmacological effects in the treatment of multiple diseases including diabetes, cancer and neurological diseases, either used individually or in combination therapies. The volatile secondary metabolites from plants, known as essential oils, are classified into distinct chemical classes as hydrocarbons (sesquiterpenes, monoterpenes, diterpenes, etc.), oxygenated hydrocarbons (terpenoids comprising phenols, aldehydes, alcohols, etc.), non-terpene compounds (eugenol, cinnamaldehyde, etc.), and other compounds (Schnitzler et al. 2011; Bora et al. 2020). Essential oils are widely used in our daily life as aromatherapeutic agents, air fresheners, perfumes and aromatic waters. Besides, essential oils also comprise an integral part of folk and traditional medicine, and exhibit multiple bioactivities including antioxidant, antimicrobial, immunomodulatory, sedative and antirheumatic properties (Brahmi et al. 2016; Dhifi et al. 2016; Bora et al. 2020). While essential oils are produced by more than 17,000 plant species, classified into diverse plant families, and extracted from multiple plant parts, namely flowers, leaves, fruits and roots, primarily an aromatic ingredient of specialized plant tissues (Schnitzler et al. 2011), with aromatic essential oils forms the basis of aromatherapy.

Plant-derived essential oils constitute a complex mixture of phytochemicals, originating from phenylpropanoids, monoterpene and sesquiterpene classes (Ma and Yao 2020; Tshibangu et al. 2020) and possess wider applications in pharmaceutical, perfume and soap industries. Regarded as a prospective strategy for tacking SARS-CoV-2 in recent times, essential oils are effective in restricting the growth of diverse pathogens, on account of their volatile components and chemical composition (Swamy et al. 2016). The use of essential oils highlights several advantages, including high lipophilicity, rapid action, small size, virucidal properties at low concentrations, high vapor pressure, low cost of preparation, and prospects as a prophylactic agent in the initial stages of viral pneumonia (Elsebai and Albalawi 2022). A key example is eucalyptol, with its vital physicochemical properties and pharmacological functions, which reveals its prospects as a drug in the prevention and treatment of COVID-19. Moreover, other major examples of essential oils as effective therapeutics against SARS-CoV-2 comprise the eucalyptus oil (jensenone and eucalyptol/1,8-cineol), garlic oil (garlicin, allitridin, ajoene), aromatic herbs (essential oils of *Laurus nobilis*, *Juniperus oxycedrus* ssp. oxycedrus), and other essential oils with potent antiviral activities (Elsebai and Albalawi 2022).

In a quest toward the discovery of potent therapeutics against SARS-CoV-2, essential oils show antiviral activity, owing to their lipophilicity, disruption of the viral membrane and viral disintegration (Elsebai and Albalawi 2022). Moreover, many bioactive components of crude essential oils act on different parts of the virus (entry in the cell, transcription, virus assembly and translation), and are gaining popularity as attractive bio-based therapeutics against SARS-CoV-2. Studies have suggested that essential oils and their bioactive molecules can be used as adjuvants for viral disease treatment, resulting in milder disease forms and improving the overall health status of patients (Damiescu et al. 2022). Consequently, randomized clinical trials are necessary for standardizing the bioactive constituents and determining the efficacy of potent active compounds, of essential oils against SARS-CoV-2.

16.2 Physicochemical and Pharmacokinetic Characteristics of Essential Oils

Some essential oils, such as eucalyptol, have distinct physicochemical properties, causing their presence in the lungs via exhalation and exerting their pharmacological action in low doses (Usachev et al. 2013). While asymptomatic patients are crucial in the diseas transmission, eucalyptol exerts virucidal effects both on oral administration in the lower respiratory tract and inhalation in the upper respiratory tract, thus preventing the virus from spreading to other body organs (Wölfel et al. 2020). Many essential oils are commercially marketed as antimicrobials and are important alternatives to chemical agents, specifically in the mileau of rising microbial resistance to conventional drugs (Gutierrez et al. 2008). Studies have documented the effects of essential oils from *Anthemis hyalina*, *Nigella sativa* and *Citrus sinensis* on coronavirus replication and TRP gene expression (Ulasli et al. 2014).

The initial progress of SARS-CoV-2 occurs via targeting lungs and airways, the primary site of infection, therefore, it is suggested that essential oils should be administered via inhalation, causing a direct action in the lungs and other parts of respiratory tract. This administration route of essential oils provides a better option to hamper the binding interactions between SARS-CoV-2 spike proteins and their ACE-2 receptors, located in the parenchymatous lung cells (Elsebai and Albalawi 2022). In addition, lung-based delivery of potent essential oils with anti-SARS-CoV-2 function constitutes a remarkable approach for achieving the desired outcome (Dent et al. 2013). Another key advantage of inhaled drugs with reference to essential oils comprises their low molecular weights and high vapor pressures, therefore these substances are exhaled from the lungs and lead to non-specific anti-inflammatory action, further improving their pharmacological function (Dent et al. 2013). These characteristics enable the eucalyptol to persist in the lungs and cause its local virucidal effect (Sharifi-Rad et al. 2017).

With the pharmacological effects of essential oils and their constituents well reported, the application of essential oils against viral diseases is widely explored in the current era. Essential oils are capable of penetrating and subsequently rupturing the viral cell membrane by their sufficient lipophilic potential (Elsebai and Albalawi 2022). The metabolism of essential oils proceeds via multiple degradative pathways and functions of different enzymes in vivo. It is equally important to determine the chemical profiles of essential oils and their respective constituents. The safety profiles of essential oils can be elucidated by the biotransformation of essential oils in phase I metabolism (reduction, oxidation and hydrolysis etc.) and phase II metabolism (Al-Harrasi et al. 2020). In addition, studies have reported the pharmacodynamics of multiple essential oils during in vitro conditions however, the availability of essential oils in different organs has been unknown. This necessitates a requirement to explicate the absorption, distribution, metabolism and excretion of essential oils for understanding the link between in vivo and in vitro studies. Moreover, it is also imperative to comprehend the bioavailability as well as the pharmacokinetic properties of essential oils and their constituents (Al-Harrasi et al. 2020).

16.3 Therapeutic Basis of Essential Oils with Reference to SARS-CoV-2 Infection

Apart from the symptomatic treatment in terms of anti-inflammatory, anticoagulant and antipyretic agents, monoclonal antibodies and antiviral drugs such as monlupiravir and remdesivir have been previously used against COVID-19 infection with varying success rates (Elsebai and Albalawi 2022). Essential oils exhibit diverse pharmacological spectra characterized by anticancer, antioxidant, anti-inflammatory, insecticide and antimicrobial effects (Galvan et al. 2021). Bioactive substances of various essential oils such as tea tree oil, thyme oil and eucalyptus oil are used as an adjunct to conventional therapeutic agents against flu and common cold, whereas, those of *Allium sativum*, *Echinacea purpurea*, *Echinacea angustifolia* and *Zingiber officinale* are useful for their immunostimulant potential (Damiescu et al. 2022). Essential oils from anise (*Illicium verum*), eucalyptus, sandalwood (*S. album*), chamomile (*Matricaria recutita*), and others have shown promising antiviral effects against HSV-1 and/or HSV-2 (Schnitzler et al. 2001), essential oils from *Artemisia glabella* (Seidakhmetova et al. 2002), *Origanum acutidens* (Sökmen et al. 2004), *Oenanthe crocata* (Bonsignore et al. 2004), against influenza viruses, essential oils from *Eucalyptus globulus* (eucalyptus), *Ocimum basilicum album* (tropical basil), *Lavandula latifolia* (lavender), and others against HSV-1, highlight the potential efficacy of essential oils against multiple viruses.

Essential oils have been extensively used in folk medicine on account of their miscellaneous pharmacological effects including antimicrobial, immunomodulatory, antioxidant, anti-inflammatory, mucolytic and antirheumatic properties (Brahmi et al. 2016; Dhifi et al. 2016). Moreover, spoilage bacteria and food-borne pathogens are highly susceptible to the combinations of essential oils (Gutierrez et al. 2008; Mutlu-Ingok and Karbancioglu-Guler 2017). The antiviral efficacy of essential oils has been documented against a wide range of pathologically important viruses including yellow fever virus, human and avian influenza viruses, human herpes viruses (HSV-1 and HSV-2), Zika virus, avian influenza A virus (H_1N_1), influenza A virus (H_5N_1), human immunodeficiency virus (HIV), and SARS-COV-2 (Astani et al. 2010; Schnitzler et al. 2011; Ma and Yao 2020; Rouf et al. 2020). The effectiveness of essential oils against enveloped single-stranded positive RNA viruses has been validated through in vitro assays as well as experimental studies using animal models (Wilkin et al. 2020). Likewise, both in vitro and in vivo studies have revealed the additive pharmacological effects of oseltamivir and germacrone combination against the influenza virus (Liao et al. 2013). Moreover, the hsp1 was successfully targeted by a synergistic combination of acyclovir and 4., piperitenone oxide which is the active ingredient of *Mentha suaveolens* essential oil (Civitelli et al. 2014). Concurrent use of *Melissa officinalis* essential oil improved the antiviral effect of oseltamivir against avian influenza A virus (Pourghanbari et al. 2016). Improved clinical outcomes characterized by reduced lung pathological index, pulmonary cytokines expression and viral titers, whereas, enhanced survival rate have been associated with the synergistic pharmacological benefit resulting from the co-administration of oseltamivir and eucalyptol (Lai et al. 2017).

Immunomodulatory, mucolytic and anti-inflammatory effects are also useful to combat viral respiratory diseases including the SARS-COV-2 infection. Consequently, the use of essential oils is gradually increasing in medicine, cosmetics, pharmaceutics, food and other industries. Simply targeting the SARS-COV-2 using specific antiviral drugs may not provide a complete solution to COVID-19 infection. Therefore, essential oils characterized by anti-inflammatory, antioxidant, antimicrobial and immunomodulatory effects can properly relieve the clinical manifestations of COVID-19 infection by suppressing the pulmonary inflammatory cascade and preventing secondary bacterial infection (Wilkin et al. 2020). Based upon their high volatility and ease of inhalational administration, essential oils can be effectively used to subside sore throat, coughing, expectoration, nasal congestion and rhinorrhea (Horváth and Ács 2015; Valussi et al. 2021). The optimal antimicrobial efficacy of essential oils entails their application for disinfecting closed areas wherein enhanced proliferation of SARS-COV-2 is projected.

16.4 Major Bioactive Constituents and Pharmacological Mechanisms of Essential Oils Against SARS-CoV-2

Essential oils and their purified bioactive substances may represent a relatively less explored source of useful antiviral drugs for add-on therapy of viral infections (Wilkin et al. 2020). Whole essential oils are usually preferred over purified constituents by virtue of multiple pharmacological actions, reduced probability of microbial resistance and synergistic effects (Popa et al. 2020). Antifungal, antibacterial and antiviral activities have been documented for many essential oils and their derivative compounds (Swamy et al. 2016; Wińska et al. 2019). Sesquiterpenes and monoterpene hydrocarbons have been implicated in triggering the potential antiviral activity of essential oils (Sobrinho et al. 2021). Different pharmacological mechanisms of essential oils have been shown in Fig. 16.1. The synergistic constituents of essential oils in combination therapies, improve the efficacy of other antiviral drugs and alleviate COVID-19 symptoms (Da Silva et al. 2020). Various steps of viral replication such as cell entry, assembly, transcription and translation

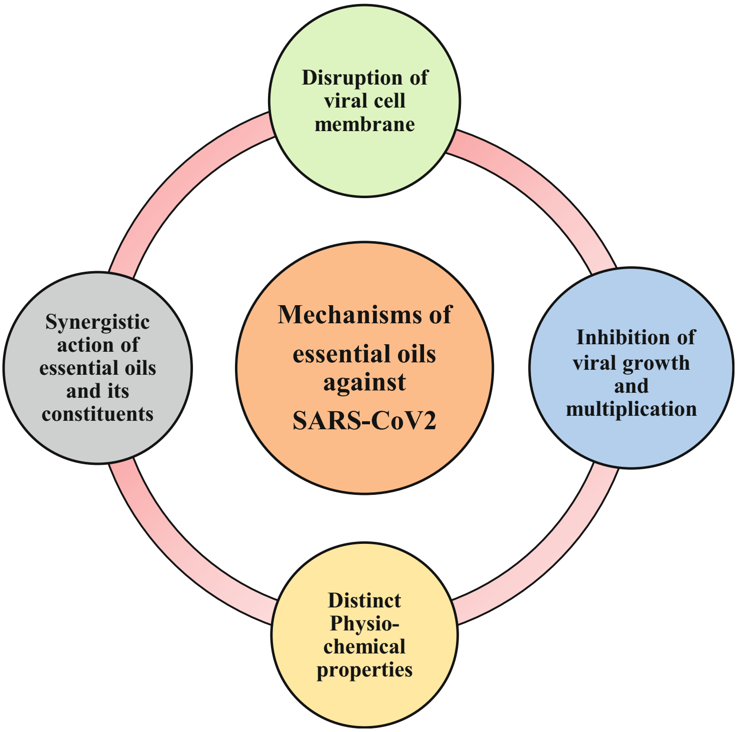

Fig. 16.1 Different mechanisms of action of essential oils against SARS-CoV-2

can be impaired by several bioactive ingredients of crude essential oils (Elsebai and Albalawi 2022). Several proteins of SARS-COV-2 have been effectively targeted using different bioactive components of essential oils including carvone, thymoquinone, camphene, limonin, carvacrol, eucalyptol and thymol (Neto et al. 2021). The majority of tested substances primarily targeted the spike protein of SARS-COV-2 that has been associated with the cell entry of virus following its attachment to specific ACE-2 receptors (Neto et al. 2021).

Molecular docking analysis revealed the synergistic inhibitory actions caused by 17 different compounds of garlic essential oil on Mpro and ACE-2 proteins of SARS-COV-2 (Thuy et al. 2020). ACE-2 antagonism has also been attributed to the principal ingredient of *Ammoides verticillata* essential oil, called isothymol (Abdelli et al. 2021). Moreover, the bioactive substance called zerumbone exhibited a high affinity for spike protein-human cell ACE-2 receptor complex (Neto et al. 2021; Sharbidre et al. 2021). Endoribonuclease which is essential for the replication of SARS-COV-2 and restricts the host defense mechanism can be efficiently inhibited using curion (Hackbart et al. 2020). Another substance known as caryophyllene demonstrated a high affinity for non-structural RNA-binding protein-9 RP1A as well as spike protein, spro (Neto et al. 2021). Likewise, the bioactive components of South Asian plant, *Melaleuca cajuputi*, including α-eudesmol, β-selinenol, γ-eudesmol, cineol, linalool, guaiol and terpineol displayed a synergistic inhibitory effect on viral replication via interacting with ACE-2 receptor (My et al. 2020). Cysteine protease enzyme having a pivotal role in the viral replication process was successfully targeted by spatholinol, himachalol and eudismol (Neto et al. 2021). Several major ingredients of different essential oils such as pulegone, menthol, camphene, cinnamaldehyde, anethole, geraniol, thymol and carvacrol inhibited viral replication by targeting the S1 element of the spike protein (Kulkarni et al. 2020). Menthol, eugenol, carvacrol and cinnamaldehyde suppressed the synthesis of proinflammatory cytokines and recruitment of macrophages in the bronchoalveolar fluid (Wani et al. 2021). Essential oils of juniper, lemon and geranium are also known for their inhibitory effects on ACE-2 receptor of SARS-COV-2 (Kumar et al. 2020). Ethanolic preparation consisting of methyl salicylate, eucalyptol, thymol and menthol (Listerine®) demonstrated significant antiviral effect during an in vitro study (Stathis et al. 2021). Moreover, in silico evidence is available regarding the blockage of S1 unit of viral spike protein by mouth rinses comprising of pinocarveol, caryophyllene, myrtenol and carvacrol (Yadalam et al. 2021).

Different bioactive compounds, including γ-terpinene, p-cymene, limonene, thymol and isothymol, derived from the Algerian plant, *Ammoides verticillate*, were screened for their in silico ACE-2 inhibitory actions. Isothymol was found as the most effective ACE-2 receptor antagonist with its binding affinity equivalent to that of chloroquine and captopril (Abdelli et al. 2021). The diverse flora of the Amazon region has also been examined for potential antiviral efficacy against SARS-CoV-2 using the molecular docking technique. Several of the tested compounds such as humulene epoxide II, hedycaryol, guaia-6,9-diene, germacrene A, azulenol, aristochene, amorpha-4,9-dien-2-ol, allo-aromadendrene epoxide, 14-hydroxy-muurolene, α-muurolene, α-calacorene, α-cadinene, α-amorphene and (E)-α-atlantone have reflected antiviral effects (Amparo et al. 2021). Buriti oil obtained from *Mauritia flexuosa* and containing α-carotene, 9-cis-β-carotene and 13-cis-β-carotene has been implicated in interacting with the viral peptidase enzyme (Costa et al. 2021). Similarly, a palm tree known as Coco de Mer (*Lodoicea maldivica*) comprising monoterpenes, bicyclogermacrene and β-caryophyllene has been linked with antimicrobial potential (Giuliani et al. 2020). Faster recovery and suppression of clinical manifestations were documented in COVID-19 patients following the twice utilization of *Nigella sativa* oil capsules (500 mg) for 10 days (Koshak et al. 2021). Based upon their preliminary antiviral actions, the essential oils of *Melaleuca alternifolia* (tea tree) and *Laurus nobilis* are also considered as potential anti-COVID agents, requiring further pharmacological screening (Loizzo et al. 2008; Schnitzler et al. 2011).

16.5 Conclusion and Future Recommendations

Essential oils obtained from medicinal plants have been traditionally used in several parts of the world for different pharmaceutical benefits. Accordingly, the pharmacotherapeutic significance of aromatherapy seems inevitable in the milieu of SARS-COV-2 infection. Different parts of cultivated or wild plants including leaves, flowers, bark, root or fruits are used for the extraction of essential oils (Damiescu et al. 2022). Standardized preparations of certain essential oils are commercially available in the form of nasal sprays, gels, creams and capsules, and are widely used for the treatment of different viral infections (Damiescu et al. 2022). Several beneficial aspects of essential oils including high lipophilicity, smaller molecular size, rapid onset of action, wide safety margin, high vapor pressure, efficient virucidal activity, ease of synthesis and formulation, convenient oral administration, and lack of first-pass metabolism reflect their therapeutic and prophylactic significance in conjunction with the typical antiviral drugs for the treatment of viral pneumonia (Elsebai and Albalawi 2022). Essential oils can be used as an adjunct to conventional antiviral agents in countries with deprived healthcare facilities and limited availability of effective vaccines (Damiescu et al. 2022). Nevertheless, highly concentrated formulations of some essential oils can give rise to detrimental effects such as vomiting, nausea, dizziness and epileptic seizures upon oral administration (Damiescu et al. 2022). Lack of standardized dosage forms, direct cytotoxic reactions and poor solubility are some of the drawbacks that limit the widespread application of some essential oils for therapeutic purpose (Damiescu et al. 2022). Besides, some essential oils can also lead to tissue irritation or a burning sensation on the cutaneous/mucosal surface. However, the nano-emulsion formulations have considerably minimized the likelihood of undesirable effects and enhanced the therapeutic utility of essential oils (Damiescu et al. 2022).

Several commercially available essential oils have been linked with efficient antimicrobial effects and thereby necessitate further investigation of their pharmacological potential to combat the extensively rising microbial resistance (Gutierrez et al. 2008; Wińska et al. 2019; Kakhki et al. 2020). Eucalyptol is considered a promising candidate drug against SARS-COV-2 infection on account of its suitable physicochemical profile and diverse pharmacological effects (Elsebai and Albalawi 2022). The currently available in silico data regarding the antiviral efficacy of essential oils against SARS-COV-2 should be further validated using in vitro assays, animal models and clinical studies (Neto et al. 2021). Apart from the confirmation of antiviral efficacy at experimental and clinical levels, the safety profile of essential oils and their purified bioactive products also require in-depth evaluation through toxicity studies. Randomized clinical studies are required for determining the efficacy and safety of standardized essential oil formulations (Damiescu et al. 2022). Keeping in view the antioxidant, immunomodulatory and anti-inflammatory properties of essential oils against SARS-COV-2 infection, their pharmacological actions and therapeutic effects should be further explored through experimental and clinical studies (Elsebai and Albalawi 2022).

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