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Essential oils and extracts of commonly used medicinal plants to fight against emerging and re-emerging infectious diseases including COVID-19

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Abstract
Introduction: In recent years, many infectious diseases are emerging as a pandemic. COVID-19 is one of the major challenges for mankind at present. The third wave of SARS-CoV-2 outbreak has already started hitting the world and new variants has also started spreading. At present, patients with severe COVID-19 are treated with antiviral drugs for controlling viral infection and supportive treatment with anti-inflammatory and antibacterial drugs to control hyper inflammatory response and secondary infection respectively. Antioxidant drugs are also gaining importance in COVID-19 patient's supportive care. Many herbal preparations are known and have been proven for their health benefits such as immune-modulatory, anti-viral, anti-inflammatory, anti-microbial and Antioxidant roles.
Methods: Four herbal plants of household use were selected for the study namely garlic, cloves, cinnamon and eucalypts. Research data was collected for all the plants for their immune-modulatory, anti-viral, anti-inflammatory, anti-microbial and Antioxidant roles and presented comprehensively in the preparation of this manuscript.
Results: Essential oils and extracts of medicinal plants such as garlic, cloves, cinnamon and eucalypts have all those characteristics required to prevent as well as control infection and supportive care which is important in the fight against COVID-19.
Discussion: There is relevance in the treatment strategy for COVID-19 and medicinal properties of plant extracts which make these medicinal plants as a potential alternative to pharmacological agents for immunity boost up, treatment and management of viral pandemics including COVID-19 outbreak.

Keywords: Medicinal plants, Immunity booster, coronavirus, COVID-19

Introduction
The coronavirus (CoV) is the causative agent of COVID-19. Coronaviruses are large enveloped viruses (Wu *et al*. 2020) [100] belong to the family Corona viridae, sub family Corona viridae grouped in to Alpha (α), Beta (β), Gamma (γ), and Delta (δ) genera based on their serological characteristics (Lim *et al*. 2016) [84]. All the coronaviruses which have infected humans were reported from α (Human CoV-NL63, Human CoV-229E) and β (Severe Acute Respiratory-Syndrome (SARS) CoV, Middle Eastern Respiratory Syndrome (MERS) CoV and Human CoV-OC43) genera's only (Lu *et al*. 2020) [87]. The coronaviruses from β genera have generally caused severe epidemic in the past (SARS and MERS) and COVID-19 also belongs to the β genera of virus SARS-CoV-2 (Yang and Wang, 2020) [54].
The COVID-19 is a lower respiratory tract infection with flu-like symptoms similar to the SARS and MERS diseases such as sore throat, cough, fever, body aches and loss of taste or smell in some cases. The second wave of SARS-CoV-2 outbreak has already started hitting countries worldwide. People with poor immunity were found to be more vulnerable to the disease (Das *et al*. 2020) [25].
The symptoms of diseases are not visible in some asymptomatic individuals however; they act as potential source of SARS-CoV-2 infection. Historical evidences indicate that human was affected by several viral epidemics, killing billions of people worldwide. The SARS-CoV-2 is also causing extensive mortality all over the globe (>2 million so far). The effective treatment is very much essential, and the scientific community is engaged in extensive search for drugs. Remdesivir has been recommended by WHO for treatment of COVID-19 patients and many other antiviral drugs and combinations are under evaluation.

According to WHO ~80% of the people in many developing countries depend on conventional plant sources for various primary health needs (Bennerman *et al*. 1983; Mahady, 2001) [10, 91] and even the roots of modern medicine lies in the traditional herbal medicinal plants as a source of active compounds. With the advancement of technological resources, various natural plant resources have been explored as antiviral agents (Ganjhu *et al*. 2015) [37]. Indian Ayurveda is one of the oldest and systematic medical practice with historical evidences back to 5000 years old. The published literature of Ayurveda mentions several healing plants for infection control and immunity improvement. Advanced research has suggested that primary and secondary metabolites of plants are the active compounds of various herbal medicines with known health benefits including immunity development against various infectious diseases and having antiviral as well as antimicrobial properties. Compounds or supplements of various medicinal plants have the tendency of enhancing immunity, antiviral activity, antibacterial activity, anti-inflammatory activity and antioxidant activities, which are supportive factors in fight against COVID-19 infection prevention as well as treatment. In this review we have discussed about the uses of common traditional plants like garlic, cloves, cinnamon and eucalypt in Indian households. Here, we have described the medicinal properties of these medicinal plants as a potential alternative to pharmacological agents for management of COVID-19 outbreak.

Pharmacological properties of Medicinal plant and COVID-19

Patients with severe COVID-19 are treated with antiviral and antibacterial drugs. As COVID-19 patients develop a systemic hyper-inflammatory response that leads to lung injury and multisystem organ dysfunction. Thus, combining an antiviral with an anti-inflammatory agent may treat the viral infection as well as dampen the potentially injurious inflammatory response that is a consequence of the infection (Iwasaki *et al*. 2004) [60]. Potential treatment strategies that are currently in the testing phase against SARS-CoV-2 include antivirals drugs and drugs that can reduce inflammation by suppressing the pro-inflammatory cytokines or corticosteroids that decrease the cytokines storm, ACE-2 inhibitor (Fantini *et al*. 2020) [33] SARS-CoV-2 specific siRNAs (Hasan *et al*. 2020) [48], immunomodulatory (Misra *et al*. 2020) [103] and anti-oxidant drugs. Here we indicate briefly various pathophysiological aspects which need to be addressed for the prevention and treatment of COVID-19 as shown in fig.1 below.

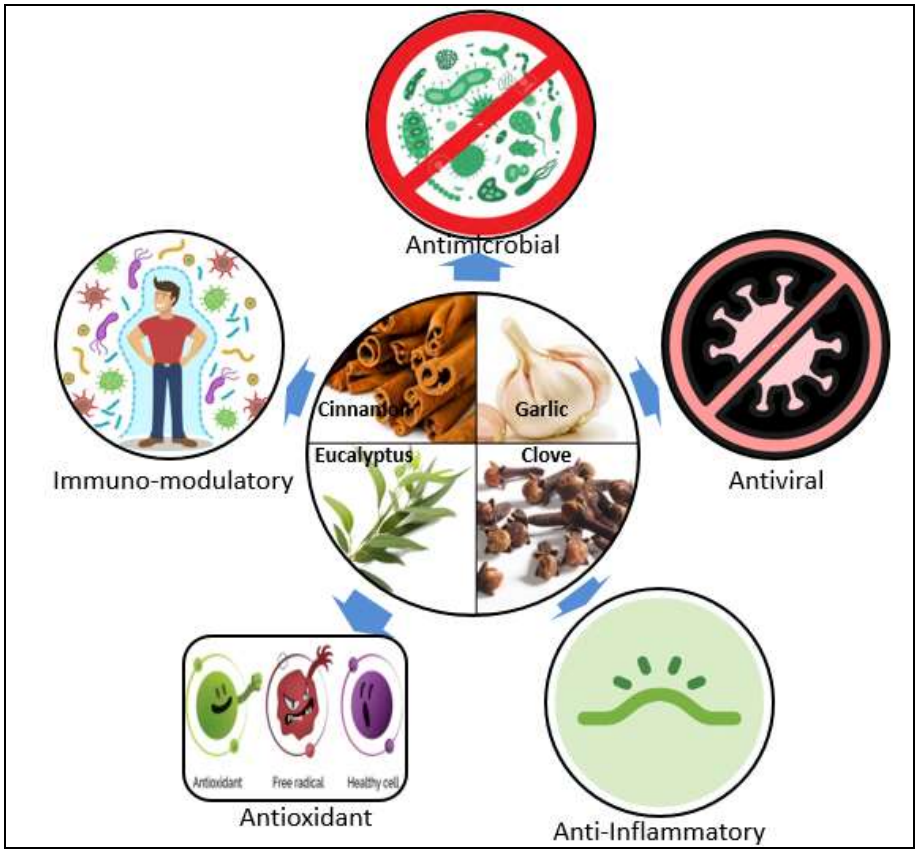

Fig 1: Various properties exhibited by medicinal plants (Clove, cinnamon, garlic and eucalypts) which can control the pathophysiological aspects which need to be addressed for prevention and treatment of COVID-19. (Please include colours)

Viral infection: SARS-CoV-2 binds to host cell through the ACE2 receptor (Li *et al*. 2003a) [81] and after endocytosis and subsequent uncoating, the components of SARS-CoV-2 use host cells machinery to produce new viruses. Finally, SARS-CoV-2 releases virions to the host cell by exocytosis, during this process, the viral replication can be inhibited at different stages by repositioned antiviral drugs.

Inflammation: A study showed that almost all COVID-19 positive patients have lung abnormalities. Abnormal and overactive inflammatory responses to SARS-CoV-2 are proposed to be the major causes of disease severity and death in COVID-19 patients (Xu *et al*. 2020; Zhou *et al*. 2020) [151, 160] This hyper-inflammatory state is associated with increased levels of circulating cytokines, profound lymphopenia, and substantial mononuclear cell infiltration in the lungs and other organs including heart, spleen, lymph nodes, and kidneys. The systemic cytokine profiles observed in patients showed

increased production of cytokines such as IL-6, IL-7, IL-8 and tumour necrosis factor (TNF) and many other pro-inflammatory cytokines (Merad and Martin, 2020) [101]. Controlling this overactive inflammatory response in time is necessary to save the COVID-19 patients.

Immunomodulation: It refers to any processes that alter the immune system either by enhancing (immunostimulation) or suppressing its function. While immunostimulation occurs by activating inactive components of the immune system or expansion of their activity, whereas reduction of the efficacy of immune responses described as immunosuppression. Immunostimulation helps in the prevention of infection by SARS-COV-2 and also in controlling the infection at an early stage. In severe cases, Covid-19 is known to cause hyper immunostimulation causing abnormal and overactive inflammatory responses. In severely infected patients, immunosuppression can be beneficial in diminishing inflammatory responses (Gea-Banacloche *et al*. 2020). There are multiple immunomodulators under evaluation for the treatment of COVID-19. The COVID-19 treatment guidelines panel of WHO have recommended the use of Dexamethasone (or other corticosteroids) with or without Remdesivir for the therapeutic management of patients with COVID-19 but the use of other immunomodulators like Interferons and kinase inhibitors is limited to a clinical trial (WHO interim guidelines 27 Dec 2020).

Bacterial co-infections: Viral-bacterial co-infections are one of the biggest medical concerns, resulting in increased mortality rates in COVID-19. So far there has been limited research on bacterial superinfections in COVID-19 patients Although highly variable, bacterial co-infection in patients with severe influenza has been reported to be as high as 20–30% (Rice *et al*. 2012; Shah *et al*. 2016; Langford *et al*. 2020) [121, 125, 76] and is associated with more severity of illness, increased use of healthcare resources as well as increased risk of death (Martín-Loeches *et al*. 2011) [96]. While antibiotics are not effective in treating COVID-19, they are prescribed to patients where COVID-19 is suspected or documented for a variety of reasons. This includes difficulty in ruling out bacterial co-infection on presentation, and possibility of bacterial secondary infection while course of the illness. During the Influenza pandemic, patients with bacterial superinfection increase in mortality and There are several guidelines to use empirical antibiotics in patients with severe COVID-19. (Alhazzani *et al*. 2020; WHO interim guidelines 27 Dec 2020) [3].

Reactive oxygen species: Clinical features of the disease COVID-19 include overproduction of reactive oxygen species. Reactive oxygen species induce oxidative stress responses and contribute to acute lung injury (Khomich *et al*. 2018) [68]. This introduces possible treatment strategy involving anti-oxidant therapy. Antioxidants that can safely react with free to terminate the chain reaction or neutralize it. Multiple clinical trials are underway to evaluate the role of antioxidants in the COVID-19 treatment. A randomized clinical trial Study to evaluate antioxidant therapy for moderate to severe COVID-19 with or without comorbidities is being funded by Obafemi Awolowo University (NCT04466657) (https://clinicaltrials.gov/). This is a supportive care type of clinical trial. Another randomized clinical trial with Anti-inflammatory/Antioxidant oral nutrition supplementation on the cytokine storm and progression of COVID-19 (NCT04323228) is recruiting individuals and being funded by King Saud University (https://clinicaltrials.gov/). The compounds present in foodstuffs play a vital role in human life, acting as health-protecting agents. Antioxidants from medicinal plants have received rapid consideration against various diseases (Suhaj, 2006) [137].

Historically, the human pharmaceutical arsenal is significantly indebted to nature and in particular to natural products obtained from traditional medicinal plants, fungi and bacteria (Luo *et al*. 2014) [90]. To date, natural products and compounds derived therefrom command a substantial market share, comprising 49% of anti-infectives approved in the past 30 years (Newman *et al*. 2012) [109]. These compounds from medicinal plants considered as bioactive natural products and may ultimately developed as drugs. In food, they would be defined as phytonutrients without therapeutic claims but with significant health benefits that can be used in disease prevention (Wolfender *et al*. 2011) [149] In the upcoming sections of this review, we will discuss in detail about antiviral, antibacterial, immunomodulatory, anti - inflammatory and antioxidant properties of clove, garlic, cinnamon and eucalypts essential oils and extracts are mentioned in Table 1.

Table 1: Medicinal properties of various parts of medicinal plants like cloves, garlic, cinnamon and eucalypts.

S no.	Name of plants (Vernacular name)	Scientific name & (Family)	Medicinal properties	References	Useful part
1	Cloves (Laung, Lavang)	*Syzigium aromaticum* (Myrtaceae)	Antiviral, Antibacterial (Bacteriostatic, bactericidal), immunomodulatory, anti-inflammatory, antioxidant, anti-viral, antimycotic, anti-carcinogenic, anaesthetic and analgesic properties.	Pulikottil and Nath, 2015 [119]	Dried Buds, Oil
2	Garlic (Lahsun)	*Allium sativum* (Amaryllidaceae)	Antibacterial, antiparasitic, immunomodulatory, lipid metabolism, cardiovascular-protective, anti-oxidant, cardioprotective, anticancerogenic, and anti-inflammatory activity	Arreola *et al*. 2015 [4]	Bulblets/ Cloves of Bulbs
3	Cinnamon (Dalchini)	*Cinnamomum verum* (Lauraceae)	Antiviral, antimicrobial and antifungal, Anti-inflammatory, antioxidant, wound healing, gynaecological, digestive and respiratory systems,	Unlu *et al*. 2010 [144]	Bark, leaves
4	Eucalypts (Nilgiri)	*Eucalypts globulus* (Myrtaceae)	Antiviral, antibacterial, immunomodulatory, antiinflamatory and antioxidant	Dhakad *et al*. 2018 [27]	Leaves

Clove (Vernacular name: Laung, Lavang):

Syzygium aromaticum (Clove) belongs to the family Myrtaceae is a tropical evergreen tree with 8-12 meters in height and large leaves (Cortés-Rojas *et al*. 2014) [24]. This plant is native to Indonesia but also grown extensively in India, Pakistan, and Sri Lanka. The small reddish brown dried flower bud is the usable part of this tree. The Leaves and flower buds of this tree have numerous oil glands on their

under-surfaces which makes it aromatic. The flowers are harvested in bud stage (1.5- 2.0 cm long). These flower buds are picked up at green stage with slightly cylindrical base and a ball like unopened corolla. These green buds are sun dried till they turn brown. Once dried they have a refreshing fragrance (Williamson, 2003) [148]. The essential oil of flower buds is an aromatic oil that is used widely as a flavoring agent or as an herbal oil.

Chemical composition: Clove are one of the major botanical sources of phenolic compounds. Essential oil in the clove was found up to 18%, with eugenol as the major and main bioactive compound with ~90% of the oil and 5% to 15% is β-cariofileno and eugenol acetate (Jirovetz *et al*. 2006) [61]. Around 9.38 to 14.65 g/100 g of fresh plant material is Eugenol (Neveu *et al*. 2010) [108]. α-humulen is another important compound found in the essential oil of clove with up to 2.1% concentrations. Gallic acid (Phenolic acids) is the compound found in higher concentrations with 0.78 g/100 g fresh weight (Shan *et al*. 2005) [126] whereas gallic acid derivates are present in higher concentrations 2.38 g/100 g (Shan *et al*. 2005) [126]. Flavonoids, kaempferol, quercetin and their derivates (glycosylated) are also found in lower concentrations. Other volatile compounds present in lower concentrations in clove essential oil are β-pinene, limonene, farnesol, benzaldehyde, 2-heptanone and ethyl hexanoate (Jirovetz *et al*. 2006) [61].

Antimicrobial properties: Eugenol, a phenylpropene compound, which is the major constituent of CEO has strong biological and antimicrobial activities. Eugenol has antimicrobial, antifungal, antiviral, antioxidant, anti-inflammatory and anticancer properties (Han and Parker, 2017a) [45]. Clove oil is used as an antiseptic in oral infections (Meeker *et al*. 1988; Shapiro *et al*. 1994) [98, 127]. The anti-microbial and anti-inflammatory properties of eugenol could be used for the treatment of oral and periodontal diseases (Pulikottil and Nath, 2015) [119]. It is also used traditionally as an antimicrobial agent in food (Lee and Shibamoto, 2001; Nuñez *et al*. 2001; Huang *et al*. 2002) [79, 112, 53]. It was also found effective against *L. monocytogenes* and *S. Enteritidis* (Smith-Palmer *et al*. 2001) [133]. It is well known that both eugenol and other phenolic compounds of clove essential oil can react with cell membrane phospholipids changing their permeability and denature proteins, inhibiting a great number of bacteria (Gram-negative and Gram-positive bacteria), yeast and molds (Chaib *et al*. 2007) [16].

Anti-inflammatory properties: the anti-inflammatory activity of Eugenol in human gingival fibroblast and pulp cells is proven (Koh *et al*. 2013) [72]. CEO has showed strong activity in inhibiting the proliferation of dermal fibroblasts in humans (Han and Parker, 2017a) [45]. It has shown significant inhibition of the several proinflammatory biomarkers such as vascular cell adhesion molecule-1 (VCAM-1), interferon c-induced protein 10 (IP-10), interferon-inducible T-cell a chemoattractant (I-TAC), and monokine induced by c interferon (MIG) (Han and Parker, 2017a) [45]. Anti-inflammatory mechanisms of clove key constituents on the specific immune system components have only recently begun to be studied in detail (Yogalakshmi *et al*. 2010; Bachiega *et al*. 2012; Grespan *et al*. 2012) [156, 7, 40].

Antiviral properties: The antiviral activity of eugeniin was tested against herpes virus strains and was found effective at 5 µg/mL, and it was found that eugeniin inhibited the viral DNA polymerase and thereby inhibited viral DNA synthesis (Kurokawa *et al*. 1998) [74]. Cloves were also found effective against Herpes Simplex Virus-1 (HSV 1) and Herpes Simplex Virus-2 (HSV 2) (Benencia and Courrges, 2000; Tragoolpua and Jatisatienr, 2007) [9, 140]. Additionally, Eugenol of *S. aromaticum* was also highly active in inhibiting replication of the hepatitis C virus (Hussein et.al, 2000) [55]. Aqueous extracts of *S. aromaticum* (L.) also showed strong anti HSV-1 activity when combined with acyclovir (Kurokawa *et al*. 1995) [75].

Antioxidant properties: Recently, the US Department of Agriculture in collaboration with Universities and private companies created a database with the polyphenol content and antioxidant activity of different kinds of foods. Based on this database, Pérez-Jiménez *et al*. (2010) [117] classified the 100 richest dietary sources of polyphenols where clove showed higher content of polyphenols and antioxidant compounds. Another study also showed a high correlation between the polyphenols content and the antioxidant activity (Shan *et al*. 2005) [126]. Clove (buds) was the spice presenting higher antioxidant activity and polyphenol content, tetraethylammonium chloride 168.6 mmol of Trolox/100g dried weight and 14.4 of gallic acid (equivalents/100g of dried weight) respectively. The major types of phenolic compounds found were phenolic acids (gallic acid), flavonol glucosides, phenolic volatile oils (eugenol, acetyl eugenol) and tannins. The huge potential of clove was highlighted as a free radical scavenger and as a commercial source of polyphenols. Gülçin *et al*. (2012) [164] compared the antioxidant activity of clove oil and synthetic antioxidants in terms of the scavenging of the DPPH radical and found decreased in the following order: clove oil> BHT> alfa-tocopherol> butylated hydroxyanisole> Trolox. Ethanol and aqueous extracts of clove at concentrations of 20 µg/ml, 40 µg/ml and 60 µg/ml showed inhibitions up to 95% when tested as metal quelants, superoxide radical capture and scavenging of the DPPH radical. The powerful antioxidant activity of both extracts may be attributed to the strong hydrogen donating ability, metal chelating ability and scavenging of free radicals (Gülçina *et al*. 2004) [42].

Immunomodulatory: The major ingredients of clove essential oil have been shown to be eugenol followed by eugenyl acetate, tanene, thymol, and *β*-cariophyllene (El-Ghorab and El-Massry, 2003) [31]. These components are known to modulate immune responses even though the mechanisms of action is not known (Choi *et al*. 2007) [22]. Effects of the clove extract on macrophage cytokine formation or release were mainly dose-related and bi-phasic for IL-6 and TNF*α*, while effects on IL-12 were mostly unremarkable. The data from previous studies suggest a narrow immunomodulatory effect from clove components. Further studies using different doses with pure eugenol on various target cell types may give a clearer picture for medicinal purposes.

Garlic (Vernacular name: Lahsun)

Allium sativum (Garlic) belongs to the family Amaryllidaceae. The long cylindrical leaves of garlic plant arise from a short hard stem just above the bulb or emerge from a pseudo stem made of overlapping leaf sheaths. The bulb is covered with membranous scales and encloses up to 20 edible bulblets called cloves. Flower stalks sometimes arise bearing tiny

bulbils and sterile blossoms. Garlic is usually grown as an annual crop and is propagated by planting cloves, top bulbils or, through seeds. The most usable part of this plant is cloves and sometimes the inflorescence and leaves. Garlic is originated from central Asia and then spread to the whole Africa, Europe. It has been used by humans for 7,000 years as medicinal and culinary purposes.

Chemical composition: Chemistry of the *Allium* has been dominated by many sulfur-containing compounds that give it a characteristic flavor. However, a variety of other components, including non-sulfur compounds, work synergistically to provide various health benefits. Intact garlic cloves generally contain nonvolatile sulfur-containing compounds. The major sulfur-containing compounds in intact garlic are γ-glutamyl-*S*-allyl-L-cysteines and *S*-allyl-L-cysteine sulfoxides (alliin). Processed garlic and garlic essential oil contains a wider variety of organosulfur volatiles than the intact garlic clove (Harunobu, 2006) [47]. Crushed garlic contains volatiles such as DAS (diallyl sulfide), DADS (diallyl disulfide), diallyl trisulfide, methylallyl disulfide, methylallyl trisulfide, 2-vinyl-4H-1, 3-dithiin, 3-vinyl-4H-1, 2-dithiin, and (E,Z)-ajoenes. The major sulfides in garlic essential oil contains57% DAS, 37% allylmethyl, 6% dimethyl mono- to hexasulfides (Lawson *et al*. 1991) [77].

Antimicrobial Properties: Allicin, is the main biologically active component of freshly crushed garlic, which is formed by enzymatic conversion of alliin to allicin. Allicin can be easily disintegrated at ambient temperature for longer time and gets converted in to stable compounds. 2-propenesulfenic acid and tioacrolein are the two key molecules obtained from garlic, which gets converted into greater molecules such as diallyl trisulfide and dithiin (Fujisawa *et al*. 2008; Guo *et al*. 2012) [36, 43]. Garlic is a potential antibiotic and effective against the bacteria resistant to antibiotics. In 1970's, scientists tested the garlic extract on 10 resistant bacterial and yeast species and found effective against *Salmonella*, *S. aureus*, *Mycobacterium* and *Proteus* species (Bergner and Rocklin, 1995) [11]. Alcoholic garlic extract was found much more stable and effective than the aqueous extract. Tests shown that allicin is sole responsible for antimicrobial activity of garlic, and it was three times more effective on Gram-positive bacteria than Gram-negative bacteria. These results may be attributed to the 10 times higher membrane lipid content in gram-negative *E. coli* than gram positive *S. aureus*. The antibacterial effects of aqueous extract of Ethiopian garlic (*A. sativum L.*) extracts on 30 different species of *S. aureus* have proven antimicrobial property (Deresse, 2010) [26].

Anti-inflammatory: Macrophages represent the usual source for an oxidative burst in immune responses as well as for inducible nitric oxide synthase (iNOS). iNOS expression can be upregulated by pro-inflammatory cytokines, LPS and hypoxia. iNOS expression can be downregulated by anti-inflammatory cytokines TGFβ and IL10, the tumor suppressor gene p53 and NO (nitric oxide) itself (Kleinert *et al*. 2003) [71]. Stimulation of the anti-inflammatory cytokine IL10 was observed in LPS-stimulated human whole-blood cultures by garlic extracts while monocyte production of pro-inflammatory cytokines (TNFα, IL1α, IL6, IL8, T-cell IFNγ, IL2 and TNFα) was significantly suppressed (Hodge *et al*. 2002) [50]. This was repeated on LPS-stimulated human placental explants and garlic extract was found to stimulate the production of anti-inflammatory cytokines and inhibiting the production of pro-inflammatory cytokines (Makris *et al*. 2005) [92]. In a study on activated macrophages, it was found that garlic oil derivatives suppressed the production of NO and prostaglandin E2 (PGE_2) and bring about an anti-inflammatory effect (Chang *et al*. 2005) [18]. The anti-oxidative effects of garlic have been linked to the maintaining intracellular glutathione level and removal of peroxides where inhibition of NFκB activation seems to be central to these effects (Ide *et al*. 2001) [59]. In an experimental study, compounds like DADS, DAS, and alliin from garlic were found to considerably reduced inflammation during dengue infection (Hall *et al*. 2017) [44].

Antiviral properties: Flavonoids present in garlic are found to have strong anti-viral activity. Phytochemicals present in garlic has been observed to block protein production and DNA replication in the viruses (Castrillo and Carrasco, 1987; Vrijsen *et al*. 1987; Zandi *et al*. 2011) [14, 145]. Garlic extract have been proven to minimize influenza A and B viral infections (Fenwick and Hanley 1985) [35]. Garlic is also effective against cytomegalovirus (Meng *et al*. 1993; Nai-Lan *et al*. 1993), rhinovirus, HIV, HSV-1 (Tsai *et al*. 1985) [141], HSV-2 (Weber *et al*. 1992) [146], viral pneumonia and rotavirus. Common cold virus considerably minimizes by garlic (Josling, 2001) [62]. Garlic also exhibited strong inhibitory effects against the poultry virus, Infectious Bronchitis Virus (IBV), which significantly affect the poultry industry (Shojai *et al*. 2016) [130]. Chemicals like Ajoene, allyl alcohol, and diallyl disulfide in garlic can act as an antiviral against HIV (Shoji *et al*. 1993; Tatarintsev *et al*. 1992) [131, 139]. Organosulfur compounds like allicin, diallyl trisulfide, and ajoene are the main chemicals which impart antiviral property to garlic (Hughes *et al*. 1989; Weber *et al*. 1992) [54, 146].

Antioxidant Properties: Garlic was found to have antioxidant properties. Ide investigated and found clear supportive data that AGE and SAC significantly prevent membrane damage, loss of cell viability, and lipid peroxidation in bovine pulmonary artery endothelial cells (PAECs) exposed to oxidized LDL (Ide *et al*. 1997). According to Yamasaki *et al*. (1997) [152] and Wei and Lau, (1998) [147], AGE suppresses hydrogen peroxide (H_2O_2) and superoxide molecule production and also significantly increases the activities of superoxide dismutase (SOD), catalase, and glutathione peroxidase. It was observed that these chemicals affected the oxidative stress response mechanism (Hall *et al*. 2017) [44].

Immunomodulatory properties: Intrinsic and extrinsic factors are responsible for Immune regulation however di*et al*.so plays a significant role in the immune system for its proper functioning and response (Lin and Karin, 2007) [86]. Immunity boosting properties of garlic are well known for ages. Numerous compounds have been detected in Aged Garlic Extract (AGE) that have the potential to affect immunity, including the lectin family, which is known to interact with pathogen recognition receptors on immune cell surfaces (Huysamen and Brown, 2009; Kingeter and Lin, 2012) [56, 70]. Nα-fructosyl arginine and Fructo-oligosaccharide are aged garlic compounds that have structures resembling pathogen-associated molecular patterns, with the potential to interact with immune cells (Chandrashekar *et al*. 2011) [17]. Nutrition scientists from the University of Florida published a

report in the journal clinical nutrition in 2012, proving that dietary uptake of Garlic/extract could reduce the severity of cold and flu symptoms faster as compared with those who did not take garlic. The scientists guessed that the garlic extract could have worked by boosting immunity. Scientists examined the effects of AGE on lymphocytes, the γδ-T cell could reduce the severity of cold and flu symptom (Nantz *et al*. 2012) [107]. Studied on a group of 120 people in extreme Cold and Flu season and found that the people on AGE intake had less Flu/cold symptoms in comparison (Percival 2016) [116].

Cinnamon

Cinnamomum aromaticum and *Cinnamomum zeylanicum* (CZ) are two main varieties of the inner bark of tropical evergreen tree cinnamon (Soliman *et al*. 2012) [134]. Cinnamon is obtained by peeling the outer side of the trees bark and allowing the inner side of the trees bark to dry and coil up into its usual cinnamon quills. Characteristic flavour of Cinnamon makes it useful as excitement in cooking. *C.* true cinnamon or Ceylon cinnamon. Coumarin content is one main important difference between the cassia cinnamon and 'true' cinnamon Coumarin content in CZ seems to be very small to be good for consumption on a regular basis (Lungarini *et al*. 2008) [89]. Cinnamon is also used as the Ayurveda medicine in the treatment of many diseases along with those of the respiratory, gynecological and digestive systems.

Chemical composition: Bark is the main useful part of the cinnamon tree, which contains around 65-80% Cinnamaldehyde and 5-10% Eugenol. Cinnamon tree leaves contain 1-5% Cinnamaldehyde and 70-95% Eugenol. Root bark contains 60% Camphor. Fruit contains *trans*- 42-54% Cinnamyl acetate and 9-14% caryophyllene. The key constituents of cinnamon essential oil are cinnamaldehyde and *trans*-cinnamaldehyde (Cin), which contribute to various biological activities and the fragrance (Yeh *et al*. 2013). Essential oil extracted from *C. zeylanicum* named (E)-cinnamaldehyde is a major-constituents and it has an antityrosinase activity (Marongiu *et al*. 2007) [95] similar to cinnamaldehyde (Chou *et al*. 2013) [23].

Antimicrobial properties: Antibacterial activities of several *C. zeylanicum* bark extracts, obtained with different organic solvents (acetate, acetone and methanol) were tested *in vitro* by the disk-diffusion method against various bacteria (*Enterobacter cloacae, Klebsiella pneumonia*, *Staphylococcus aureus*, *Escherichia coli*, *Corynebacterium xerosis*, *Bacillus megaterium*, *Pseudomonas aeruginosa Streptococcus faecalis*). The antibacterial activity was in the range of 7 to 18 mm zone of inhibition for 30 µL, suggestive of high antibacterial activity (Keskin and Toroglu, 2011) [67]. A study showed that the ethanolic extract of stem bark of *C. zeylanicum* exhibited antibacterial activity against methicillin resistant *S. aureus* (MRSA) (Mandal *et al*. 2011) [94]. The extract, which showed a zone of inhibition of 22 to 27 mm was found to be bactericidal after 6 hrs of incubation. Authors concluded that *C. zeylanicum* could be considered value in the treatment of infection and a source of molecule for the development of potential antimicrobial agents against MRSA bacteria (Mandal *et al*. 2011) [94]. Cinnamon bark essential oil was tested for antibacterial activity (expressed as MIC) against several pathogenic bacterial strains (*Salmonella typhi*, *Salmonella paratyphi A*, *E. coli*, *S. aureus*, *Pseudomonas fluorescens* and *Bacillus licheniformis*), tested sample showed excellent activity against all the selected bacterial strains (MIC values ranged from 2.9 to 4.8 mg/mL). The analysis revealed the presence of *t*-cinnamaldehyde (which was the most abundant substance, corresponding to 4.3%), eugenol (0.32%) and minor components such as cuminaldehyde, and γ-terpinene (Mandal *et al*. 2011) [94].

Anti -inflammatory properties: Several studies have shown the anti-inflammatory activities of cinnamon (Li *et al*. 2003b; Matu and Staden, 2003) [82, 97] and its essential oil (Tung *et al*. 2008, 2010) [143, 142]. Several flavonoid compounds have been isolated from cinnamon (e.g, gossypin, gnaphalin, hesperidin, hibifolin, hypolaetin, oroxindin, and quercetin) that have anti-inflammatory activities (Cho *et al*. 2013; Stoner *et al*. 2013) [21, 135]. Anti-inflammatory properties of cinnamon have been proven using an animal model with induced inflammation is suppressed by trans-cinnamaldehyde (Chen *et al*. 2016) [19]. Anti-inflammatory activity of cinnamaldehyde has been described in another study (Mendes *et al*. 2016) [99]. The cinnamon (*C. zeylanicum*) bark essential oil (CBEO) inhibitory effect on highly inflamed skin suggests that cinnamaldehyde and CBEO may be promising molecules in the wound healing. CBEO has also shown significant inhibition of inflammatory cytokinesis showing Anti-inflammatory activity (Han and Parker, 2017b) [165]. A recent study reported that 2′-hydroxycinnamaldehyde exhibited an inhibitory effect on the production of nitric oxide by inhibiting the activation of the NF-*κ*B, indicating the anti-inflammatory activity (Lee *et al*. 2005) [80]. The ethanolic extract also showed anti-inflammatory activity by reducing the activation of Src/spleen-tyrosine-kinase- (Src/Syk-) mediated NF-*κ*B (Youn *et al*. 2008; Yu *et al*. 2012) [157, 158]. Various compounds contained in *C. ramulus* also showed anti-inflammatory effects by suppressing the expression of iNOS, COX-2, and NO production in the central nervous system (CNS), suggesting, *C. ramulus* could be a potential source for medication of inflammation-mediated neurodegenerative diseases (Hwang *et al*. 2009) [57].

Antiviral properties: Cinnamon has been used as a medicine around the world because of its health benefits. Trans-cinnamaldehyde of cinnamon could inhibit influenza A/PR/8 virus transmission *in vitro* and *in vivo* (Hayashi *et al*. 2007) [49]. In another study, incubation of virus with Cinnamon bark extract before influenza infection showed 45% reduced infectivity at 500 µg/ml concentration. Hence, it is speculated that cinnamon components possibly blocked viral entry. In addition, treatment of cells with cinnamon after viral entry also showed up to 45% reduction of infection at 500 µg/ml concentration. This could be due to inhibition viral replication by inhibiting certain pathways essential for replication. Extract of cinnamon cassia bark was found highly effective against replication of HIV virus, by effectively controlling cell athogenicity in HIV infected MT-4 cells (Premanathan *et al*. 2000) [118].

Antioxidant properties: Cinnamon bark contains procyanidins and catechins (Nonaka *et al*. 1983; Peng *et al*. 2008; Tanaka *et al*. 2008) [111, 115, 138]. These procyanidins extracted from cinnamon possess antioxidant activities (Peng *et al*. 2008; Tanaka *et al*. 2008) [115, 138]. various extracts of cinnamon (ether, aqueous, and methanol) have shown considerable antioxidant activities (Mancini- Filho *et al*. 1998) [93]. A study on rats reported that the administration of

the 10% *C. verum bark powder* for 90 days produced antioxidant activities (Dhuley *et al*. 1999) [29]. A research group reported that cinnamon oil potentially exhibits SOD like activity (Kim *et al*. 1995) [69]. Aqueous and alcoholic extract in 1:1 ration, significantly inhibited fatty acid oxidation and lipid peroxidation (Shobana *et al*. 2000) [129]. Studies reveal that, different flavonoids isolated from cinnamon have antioxidant properties (Okawa *et al*. 2001) [113]. In a study, the major compounds present in cinnamon were investigated for antioxidant activity. Eugenol and the essential oil were effective antioxidants (Chericoni *et al*. 2005) [20]. In a comparative study among 26 spices, cinnamon showed the highest antioxidant activity (Shan *et al*. 2005) [126]. Another study examined the effectiveness of a mixture of spices with 1 g/100 g cinnamon bark, showed a significant antioxidant activity as compared with control (Suganthi *et al*. 2007) [136]. Research showed that cinnamaldehyde possesses possible inhibitory activity against the production of nitric oxide. The highest activities were reported as 81.5%, 71.7%, at 1.0, and 0.5 µg/µL, respectively (Lee *et al*. 2002) [78]. Lin *et al*. (2003) [85] reported the antioxidant activity of ethanolic and hot water extracts of the dry bark of *C. cassia, where* ethanoilc extract exhibited 96% inhibition, compared to the natural antioxidant *α*-tocopherol (93.7%). Overall, cinnamon exhibited higher antioxidant activities compared to that of other dessert spices (Murcia *et al*. 2004) [104].

Immunomodulatory properties: The immunomodulatory effects of cinnamon were studied using different experimental studies. Mice orally administered the bark extracts at doses of 10 and 100 mg/kg and levamisole (2.5 mg/kg p.o.) was used as standard drug. The low dose of cinnamon bark (10 mg/kg p.o.) produced increase in serum immunoglobulins levels 100 mg/ kg p.o. decreased *Pasteurella multocida*-induced mortality by 17%, and increased serum antibody titer values. The research showed that cinnamon at high dose increases both humoral immunity and cell-mediated immunity, however at low dose only humoral immunity gets activated. Cinnamon at the higher dose showed protection against viral challenge as in levamisole. Cinnamaldehyde from cinnamon bark is reported to inhibit lymphocyte proliferation and NF-B stimulation (Koh *et al*. 1998; Reddy *et al*. 2004) [73, 120]. Though the exact immunostimulant component of cinnamon is not known, studies confirm that the high dose has immunostimulant activity (by S.R. Niphade *et al*. 2009) [110].

Eucalypts

Eucalypts is a genus which includes more tha 700 species in the Myrtaceae family. Plants in the genus *Eucalypts* have bark that is either smooth, fibrous, hard or stringy, leaves with oil glands. Most of the eucalypts species are native to Australia and few of them are native of nearby islands. *Eucalypts* is being grown in many countries worldwide for timber, pulpwood or essential oils. Fast growth makes eucalypts a suitable for windbreaks and erosion control and additionally it is an economically important trees (Seely, 2017) [123]. *Eucalypts* have attracted attention because of desirable traits such fast-growth, oil production for cleaning and as a natural insecticide. *Eucalypts* oil has many uses in fragrances, insect repellence and antimicrobial activity. *Eucalypts* trees release secondary metabolite compounds which inhibit other plant species from growing in vicinity. Aromatherapists have adopted eucalypts oils for a wide range of purposes (Nanko *et al*. 2005) [106]. *Eucalypts* oil is used for in very small quantities in food supplements, especially sweets, cough drops, toothpaste, and decongestants. *Eucalypts* globulus is the principal source of eucalypts oil worldwide.

Chemical composition: essential oils of many *Eucalypts* species (*E. globulus, E. maideni; E. astrengens; E. cinerea; E. leucoxylon; E. lehmani; E. sideroxylon; E. bicostata*) was studied and found to contain α-pinene, 1,8-cineol and pinocarveol-trans for all *Eucalypts* species studied. The 1,8-cineol was found as a major compound in all studied species. The essential oil composition of the Eucalypts species from the region of Bizerte showed that all of them contained 1,8-cineole, the highest content was obtained from *E. maideni* (83.59%) followed by *E. cinerea and E. lehmani* (respectively 79.18% and 49.07%). Though, the studied species were from the same region, they had shown differences in the levels of some compounds. This may be due to genetic effects. Essential oils extracted from species from Aindraham arboretum (*E. sideroxylon and E. bicostata*) had same level of 1,8 cineole and the species from Korbous arboretum (*E. lehmani*) had the lowest level of 1,8-cineole (49.07%) but the highest level of α-pinene (26.35%). Ben jemâa *et al*. (2012) reported that GC and GC-MS analyses showed that chemical composition varied with Tunisian Eucalypts species and seasons The five essential oils contained 1,8-cineole, α-pinene, and α-terpineol as major common compounds. The essential oils of twenty Eucalypts species harvested from North West and North of Tunisia were studied and the authors identified, by GC and GC/MS, eighteen major compounds and the main ones were 1,8-cineol followed by α-pinene, p-cymene, borneol, cryptone, spathulenol, viridiflorol and limonene. Authors showed that 1,8-cineol was the major molecule followed by trans-pinocarveol and α-terpineol from the class of oxygenated monoterpenes. The second major class of compounds found was oxygenated sesquiterpenes. Borneol, spathulenol, viridiflorol and globulol were the oxygenated sesquiterpenes found in the eucalypts oil. The third major class of compounds found in eucalypts was the monoterpene hydrocarbons constituted by a high level of α-pinene, p-cymene and limonene (Elaissi *et al*. 2011) [30].

Antimicrobial properties: Bacteriostatic and bactericidal effects both are exhibited by Blends of *Eucalypts globulus*, *Daucus carota*, *Rosmarinus officinalis* and *Cinnamomum zeylanicum* against all Gram-negative and Gram-positive bacteria tested, with MBCs stretching from <0.01% to 6% v/v and MICs stretching from 0.01% to 3% v/v (Brochot *et al*. 2017) [13]. Many gram-positive bacteria like *Bacillus subtilis*, *Enterococcus faecalis*, *Staphylococcus epidermidis and Staphylococcus aureus* has significant sensitivity to EO (Ashour, 2008) [5]. In a case report, inhalation of EO vapours by a tuberculosis patient for about ten days resulted relieving the symptoms like breathing difficulty, reduction in the body temperature and sputum culture was negative (Sherry *et al*. 2004). In an *Eucalypts* plant different parts also have anti-fungal activity against major fungal species like *Aspergillus flavus, Candida albicans and Aspergillus niger* (Ashour, 2008) [5]. Oyedeji *et al*. (2009) [114] showed significant antibacterial activity on gram-positive and gram-negative and antifungal activity on Candida albicans with essential oils of five varieties of *Eucalypts* from Nigeria. Various scientists tested essential oils of *Eucalypts* by Simeon method (Simeon, 1976) and reported antimicrobial activity against bacteria as well as fungi (Beylier and Givaudan, 1979. Gilles *et al*. 2010) [12, 39].

Anti-inflammatory properties: One study has demonstrated that pre-treatment of LPS/ IFN-® stimulated cells with *E.*

globulus extracts leads to a significant reduction in nitric oxide levels in the medium without affecting cell viability. This effect is mediated (a) by inhibition of inducible nitric oxide synthase (iNOS) mRNA expression and/or (b) by NO scavenging. Study has proven that EO has anti-inflammatory effect by reducing the inflammations caused lipopolysaccharide, without any side effects (Serafino *et al*. 2008) [124]. Major EO component 1,8-cineole significantly showed anti-inflammatory effect by inhibiting the IL-1B (74%), TNF-A (99%), thromboxane B2 (91%) and leukotriene B4 (47%) (Juergens *et al*. 1998) [64]. Anti-inflammatory effect of alfa-pinene showed by reducing the activity of NF-kB (Zhou *et al*. 2004) [161]. 300 mg/Kg of EO used for treating the bronchitis and lowering the infiltration of inflammatory cells (Lu *et al*. 2004) [88]. Thus, these findings indicate that *E. globulus* extracts may be useful anti-inflammatory drugs in some respiratory pathologies, in line with their traditional use. *E. globulus* also showed No scavenging activity, which could be due to their phenolic components.

Anti-viral properties: Significant antiviral activity is found in different secondary plant metabolites like tannins, saponins, lignans, flavonoids, alkaloids, thiophenes, polyines, phenolic acids and other sugars against different viruses (Chiang *et al*. 2003; Palomino *et al*. 2002) [162, 163]. In Eucalypts, essential oils, phenylpropanoids and erpenes are the main biologically active components (Astani *et al*. 2010; Dhifi *et al*. 2016) [6, 28]. The *E. torelliana* acrude methanolic extracts of Ec were found to be active against human enteroviruses: Coxsackievirus B, Echovirus 6, Poliovirus type I (Adeniyi *et al*. 2015) [2]. Significant activity has been shown by the aqueous extract of the Eucalypts fruit against HSV-1 whereas little anti-HSV-1 activity shown by the ethanolic extracts (Ju *et al*. 2011) [63]. EO has significantly impacted on herpes simplex virus type 1 by reducing 96% of viral replication activity. EO has shown plaque reduction for mumps virus (Cermelli *et al*. 2008) [15]. Antiviral activity shown by *the E. globulus* and *C. zeylanicum* Eos on HSV1 and H1N1 (Astani *et al*. 2010) [6]. Vimalanathan and Hudson, 2014) Significant reduction of viral units for HSV1 and H1N1 with reduction more than 99.99% (>4 log) with 80% and 40% AB1 after 60 min and a reduction more than 99% (>2 log) was observed with 1% AB1 with a 60-min contact time for H1N1 (Brochot, *et al*. 2017) [13]. Antiviral activity is strongly shown by the Ec ethanolic extract against different members of the herpes viruses' family (VZV, HSV-1 and HSV-2). Between the MeOH fraction of Ec and ACV (acyclovir) there is found to be 80% strong cooperative antiviral activity of EC. Significantly the viral infection inhibition (~75%) was observed when the cells treated with both 0.1 µg/ml of Ec fraction mixture and 0.01µg/ml ACV mixture (Abu-Jafar and Huleihel, 2017) [1]. Antiviral activity of EO is mild against enveloped viruses like simplex virus and mumps virus (Cermelli*et al*. 2008) [15].

Antioxidant: The free radical scavenging activity of the different concentrations of the leaf oil (10, 20, 40, 60 and 80% (v/v) in DMSO) of *E. globulus* increased in a concentration dependent fashion. In DPPH method, the oil in 80% (v/v) concentration exhibited 79.55 ± 0.82%. In nitric oxide radical scavenging assay method, it was found that 80% (v/v) concentration exhibited 81.54 ± 0.94% inhibition. It was concluded that leaf oil is potent inhibition of free radicals (Mishra *et al*. 2010) [102]. The antioxidant activity against DPPH, ABTS and B-carotene bleaching methods of the methanolic extract is 75.6, 81.60 and 60.40% at 50 µg/ml respectively, and is increased to 90.24, 94.8 and 71.6% respectively on doubling the extract concentration to 100 µg/ml. However, petroleum ether extract used to show an antioxidant activity lower than methanolic extract at 50 and 100 µg/ml when compared to BHT as a synthetic standard and ascorbic acid as a natural standard (ranged from 78 to 87%). The obtained data clearly shows that the ABTS method recorded the highest antioxidant activity (94.8%), at the extract concentration of 100 µg/ml, which exceeds that of the standard BHT (84.6%), ascorbic acid (87%) and petroleum ether extract at the same concentration (22.84%). The dose response curves of promising sample (Crude methanolic extract) was analysed, suggesting that there is a positive correlation between the concentration of the sample (5-50 µg/ml) and the antioxidant activity against DPPH radical (12-70%) (El-Moein *et al*. 2012) [32]. These results went parallelly with Lim *et al*. who reported that dichloromethane fraction from methanol extract exhibited the strongest antioxidant activity in red blood cell haemolysis and lipid peroxidation assays (Lim *et al*. 2011) [83].

Immunomodulatory: in a study, E. globulus essential oil (EO) had shown stimulated phagocytic activity in cultured human monocyte-derived macrophages (MDMs), independently of LPS treatment (Serafino *et al*. 2008) [124]. The effects on phagocytic activity of eucalypts (E. globulus) EO were investigated by Serafino *et al*. (2008) [124]. EO was also studied by administering in drinking water of immuno-competent rats with and without immunosuppression induced by 5-fluorouracil (5-FU). A EO treatment study in rats had shown significantly increased circulating monocytes and their phagocytic activity in comparison with untreated controls rats (Sadlon *et al*. 2010) [122]. EO treatment also showed inhibition of 5-FU induced myelotoxicity simultaneously restoring the phagocytic ability of monocytes and MDMs (Sadlon *et al*. 2010) [122]. Eucalypts globulus EO treatment also induced the primary antibody response in broiler chickens but the secondary antibody response did not differ significantly (Farhadi *et al*. 2017) [34]. Data from Various *in vitro* and *in vivo* studies demonstrate marked immunomodulatory properties of both eucalypts oil and its active ingredient, i.e. eucalyptol on monocytes and macrophage recruitment in response to lung infections and inflammation. These studies had ahown release of pro-inflammatory cytokines from monocytes and macrophages. (Sadlon and Lamson, 2010; Juergens *et al*. 2020) [122, 65]. Eucalyptol is also known to have mucolytic and bronchodilatory properties (Juergens *et al*. 2020) [65]. Taken together, data from both preclinical and clinical trials point towards the promising therapeutic potential that resides in eucalypts oil and its active constituent, i.e. eucalyptol in the prevention and treatment of COVID-19. Therefore, further studies are urgently warranted in this regard.

Conclusion

There is a paucity of availability of effective treatment for COVID-19, hence there is a crucial requirement of antiviral agent. Although there is no specific drug developed for SARS-COV-2, already known antivirals Remdesivir is recommended by WHO as primary drug along with immunomodulatory, antibacterial and anti-inflammatory drugs (dexamethasone) as supportive therapy. Antibiotics are recommended for ruling out bacterial *co-infection* and

possibility of bacterial *secondary infection* during the course of the illness. Clinical features of the disease (COVID-19) comprise oxidative stress induced acute lung injury. This presents antioxidant therapy as a potential treatment strategy. In sum, primarily the immunity of an individual has to be strongly active to avoid infection and if infection has occurred, the treatment has to combinatorial approach of antiviral, anti-inflammatory, antibacterial and antioxidant medicines.

As discussed in this manuscript Many traditional medicinal plants which are easily available in household like clove, garlic, cinnamon and eucalypts have been studied scientifically and proven to have antiviral, anti-inflammatory, anti-microbial and anti-oxidant properties in their essential oils and/or extracts. Clove has Eugenol as a major constituent which has strong antimicrobial activities. Eugenol has antimicrobial, antifungal, antiviral, antioxidant, anti-inflammatory properties. Garlic is also well known for ages for its Iimmunity boosting properties. Compounds like DADS, DAS, and alliin from garlic extract have been shown to have immunomodulatory, anti-inflammatory, antiviral and antibacterial properties. Cinnamon has been used as medicine around the world and reported that trans-cinnamaldehyde of cinnamon could inhibit influenza virus propagation whereas bark essential oil has antibacterial activity against several pathogenic bacterial strains. To date, there are several flavonoid compounds have been isolated from cinnamon which have anti-inflammatory activities. The eucalypts essential oils, phenylpropanoids and terpenes are the main biologically active components having strong antiviral activity against HSV-1, HSV-2, H1N1, VZV, simplex virus and mumps virus. Major EO component 1,8-cineole significantly showed anti-inflammatory effect by inhibiting the IL-1B, TNF-A, thromboxane B2, and leukotriene B4. Bacteriostatic and bactericidal effects are exhibited by various *Eucalypts* sp. essential oil whereas methanol extract exhibited the strongest antioxidant activity and marked immunomodulatory properties.

Inclusion of these essential oils and/or preparations in day to day life as spices or decoction could help us with all their combinatorial medicinal properties to fight against COVID-19 as well as emerging infectious disease in today's environment. Scientific community should look at these plants and their extracts as a potential source of therapeutic agents not only for COVID-19 but for various emerging pathogens.

Declarations of interest: none

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