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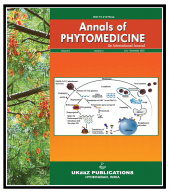

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Micronutrients and phytochemicals against COVID-19: Mechanism and molecular targets

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Abstract

The recent emergence of coronavirus disease (COVID-19) caused a continuous threat to humans. Currently, the race for COVID-19 vaccines through laboratory tests has generated more than 180 vaccine candidates, however the scientific community remains skeptical regarding their administration for the general public. Plants are a rich source of medicinally active constituents that have long been used over the years in aromatherapy and phytomedicine due to their biological properties including antiviral, antimicrobial, antioxidant, anticancer, immunomodulatory and anti-inflammatory effects. Likewise, evidence from *in vitro* studies and controlled clinical trials highlighted the health benefits of some vitamins, micronutrients, and trace elements in viral infections. The purpose of this article is to describe the current knowledge about micronutrients and phytochemicals that can help prevent and inhibit COVID-19.

1. Introduction

The world is currently facing a pneumonia outbreak caused by the new coronavirus (SARS-CoV-2). The disease can be asymptomatic or present mild affection of the upper respiratory tract (Khan *et al.,* 2020; Subbarao and Mahanty, 2020). Patients with the most severe forms of COVID-19 are often elderly and affected by acute respiratory distress syndrome (Liu *et al.,* 2020; Perrota *et al.,* 2020). SARS-CoV-2 mainly attacks the lower respiratory system to cause viral pneumonia, but it may also affect the gastrointestinal system, heart, kidney, liver, and central nervous system leading to multiple organ failure (Zhu *et al.,* 2020). Several combined therapies have been used to treat complications associated to virus infection (Fernandes *et al.,* 2020; Sarkar *et al.,* 2020), and more than 180 vaccines are currently in development (Krammer, 2020), however, until now, there has no specific and effective drug or vaccine to treat COVID-19.

Plants provide a valuable and powerful resource of phytochemicals components including phenols, flavonoids, volatile oil, *etc*., displaying antiviral properties (Haslberger *et al.,* 2020 ; Mani *et al.,* 2020). Existing evidences suggest that the consumption of plant-derived regiments can strengthen the immune system and help to fight against COVID-19 (Chojnacka *et al.,* 2020; Fernández-Quintela *et al.,* 2020). Naturally occurring phytochemicals have the advantages of low toxicity and high efficiency to inhibit virus proliferation and can also regulate the host immune response (Cowan, 1999). Likewise, adequate intake of vitamins A, B, C, D, E, zinc, and iron is essential to maintain a strong immune system (Jayawardena *et al.,* 2020).

This review aims to present an overview of coronavirus morphology, biology, and pathogenesis with a particular focus on mechanism of action of natural bioactive compounds including vitamins, trace elements, flavonoids, phenolic acids, and alkaloids against SARS-CoV-2 infection and replication and their role in enhancing the immunity. These natural molecules were selected based on their effectiveness against SARS-CoV-2 infection as well as other RNA viruses including SARS-CoV, MERS-CoV, and influenza.

2. Mechanism of virus infection

Coronaviruses (CoVs) are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope (Cascella *et al.,* 2020). Coronaviruses belong to the family *Coronaviridae* and are divided into alpha (α-CoV), beta (β-CoV), gamma (γ-CoV), and delta (δ-CoV) coronaviruses. The alpha and beta coronaviruses can infect mammals, the viruses infecting humans are genetically similar to β-CoV genus (Letko *et al.*, 2020). Structural analysis of SARS-CoV-2 shows the virus as cylindrical with four specified proteins encoded by the minor sections of the genome (Song *et al.*, 2018). These include membrane (M) protein, spike (S) protein, envelope (E) protein, and nucleocapsid (N) protein (Figure 1). The protein (S) is the greatest structure and makes distinct spikes on the virus surface (Suhail *et al.*, 2020).

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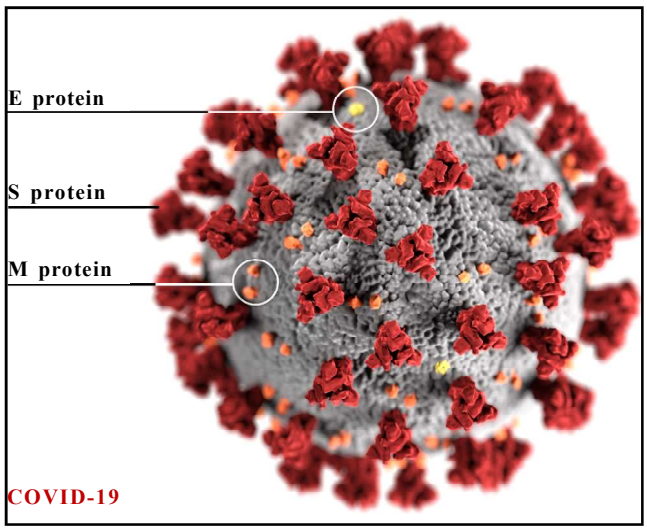

Figure 1: Coronavirus virion structure

Corona virus - Photo credit: CDC/Alissa Eckert, MS; Dan Higgins, MAMS. (**Source:** Khan *et al.*, 2020: The COVID-19 pandemic: A scoping review.)

2.1 Virus attachment and entry

The major place of entry for viruses into the body is the respiratory tract (Subbarao and Mahanty, 2020). Infection is initiated by interaction of the viral particle with specific proteins on the cell surface. After initial binding with receptor, enveloped virus fuse its envelope with host cell membrane to deliver its nucleocapsid to the target cell. The spike (S) protein plays a role in entry by mediating receptor binding and membrane fusion (Belouzard *et al.,* 2012).

2.2 Role of spike protein

The spike glycoprotein (S) plays a primary role in viral attachment and entry, cell tropism, and pathogenesis (Belouzard *et al.,* 2012). The S protein contains two functional domains: the subunit (S1), an extracellular receptor-binding domain (RBD) responsible for virus binding, and the subunit (S2) anchored to the membrane which contains sequences responsible for membrane fusion (Holmes, 2003; Hofmann and Pöhlmann, 2004; Hoffmann *et al.,* 2020). Membrane fusion requires spike (S) protein cleavage and activation by host cell proteases (Hoffmann *et al.,* 2020).

The subunit S1 binds to the host cell receptor *via* two independent subdomains, an N-terminal domain (NTD) and C-terminal domain (CTD), capable of binding variety of proteins and sugars (Belouzard *et al.,* 2012). The S2 subunit contains a fusion peptide with a transmembrane domain and a cytoplasmic domain which is highly conserved. While, spike receptor-binding domain (RBD) presents only 40% sequence identity with other SARS-CoVs.

RBD represents a binding site for the human angiotensin-converting enzyme 2 (ACE2) receptor and has a pivotal role in viral infection and pathogenesis (Abajo *et al.,* 2020). ACE2 are metallopeptidase receptors present in every human organ, including lung (principally type II alveolar cells), heart, intestinal epithelium, kidney, vascular endothelium, and smooth muscle cells (Letko *et al.,* 2020), ACE2 receptors are considered as an entry site for SARS-CoV and SARS-CoV-2 into human respiratory epithelial cells (Cascella *et al.,* 2020). Following the conjunction with the target receptor, the S1 subunit is bound to the peptidase domain of ACE2. Coronavirus fuses its envelope with the host cell membrane through the conformational change of S protein which is triggered by the target receptor binding, pH acidification, and proteolytic cleavage by endosomal proteases like transmembrane protease serine 2 (TMPRSS2) (Simmons *et al.,* 2004; Millet and Whittaker, 2014).

The S protein is cleaved between S1 and S2 subunit and at the conserved site up stream of the fusion peptide (S2') (Figure 2) (Belouzard and Whittaker, 2009; Belouzard *et al.,* 2012). After cleavage, the fusion between the two membranes is completed by the S2 portion (Suhail *et al.,* 2020).

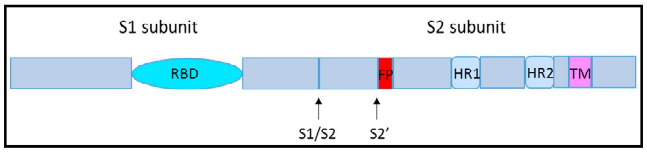

Figure 2: Schematic representation of the SARS-CoV spike protein (S).

The S1 subunit of S protein, containing RBD, responsible for specific recognition and binding of the target receptors. The S2 subunit, is in charge of the membrane fusion, contains the putative fusion peptide (FP) and the heptad repeat (HR1 and HR2), the transmembrane domain (TM). S1/S2 and S2' protease cleavage sites.

Depending on the specific coronavirus, RBD is used to recognize different functional receptors. The presence of an amino acid site (polybasic site) within the spike protein allows the functional processing by the human furin protease. This process allows the exposure of the fusion sequences and therefore the fusion of the viral and cell membranes, then the virus enters into the host cell (Cascella *et al.,* 2020).

The importance of disulfide thiol balance in the viral entry of SARS-CoV-2 has been also demonstrated. Thiol and disulfide groups could act as electron donors and acceptors, respectively (Lavillette *et al.,* 2006).

2.3 Virus replication

During virus infection, viral genetic material is fully released into the cytoplasm where takes place the replication and transcription process mediated by the replication/transcription complex (RTC) (Boopathi *et al.,* 2020). The single stranded RNA is translated from open reading frame 1a/b into pp1a and pp1ab (viral replicase polyproteins), and then cleaved into nsps (Yesudhas *et al.,* 2020). Viral replicase polyproteins use the genome as a template to generate full-length negative sense RNAs, themselves serving as templates to generate additional full-length genomes (Song *et al.*, 2004). RNA polymerase produces upon transcription a series of subgenomic mRNAs translated into viral structural proteins S, E, N and M (Figure 3).

Viral proteins and RNA genome are assembled into new virions in Golgi and endoplasmic reticulum (ER). Indeed, the encapsidation of replicated genomes by N protein forms nucleocapsids in the cytoplasm, and they coalesce within the ERGIC (ER, Golgi

intermediate compartment) membrane and then assembled into new virions. The newly formed virions are transported to the cell membrane in smooth walled vesicles and then outside secreted via exocytosis, so that can infect other cells (Figure 3).

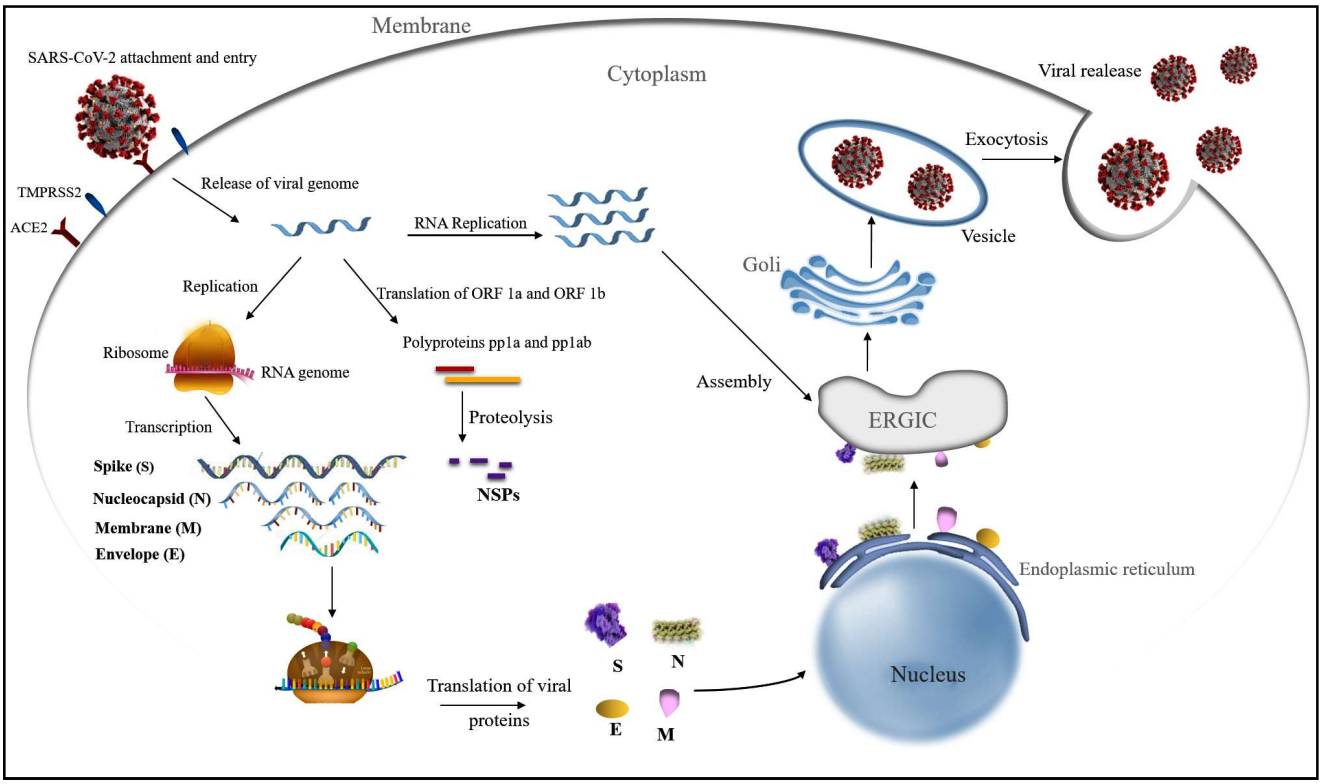

Figure 3: Schematic representation of SARS-CoV-2 attachment, internalization, and replication.
ACE2: angiotensin-converting enzyme 2, ERGIC: endoplasmique-reticulum-Golgi intermediate compartment, ORF: open reading frame, NSPs: non-structural protein. TMPRSS2: Transmembrane protease serine 2.

2.4 Pathogenesis of SARS-CoV-2

The mechanism of virulence of SARS-CoV-2 is mainly associated to the function of the nsps and structural proteins. Recent evidence showed that nsp is able to block the host innate immune response (Lei *et al.,* 2018). Another mechanism is the severe inflammatory response induced by the viral infection in the lung as well as other organs (Lei *et al.,* 2018). In fact, once the SARS-CoV-2 gains access inside the cells, it activates T lymphocytes and induces an intense immune response with subsequent release of cytokines which can cause real damage if they are not controlled (Song *et al.,* 2018). As well, the SARS-CoV-2 utilizes its structural proteins to gain entry into the host cell cytosol as well as suppress signaling pathways particularly with the Toll-like receptors (TLR) (Weiss and Navas-Martin, 2005).

3. Inflammatory responses associated to COVID-19

Accumulating evidence from epidemiological and clinical studies demonstrated that SARS-CoV-2 infection causes severe acute respiratory illness associated with massive inflammatory responses and cytokine storm secretion. Among these cytokines, tumor necrosis factor (TNFα) and interleukin 1 (IL-1) are of considerable importance (Borthwick, 2016; Conti *et al.,* 2020; Kritas *et al.,* 2020).

The activation of toll like receptor (TLR) after SARS-CoV-2 binding induces a biochemical cascade that causes the secretion of pro-IL-1 cleaved by caspase-1 into a mature fragment (IL-1), followed by the activation of the inflammasome (Chen *et al.,* 2019; Conti *et al.,* 2020; Tay *et al.,* 2020). As well, SARS-CoV-2 entry, *via*, ACE2 activates pro-inflammatory cytokines including IL-6, TNF-α, and inflammasome (Conti *et al.,* 2020; Paniri and Akhavan-Niaki, 2020). Recently, increasing studies have reported that interleukin-6 (IL-6) and NOD-like receptor protein 3 (NLRP3) inflammasome are the main cause of the inflammatory cytokine storm and pathological complications in infected patients with SARS-CoV-2 (Paniri and Akhavan-Niaki, 2020; Tay *et al.,* 2020).

Previous *in vitro* cell experiments have shown delayed secretion of pro-inflammatory cytokine and chemokine (IL-6, TNF-α, IL-1β, IL-8, MCP-1, CCL2, CCL5, and IFNs) in respiratory epithelial cells, dendritic cells, and macrophages at the initial stage of SARS-CoV infection, then the release of cytokines and chemokines is enhanced by activated macrophages and other recruited lymphocytes (Cheung *et al.,* 2005; Law *et al.,* 2005; Lau *et al.,* 2013).

Several other pro-inflammatory cytokines are produced following SARS-CoV-2 infection, notably CC chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 2 (CXCL2), CCL8, CXCL1, IL33,

CCL3L1 in bronchoalveolar lavage fluid (BALF), and IP-10, tumor necrosis factor superfamily 10 (TNFSF), tissue inhibitors of metalloproteinases (TIMP)1, C5, IL18, amphiregulin, neuregulin1, and IL10 in peripheral blood mononuclear cells (PBMC), indicating sustained inflammation and cytokine storm in the patients. Pathway analysis of PBMC transcriptome revealed that lymphopenia in COVID-19 patients was more likely caused by the activation of apoptosis and P53 signaling pathway in lymphocytes (Xiong *et al.,* 2020).

Zhou *et al.* (2020) demonstrated that BALF of patients with severe COVID-19 was enriched in CCL2 and CCL7, which are considered the most potent chemokines for the recruitment of CC-chemokine receptor 2-positive (CCR2+) monocytes. Likewise, Liao *et al.* (2020) found increased proportions of mononuclear phagocytes (MNPs) in BALF (up to 80% of total BALF cells in patients with severe COVID-19 versus only 40% and 60% of total BALF cells in healthy or patients with moderate COVID-19, respectively).

Similarly, in severely affected patients, lymphopenia and interstitial pneumonia with elevated levels of pro-inflammatory cytokines, including IL-2, IL-6, IL-7, IL-1, G-CSF, IP-10, MCP-1, MIP-1α and TNFα can be observed (Dong *et al.,* 2020a ; di Mauro *et al.,* 2020). However, Huang *et al.* (2020) detected elevated expression of IL-1 β, IFN-γ, IP-10 and monocyte chemo-attractive protein 1 (MCP-1) in patients with COVID-19. These inflammatory cytokines may activate the T-helper type 1 (Th1) cell response and play a key event in the activation of specific immunity (Huang *et al.,* 2020; Marchingo *et al.,* 2020). Moreover, these cytokines induce the recruitment and activation of neutrophils, NK cells, and adaptive immune T cells, with additional production of pro-inflammatory cytokines, causing consequently cytokine storm and tissue damage (Lingeswaran *et al.,* 2020). While, Chen *et al.* (2020) recorded high levels of cytokines secreted by Th2 cells such as IL-4 and IL-10 in patients with COVID-19 responsible for inhibiting the inflammatory response.

SARS-CoV-2 induces a particular signature and differs from other coronaviruses in its capacity to replicate within pulmonary tissue. The virus can counteract the antiviral effects of IFN-I and IFN-III, activate innate responses with subsequent production of cytokines that regulate adaptive immunity (García, 2020).

A fatal inflammatory response and acute respiratory distress syndrome may be seen in patients with SARS-CoV-2 following rapid viral replication. This phenomenon can be explained by the cell lysis induced by over activation of the complement system following an interaction of the nucleocapsid dimers of the coronavirus released with the serine proteases associated to the lectin bound to mannose (Tok and Tatar, 2017; Shurin *et al.,* 2020). Moreover, Dong *et al.* (2020b) suggest that the etiology of severe COVID-19 infection may be haemophagocytosis or macrophage activation syndrome.

4. Oxidative stress and SARS-CoV infection

During COVID-19 pandemic, very old patients and centenarians were more vulnerable to virus infection. Several *in vitro* and *in vivo* studies have demonstrated that age-related diseases are correlated with an elevated oxidative status (Schöttker *et al.,* 2015; Schöttker *et al.,* 2016 ; Gào *et al.,* 2019). Emerging data and the clinical reports suggest that oxidative stress contributes to viral pathogenesis of SARS-CoV-2 (Cecchini and Cecchini, 2020; Delgado-Roche and Mesta, 2020). In fact, increases in ROS generation during aging lead to functional alterations, pathological conditions, and even death (Hagen, 2003; Kregel and Zhang, 2006).

Lin *et al.* (2006), reported that SARS-CoV 3C-like protease caused a significant increase in ROS production in HL-CZ promonocyte cells. The authors indicated that SARS-CoV-3C-like protease activates NF-kB-dependent reporter gene, which induced apoptosis of human promonocyte cells. Other studies have also reported that ROS mediated apoptosis in viral infections, such as Japanese encephalitis virus (Yang *et al*., 2010) and influenza virus (Uchide *et al.,* 2002). Shao and coworkers (2006) identified that genes encoded in mitochondria, the main origin of intracellular free radicals production, and some genes responding to oxidative stress wes upregulated in peripheral blood mononuclear cells of convalescent SARS-CoV patients.

ACE2 receptor emerges as a key regulator in oxidative stress-mediated SARS-CoV-2 infection. ACE2 is a membrane-bound protein responsible for the degradation of Ang II (Zheng *et al*., 2020). The latter enhances the production of ROS through enhancing NADPH oxidase activity, as a result, cysteine residues are oxidized to form disulfides, which in turn increase the affinity of SARS-CoV-2 S proteins for the ACE2 receptor, and therefore, increase the severity of COVID-19 infection (Busse *et al*., 2020; Hati and Bhattacharyya, 2020).

SARS-CoV-2 infection causes acute lung injury and aggressive inflammatory response with excessive production of cytotoxic mediators such as ROS and RNS, tumor necrosis factor α (TNFα), interleukins (IL-2, IL-6, IL-7), interferons (IFN-γ), granulocyte macrophage colony-stimulating factor (GM-CSF), monocyte chemotactic protein 3 (MCP-3), interferon-γ-inducible protein 10 (IP-10) (Kaur *et al.,* 2020) which are the source of oxidative stress associated with acute lung injury (Valavanidis *et al.,* 2013).

During a SARS-CoV-2 infection, human erythrocytes are particularly prone to viral invasion and the pathophysiology of COVID-19 because of their high content of iron which is a critical redox catalyst for diverse viral processes including genome replication and protein synthesis (Abraham, 2020). Therefore, the lysis of erythrocytes leads to an increase of inflammatory cytokines, free heme, and free iron. A meta-analysis study of 1210 COVID-19 patients showed a dramatical decrease of hemoglobin levels of 7.1 g/l or even 5.9 g/l in severe cases (Lippi and Mattiuzzi, 2020). In fact, erythrocytes lysis increases the amount of extracellular Hb which in the highly oxidative environment leads to MetHb formation and the release of free heme (Dutra and Bozza, 2020). The prooxidant effects of free Hb are mainly attributed to heme release from oxidized Hb. Free heme can react with lipids in cellular membranes, inducing lipid peroxidation, and increase cell permeability leading to hemolysis (Bellik and Iguer-Ouada, 2016). Moreover, free Hb can react with NO to generate peroxynitrite

($ONOO^-$) which in turn generates reactive hydroxyl radical (HO•) by the reaction with iron. HO• can also cause membrane lipid peroxidation and cellular damage (Halliwell and Gutteridge, 1999; Authen and Davis, 2009). In addition, it has been demonstrated that iron induces blood coagulation *via* hydroxyl radicals which convert soluble plasma fibrinogen into abnormal fibrin clots in the form of dense matted deposits resistant to enzymatic degradation (Pretorius *et al.,* 2013).

5. Phytochemicals as potential agents against coronaviruses

Plants have been the basis of traditional medicine and are a rich source of pharmacologically-active compounds used to develop new drugs. A wide range of bioactive components have been shown to modulate inflammatory responses. Table 1 summarizes the most studied and well-known phytochemicals with antiviral activity and their cellular and molecular mechanism. It is worth noting that several other reports demonstrating similar results are not represented here.

Table 1: Antiviral activity of selected phytochemicals against coronaviruses

Plant	Bioactive compound	Virus type	Mechanism	Effect/dose	Reference
Green tea (*Camellia sinensis*)	Catechins (catechin; epigallo-, -epi, - gallo, -catechin gallate ; -epigallo, -epi, -gallo catechin)	SARS-CoV-2	Inhibition of major protease (H-bonds with amino acids of catalytic site)	n.a.	Ghosh *et al.* (2020)
Brown algae (*Ecklonia cava*)	Phlorotannins (8,8'-Bieckol, 6,6'-Bieckol, Dieckol)	SARS-CoV-2	Inhibition of major protease (H-bonds with His_{41} and Cys_{145} and hydrophobic interaction with Leu_{27}, Met_{41}, Met_{49}, $Met1_{65}$, $Leu1_{67}$ and $Leu1_{67}$)	n.a.	Gentile *et al.* (2020)
Marine sponge (*Theonella swinhoei*)	Pseudotheonamide D and C	SARS-CoV-2	Inhibition of major protease (Covalent bond with Cys_{145} and hydrophobic interaction with Leu_{27}, Met_{49}, Phe_{140} and $Leu1_{67}$)	n.a.	Gentile *et al.* (2020)
Paper birch (*Betula papyrifera*)	Papyriflavonol A	SARS-CoV	Inhibition of proteases (3-chymotrypsin-like protease and papain-like protease)	IC50: 3.7µM	Park *et al.* (2017)
Paulownia (*Paulownia tomentosa*)	Geranylated flavonoids (tomentin A, B, C, D and E)	SARS-CoV	Inhibition of papain-like protease	IC50: 5.0-14.4 µM	Cho *et al.* (2013)
Chinese rhubarb *(Rheum officinale) and* polygoni multiflori (*Polygonum multiflorum*)	Emodin (6-methyl-1,3,8-trihydroxyanthraquinone)	SARS-CoV	Blocks the binding of spike protein and angiotensin-converting enzyme 2 to host cells	1 to 10 µg/ml	Ho *et al.* (2007)
Flavonoids rich plants	Herbacetin (flavonol), rhoifolin and pectolinarin (flavones)	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (H-bonds with amino acids of catalytic site)	IC50: 27.5-37.8 µM	Jo *et al.* (2020)
Chinese mahogany (*Toona sinensis*)	Quercetin	SARS-CoV	Inhibition of virus replication	IC50:500 µg/ml	Chen *et al.* (2008)
Red spider lily (*Lycoris radiate*)	Lycorine	SARS-CoV	Inhibition of cytopathic effect	EC50: 2.4 µg/ml	Li *et al.* (2005)
Brown algae (*Ecklonia cava*)	Dieckol	SARS-CoV	Inhibition of 3-chymotrypsin-like cysteine protease (H-bond with catalytic dyad : His_{41} and Cys_{145})	IC50: 2.7 µM	Park *et al.* (2013)
Plants rich in flavonoids	Flavonoids: Herbacetin, isobavachalcone, quercetin 3 β d glucoside and helichrysetin	MERS CoV	Inhibition of 3-chymotrypsin-like cysteine protease (H-bonds and hydrophobic interactions)	IC50: 36-67 µM (20 µM)	Jo *et al.* (2019)
Babchi (*Psoralea corylifolia*)	Flavonoids: Bavachinin, neobavaisoflavone, isobavachalcone, 4'-O-methylbavachalcone, psoralidin and corylifol A.	SARS-CoV	Inhibition of papain-like protease	IC50: 4.2 and 38.4 µM	Kim *et al.* (2014)
Ashitaba (*Angelica keiskei*)	Xanthoangelol E	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (H-bonds with His_{163}, Ser_{144} and Cys_{145})Inhibition of papain-like protease (H-bonds with His_{176} and His_{172})	IC50: 11.4 µM IC50: 1.2 µM	Park *et al.* (2016)

Plant	Bioactive compound	Virus type	Mechanism	Effect/dose	Reference
Woad (*Isatis indigotica*)	Indigo Sinigrin Beta-sitosterol Aloeemodin Hesperetin Daidzein	SARS-CoV	Inhibition of 3-chymotrypsin-like protease	IC50: 37.3 μM (300 μM) IC50: 50.3 μM (121 μM) IC50: 47.8 μM (115 μM) IC50: 35.7 μM (132 μM) IC50: 18.1 μM (60 μM) IC50: 6.8 μM (105 μM)	Lin *et al.* (2005)
Plants rich in anthocyanins	Quercetin-3-β-galactoside	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (H-bonds with Gln_{189})	42.8 μM	Chen *et al.* (2006)
Coniferous tree (*Torreya nucifera*)	Amentoflavone	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (Interaction with His_{163}, Leu_{141}, $Gln_{189\&192}$ and Val_{186})	IC50: 8.3 μM (14 μM)	Ryu *et al.* (2010a)
Plants rich in flavonoids	Quercetin, epigallocatechin gallate and gallocatechin gallate	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (Hydrophobic interaction with Met_{165}, Glu_{166}, Asp_{187}, Arg_{188} and $Gln1_{89}$; H-bounds with His_{41}, Tyr_{54}, $Leu1_{41}$, Gly_{143}, Ser_{144}, His_{163} and Glu_{166})	IC50: 73, 73 and 47 μM	Nguyen *et al.* (2012)
Baikal skullcap (*Scutellaria baicalensis*)	Scutellarein	SARS-CoV	Inhibition of NTPase/helicase (Interaction with Asn_{265}, Tyr_{269} and Arg_{443})	IC50: 0.86 μM	Yu *et al.* (2012)
Tea (*Camellia sinensis*)	(-)-Catechin gallate and (-)-Gallocatechin gallate	SARS-CoV	Inhibition of nucleocapsid protein activity	50μM	Roh *et al.* (2012)
Bitter orange (*Citrus aurantium*)	Hesperidin	SARS-CoV-2	Inhibition of 3-chymotrypsin-like protease and blocks the binding of angiotensin-converting enzyme 2 to Spike-receptor binding domain	n.a.	Wu *et al.* (2020)
Citrus fruits	Naringenin	SARS-CoV-2	Inhibition 3-chymotrypsin-like protease and reduction of angiotensin converting enzyme activity	n.a.	Tutunchi *et al.* (2020)
Plants riche in phenolic compounds	Theaflavins, hesperidin, quercetagetin and myricetin	SARS-CoV-2	Inhibition of RNA replication (Binding to RNA-dependent RNA polymerase)	n.a.	Singh *et al.* (2020)
Bupleurum spp., *Heteromorpha spp.* and *Scrophularia scorodonia*	Saikosaponin B2	SARS-CoV	Prevent viral adsorption and penetration into cell hosts	IC50: 1.7 μM	Cheng *et al.* (2006)
Prunella vulgaris and *Saussurea lappa*	Tetra-O-galloyl-β-d-glucose and luteolin	SARS-CoV	Prevent viral penetration into cell hosts	EC50: 4.5 and 10.6 μM	Yi *et al.* (2004)
Alder (*Alnus japonica*)	Hirsutenone, rubranoside and curcumin	SARS-CoV	Inhibition of 3-chymotrypsin-like protease	IC50: 4.1, 7.2 and 5.7 μM	Park *et al.* (2012a)
Burra gokharu (*Tribulus terrestris*)	Terrestrimine, terrestriamide, N-trans-feruloyloctopamine	SARS-CoV	Inhibition of 3-chymotrypsin-like protease	IC50: 15.8, 21.5 and 26.6 μM	Song *et al.* (2014)
Calophyllum blancoi	Blancoxanthone and pyranojacaeubin	HCoV 229E	/	EC50% : 3 and 15 mg/ml	Shen *et al.* (2005)
Regel's threewingnut (*Tripterygium regelii*)	Iguesterin, pristimerin, tingenone and celastrol	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (Interaction with $Cys_{44\&145}$, $Gln_{166\&189}$, Gly_{143}, His_{164}; Ser_{144} and $Thr_{24\&25}$)	IC50: 2.6, 5.5, 9.9 and 10.3 μM	Ryu *et al.* (2010b)
Assam indigo (*Strobilanthes cusia*)	Tryptanthrin	SARS-CoV	Inhibition of 3-chymotrypsin-like protease (Interaction with Ile_{106}, Val_{104} and Gln_{110})	IC50: 1.25 μM	Narkhede *et al.* (2020)
Red sage (*Salvia miltiorrhiza*)	Tanshinone I and dihydrotanshinone I	SARS-CoV	Inhibition of 3-chymotrypsin-like protease	IC50: 0.7 and 1.2 μM	Park *et al.* (2012b)

6. Roles of essential oils

Essential oils (EOs) are valuable natural products that have been used over the years in aromatherapy and phytomedicine due to their antiviral, antibacterial, antifungal, antioxidant, immunomodulatory and anti-inflammatory effects (Asif *et al.,* 2020; Astani and Schnitzler, 2014; Gilling *et al.,* 2014).

Most research studies on the antiviral activity of the essential oils have been conducted towards enveloped viruses. Still, little works were performed on non-enveloped viruses (Gilling *et al.,* 2014).

EOs could act by destabilizing virions, protecting host cell or inhibiting replication once the virus invades the host cell (Astani and Schnitzler, 2014). Five mechanisms of action induced-antiviral activity of essential oils have been described: direct actions on free viruses, inhibition of steps involved in virus attachment, penetration, intracellular replication, and release from host cells, and inhibition of vital enzymes (Schnitzler *et al.,* 2010; Asif *et al.,* 2020; Ma and Yao, 2020).

6.1 Direct actions on free viruses

Several studies have shown the ability of many EOs to disrupt biological membranes as well as viral envelopes (Siddiqui *et al.,* 1996; Nguefack *et al.,* 2004; Xu *et al.,* 2008). Due to their lipophilic nature (Wink, 2020), EOs are able to insert nonspecifically into the viral envelope lipid bilayer which can result in the alteration of normal membrane fluidity (Ben-Shabat *et al.,* 2020; Wink, 2020). Membranes can also be ruptured if the EOs are present at higher concentrations (Wink, 2020). Siddiqui *et al*. (1996) demonstrated that oregano oil (*Origanum vulgare*) and clove oil (*Syzygium aromaticum*) destroyed human pathogen herpes simplex virus type 1 (HSV-1) envelope. Likewise, Brochot *et al*. (2017) reported that 1,8-cineole, derived from eucalyptus oil, damaged the envelope structures of the free *Influenza A* virus and could inactivate this virus. Reichling *et al*. (2006) found that monoterpenes increased the fluidity and permeability of the cytoplasmic membrane and disrupted the order of membrane proteins.

Moreover, the antiviral activity of EOs may be the result of a disruption or interference with the viral membrane proteins involved in the attachment of host cells (Schuhmacher *et al.,* 2003). Mediouni *et al.* (2020) showed that carvacrol obtained from oregano was effective at blocking the entry of HIV-1 virus into the host system by inhibiting the fusion of host viral cells via depletion of viral cholesterol from HIV-1 envelope membrane.

6.2 Inhibition of virus attachment and penetration

In vitro and *in vivo* results showed that the total amount of pulmonary nuclear factor-erythroid 2-related factor 2 (Nrf2) and the nuclear translocation of Nrf2 was high in treated rats with diallyl sulfide (DAS), the main sulfur component of *Garlic* essential oils (Ho *et al*., 2012; Dziri *et al.,* 2014). McCord *et al.* (2020) observed that potent activation of Nrf2 causes a decrease in the expression of ACE2 and TMPRSS2 mRNA in HepG2 cells of human hepatic origin. Based on these findings, it has been proposed that *Garlic* essential oils and their isolated constituents, especially DAS, have the potential to prevent entry of viruses into host cells (Asif *et al.,* 2020). Similarly, the results obtained by Thuy *et al*. (2020) using molecular docking technique showed that 17 organosulfur compounds, representing 99.4% of the *Garlic* essential oil, have strong interactions with the amino acids of the ACE2 protein and the main protease PDB6LU7 of SARS-CoV-2. Senthil Kumar *et al.* (2020) examined the ACE2 inhibitory effects of major constituents of *Geranium* and *Lemon* essential oils, namely; citronellol (50 µM), geraniol (50 µM), limonene (50 µM), and neryl acetate (50 µM). The results showed that these compounds reduced the ACE2 levels from 18.0 ng/ml (control) to 7.67 ng/ml, 10.44 ng/ml, 12.92 ng/ml, and 16.63 ng/ml, respectively.

In silico study showed that isothymol, thymol, limonene, *p*-cymene, and γ-terpinene from *Ammoides verticillata* essential oil could have inhibitory effect on ACE2. The study revealed also that isothymol, a major component of the plant, could be a very effective inhibitor of the enzyme ACE2 (Abdelli *et al*., 2020). Another *in silico* study reported that thymoquinone, the main compound of *Nigella sativa* essential oil, would be the best candidate drug that may inhibit protease SARS-CoV-2 and ACE2 (Sekiou *et al.,* 2020).

6.3 Inhibition of intracellular replication

Recent studies performed by the use of molecular docking to investigate the effects of two components of *Eucalyptus* essential oil (jensenone and 1,8-cineole) on viral proteinase (Mpro/3CLpro) showed that 1,8-cineole can bind with Mpro via hydrophobic interactions, hydrogen bonding interactions, and strong ionic interactions and thus inhibit viral reproduction (Sharma and Kaur, 2020a; Sharma and Kaur, 2020b).

Kulkarni and coworkers (2020) carried out *in silico* study and found that anethole, cinnamaldehyde, carvacrol, geraniol, cinnamyl acetate, L-4-terpineol, thymol, and pulegone from essential oils inhibit the S1 subunit of S protein and that cinnamaldehyde had more favorable interaction points at the binding site than other compounds. Silva *et al*. (2020) studied 171 essential oil components against protease SARS-CoV-2 (SARS-CoV-2 Mpro), endoribonucleoase SARS-CoV-2 (SARS-CoV-2 nsp15/NendoU), SARS-CoV-2 ADP-ribose-1"-phosphatase (SARS-CoV-2 ADRP), RNA-dependent RNA polymerase of SARS-CoV-2 (SARS-CoV-2 RdRp), the spike protein binding domain SARS-CoV-2 (SARS-CoV-2 rS) and human angiotensin converting enzyme (hACE2). It was found that the best docking ligands for the SARS-CoV target proteins were (*E, E*)-α-farnesene, (*E*)-β-farnesene, and (*E, E*)-farnesol.

6.4 Other effects of essential oil

There are several reports showing the ability of essential oils to modulate immune system. The protective effects of cinnamaldehyde and eugenol in lipopolysaccharide (LPS)-induced acute lung injury has been reported (Huang and Wang, 2017; Barboza *et al.,* 2018). Cinnamaldehyde treatment inhibits neutrophils, macrophages, and total cell number in the bronchoalveolar lavage fluid and decreased the levels of inflammatory cytokines such as TNF-α, IL-6, IL-13 and IL-1β, respectively (Huang and Wang, 2017). Similarly, the levels of interleukin-1, interleukin-23, and tumor necrosis factor α (TNF-α) decreased considerably in treated rats with menthol (Rozza *et al.,* 2014; Bastaki *et al.,* 2018). Eugenol was also found to

inhibit the recruitment of leukocytes into the lung and downregulated the expression of pro-inflammatory cytokines (IL-6 and TNF-α) (Barboza *et al.,* 2018). Furthermore, monoterpenes thymol, carvacrol and p-cymene reduced the positive cells to NF-κB in lung which consequently reduced inflammatory response (Edwards *et al.,* 2009). In addition, Games *et al.* (2016) demonstrated that the treatment with thymol, carvacrol and p-cymene isolated from essential oil of *Lippia sidoides* Cham. (Verbenaceae) leaves reduced alveolar enlargement, macrophage recruitment, cytokine levels (IL-1β, IL-6, IL-8, and IL-17) in bronchoalveolar lavage fluid, and collagen fibers, MMP-9 as well as p-65-NF-κB-positive cells in lung parenchyma.

In vitro and *ex vivo* studies have demonstrated marked immunomodulatory properties of both *Eucalyptus* essential oil and its active ingredient, namely eucalyptol. Treatment with *Eucalyptus* essential oil and its main compound eucalyptol reduced the release of pro-inflammatory cytokines by monocytes and macrophages, without affecting their phagocytic properties (Sadlon and Lamson, 2010; Juergens *et al.,* 2020).

7. Roles of oligoelements and vitamins

Many vitamins and oligoelements are essential for the proper functioning of the immune system (Wintergerst *et al.,* 2007), because of their anti-inflammatory, antioxidant, and antiviral properties (Beard *et al.,* 2011). The efficiency of innate and adaptive immune responses depends on the level of these elements. Below are described some of the most studied vitamins and trace elements that have shown promising effects against COVID-19.

7.1 Vitamin C

Vitamin C is one of the most used therapeutic agents in the treatment of human diseases. It is considered as an antioxidant and an enzymatic cofactor for many physiological reactions in the body, such as hormone production, collagen synthesis, and immune potentiation (Kim *et al.,* 2013). It has been proposed as a promising therapeutic approach for reducing the susceptibility of people at high risk to lower respiratory infection under certain conditions (Hemilä, 1997). Vitamin C is essential for innate and adaptive immunity. *In vitro* study showed that vitamin C supplementation improved the proliferation and activation of lymphocytes in dose dependent manner (Huijskens *et al.,* 2014). Liugan and Carr (2019) reported that neutrophil's chemotaxis, phagocytosis, and oxidative burst activity are enhanced in the presence of vitamin C. It also displayed specific epigenetic characteristics on immune cells such as dendritic cells, monocytes/macrophages, T cells, NK cells (Ang *et al.,* 2018). Treatment with vitamin C reduced pro-inflammatory cytokines TNF, IL-6, and IL-1β. Administration of 1 g/day vitamin C was shown to enhance PBMC, IL-10, IL-1, and TNF-α following stimulation with LPS (Jeng *et al.,* 1996; Canali *et al.,* 2014).

Interestingly, it has been demonstrated that intravenous administration of vitamin C high-dose reduces cytokine storm in acute respiratory distress syndrome, improves immune system function, and increases antiviral properties during SARS-CoV-2 infection (Boretti and Banik, 2020). Similarly, Cheng (2020) pointed out that intravenous administration of early and adequate dose of vitamin C can be used to reduce the mortality and morbidity due to COVID-19.

7.2 Vitamin E

Vitamin E is a potent fat-soluble antioxidant capable of modulating host immune functions (Moriguchi and Muraga, 2000). Vitamin E is essential for the humoral and innate immune systems. In fact, the scavenger properties of vitamin E gives them the ability to reduce oxidative stress, protect polyunsaturated fatty acids (PUFA) and immune cells against oxidation and also to exert anti-inflammatory effects. But there are very few reports regarding the use and/or dosage of vitamin E as a prophylactic or therapeutic agent against COVID-19 (Fernández-Quintela et *al.,* 2020). Combination of vitamin E with vitamin C should be considered in clinical trials. de la Fuente *et al.* (2008) found that supplementation of the diet of elderly men and women with 200 mg/day vitamin E, in combination with vitamin C, enhanced phagocytic functions of polymorphonuclear.

7.3 Vitamin D

Vitamin D, a fat soluble vitamin, plays an important role in modulating both innate and adaptive immune responses (Aranow, 2011). Previous studies have shown that vitamin D increased chemotaxis, autophagy, and phagolysosomal fusion of innate immune cells (Liu *et al.,* 2007; White *et al.,* 2010). Vitamin D can also enhance the antimicrobial activity of macrophage and monocyte keratinocytes.

Vitamin D exerts its anti-inflammatory effects by suppressing the production of pro-inflammatory cytokines such as IFN-γ, IL-6, IL-2, and TNF-α (Xie *et al.,* 2015; Carvalho *et al.,* 2017). It is strongly involved in respiratory homeostasis by stimulating the expression of antimicrobial peptides and by interfering with replication of respiratory viruses (Zdrenghea *et al.,* 2017). Moreover, vitamin D preserves tight junctions, disrupts enveloped viruses by inducing cathelicidin and defensins, and prevents the cytokine storm that leads to pneumonia (Muscogiuri *et al.,* 2020). Recently, randomized controlled trials showed that high-dose vitamin D supplementation improved the health status of mechanically ventilated critically ill patients (enhancing the capacity of blood for oxygen transport and increasing hemoglobin levels) (Han *et al.,* 2016; Smith *et al.,* 2018).

Among the consequences of SARS-CoV-2 infection, the decreased levels of circulating vitamin D. Vitamin D receptors are highly expressed by several immune cells in particular monocytes, T and B lymphocytes. Therefore, vitamin D deficiency is associated with increased risk of respiratory viral infection (Fernandes *et al.,* 2020). Ilie and collaborators (2020) have studied the role of vitamin D in the prevention of COVID-19 infection and mortality among 20 European countries. They found a negative correlation between the level of vitamin D and the number of COVID-19 cases, as well as COVID-19 mortality.

7.4 Zinc

Zinc is an important trace element which plays a pivotal role in growth, development, and the maintenance of the immune system (Prasad, 2013; Read *et al.,* 2019). It increases activity of macrophages, production of immunoglobulins and cytolysis of natural killer (Shankar and Prasad, 1998).

Zn has a direct action on viruses, such as influenza and coronavirus, maybe through inhibition of RNA-dependent RNA polymerase or by inhibiting the formation of the viral coating and processing of its structural components (Read et *al.,* 2019). Zn interacts with interferon-lambda3 binding to IFNL receptor 1 on HCV and influenza (Read et *al.,* 2017). Zhang and Liu (2020) confirmed that the combination of zinc and pyrithione at low concentrations contributes to the reduction of SARS-CoV replication.

Administration of 75 mg of zinc per day has been shown to alleviate symptoms of illness in patients with viral infections (Singh and Das, 2013). It has been suggested that zinc intakes of 30-50 mg per day might aid control of RNA viruses including influenza and coronavirus (McCarty and DiNicolantonio, 2020). Xue *et al.* (2014) demonstrated a synergistic effect of chloroquine with zinc in terms of cytotoxic effect on human cancer cells, this reinforces the fact of combining between the antimalarial and zinc for other conditions such as viral infections.

7.5 Selenium

Selenium is an essential oligoelement, which plays an important role in multiple metabolic reactions in the organism (Prabhu and Lei, 2016). It is a cofactor of many enzymes such as glutathione peroxidase or thioredoxin reductase and exerts its functions linked with protein forming selenoprotein (Duntas and Benvenga, 2015). It has antioxidant and immune properties. Adequate levels of selenium can reduce inflammation by decreased expression of pro-inflammatory mediators such as cytokines, the redox-sensitive transcription factor NF-kappa B, increase the production of interferon-gamma (Gombart *et al.,* 2020).

Zhang *et al.* (2020) showed that infected patients with increased selenium levels were more prone to recover from COVID-19. This has been also reported previously on other viral infections such as HIV (Taylor *et al.,* 2016), hepatitis B-mediated liver cancer (Steinbrenner *et al.,* 2015), or epidemic hemorrhagic fever (Hou, 1997).

8. Future perspectives

The recent emergence of the novel coronavirus along with the rapid and continuous evolution of the pandemic has caused serious threats to public health and greatest economic, social, and medical losses worldwide. Nowadays, there is an increasing gravity of the situation, a lack of appropriate detection assays for the identification of SARS-CoV-2 infected patients, and an incapacity of the existent therapeutic interventions to manage COVID-19. Therefore, there is a global emergency that needs new approaches to eradicating this global crisis. Evidence from this work supports the fact that plant phytochemicals could be a successful target-specific drug against viral infections. At the moment, scientists and clinicians are dedicating all the efforts to ameliorate prevention, treatment, and control of COVID-19. It is well understood that an effective or ideal vaccine will take more time to fully develop, so nations and officials will need massive efforts to minimize the impact of future epidemics.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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