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Natural compounds may contribute in preventing SARS-CoV-2 infection: a narrative review

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ABSTRACT

Coronavirus pandemic infection is the most important health issue worldwide. Coronavirus disease 2019 is a contagious disease characterized by severe acute respiratory syndrome coronavirus 2. To date, excluding the possibility of vaccination, against SARS-CoV-2 infection it is possible to act only with supportive care and non-virus-specific treatments in order to improve the patient's symptoms. Pharmaceutical industry is investigating effects of medicinal plants, phytochemical extracts and aromatic herbs to find out natural substances which may act as antiviral drugs. Several studies have revealed how these substances may interfere with the viral life cycle, viral entry, replication, assembly or discharge, as well as virus-specific host targets or stimulating the host immune system, reducing oxidative stress and inflammatory response. A natural compound can be used as a prophylaxis by people professionally exposed to the risk of contagion and/or positive patients not in intensive care. The aim of this paper is to perform a narrative review of current literature in order to summarize the most studied natural compounds and their modes of action.

1. Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease characterized by several systemic events, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 or 2019-nCoV). This virus primarily affects the respiratory system causing cough, fever and in more severe cases difficulty breathing [1]. The most of cases result in mild symptoms but some evolve to severe pneumonia and multi-organ failure [2]. This pathogen has been found in swabs performed on the throat and nose of patients who endure from or are suspected of the disease [3].

Coronaviruses (CoVs) are a group of viruses with envelope, with a single-stranded RNA genome [4]. CoVs are part of the Coronaviridae family and these have been classified into four genera: α-, β-, γ-, and δ-coronaviruses [5]; α- and β- CoVs infect mammals (SARS-CoV-2 is a β-coronavirus), γ-coronaviruses infect avian species, δ-coronaviruses infect aves and mammals [6]. SARS-CoV-2 is very infectious because to the high adhesion capacity on the oral cell surface [7] and for the ability to enter in the host cells through the ACE2 receptor on the lung cell surface [8].

In the last decade, the number of studies published dealing with natural compounds has increased [9], showing growing interest in different branches of medicine, from cancer [10-13], auto-immune [13-15] to infective disease [16,17].

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The aim of this paper is to create a narrative review of current literature in order to illustrate various natural compounds and their modes of action, able to prevent virus infection.

2. SARS-CoV-2 structure

One of the ways to interact in the complex mechanism of virus infection is understanding their structure in order to investigate targeted effective preventive and antiviral substances. In this contest, SARS-CoV-2 genome mainly encodes for:

1) Two big polyproteins: ORF1a and ORF1ab from which derive, with proteolytic cut, 16 nonstructural proteins (NSPs) [18]. Among these, there are: NSP1 (leader protein), NSP3 (papain like proteinase), NSP5 (3C-like proteinase), NSP12 (RNA dependent RNA polymerase) and NSP13 (helicase) [18].
2) Structural proteins, that include: spike (S) glycoproteins, envelope (E) proteins, membrane (M) proteins, nucleocapsid (N) proteins [18]. These proteins are very similar to the corresponding proteins found in SARS-CoV and MERS-CoV [19].
3) Six accessory proteins: ORF3a, ORF6, ORF7a, ORF7b, ORF8a and ORF8b [18]. Though these accessory proteins are not dispensable for viral replication *in vitro*, some have been demonstrated to have an important role in virus-host interactions *in vivo* [18].

2.1 Nonstructural proteins (NSP)

The viral genome codes many NSPs that play numerous roles in the replication and assembly processes of the virus [20]. These proteins are involved in viral pathogenetic mechanisms, such as modulation of early transcription regulation, helicase activity, gene transactivation, countering the antiviral response and immunomodulation [21-23].

NSP1 (leader protein) is a strong inhibitor of host gene expression. In fact, when NSP1 binds to the host cell 40S ribosome, it inactivates the translation and selectively favors the degradation of host mRNA, while the viral SARS-CoV-2 mRNA remain untouched [24].

NSP3 (papain like proteinase, PL^{pro}) is the biggest protein, excluding the polyproteins ORF1a and ORF1ab, encoded by the SARS-CoV-2. Considering its remarkable protease activity with the release of proteins essential for viral activity, inhibition of NSP3 activity is an important target for antiviral activity [25].

NSP5 (chymotrypsin-like cysteine protease, 3C-like proteinase, $3CL^{pro}$) is a key enzyme, as it cleaves several sites to produce non-structural proteins that are essential for genome replication and coronavirus virion production, such as an RNA-dependent RNA polymerase (RdRp), a helicase, ribonucleases and $3CL^{pro}$ itself, from 2 types of polyproteins (polyprotein 1a and polyprotein 1ab) [26]. It has also known as main protease (M^{pro}) and it is a possible target for anti-CoV drug design [27]. M^{pro} is called PDB6LU7 protein too [28].

NSP12 (RdRp) modulates viral RNA genome replication and transcription [19].

NSP13 (helicase) unwinds duplex RNA [29]. In addition to its helicase activity, NSP13 has 5′-triphosphatase activity, that causes the introduction of the 5′-terminal cap on the viral mRNA [30]. This 5′-terminal cap is the most important site for translation and plays a role in splicing, nuclear export and stability of mRNA too.

2.2 Structural proteins

S protein is a glycoprotein that binds to the host cell through its receptor binding domain (RBD) [31]. It is composed of three subunits, S1, S2, and S2', that act in different way during the adherence process to the host cell [19]. The S1 subunit is responsible of binding virions to the host cell membrane by directly interacting with the human ACE2 receptor [32]. During this event, S protein undergoes conformational changes when it enters into the host cell endosomes [33]. The subunit S2 of the S protein is involved in the fusion process of virion with the host cell membrane [19]. The last subunit, S2', works as a fusion peptide [19]. Besides, the sequence of SARS-CoV-2 S2 subunit is very similar to bat SARS-like CoVs and human SARS-CoV (about 99%), showing that a wide spectrum use of antiviral compounds created against S2 domain of these viruses could be useful in COVID-19 therapy [34]. The RBD of spike protein is the most changing part of the SARS-CoV-2. The receptor angiotensin converting enzyme 2 (ACE2) is the preferable receptor for SARS-CoV-2 spike glycoprotein [35]. Therefore, spike glycoprotein RBD is a preferable candidate for drug target to inhibit the initiation process of virus infection [35]. ACE2 ligand binding side is recognized as protease domain (PD) which plays a role in the cleavage of the trimeric structure of spike glycoprotein [36-38]. Therefore, the inhibitory effect of some compounds in this receptor suggests giving protection from virus recognition.

E proteins are relatively small and help in the assembly and release processes of the virions [65]. E protein works as a viroporins that assemble into membrane of host cell forming protein-lipid pores responsible for ion transport [19].

M proteins is an integral membrane protein having a major role in the RNA packaging and viral assembly [39].

N protein is a structural protein that connects to RNA of virus creating stability [40].

3. Natural compounds against SARS-CoV-2

Unfortunately, no drug for treating SARS-CoV-2 infection has proven reliability efficacy and safety yet [41]. Pharmaceutical industry is testing phytochemical extracts (Table 1), medicinal plants and aromatic herbs in order to identify lead compounds such as alternative antiviral drugs. Studies on the antiviral mechanisms of these natural products are pointing out how they can interfere with the viral life cycle, i.e., during viral penetration, replication, assembly or liberation, as well as virus-specific host targets [42,43].

In China, traditional Chinese medicine (TCM) is already playing an important role in the treatment of SARS-CoV and SARS-CoV2 infections [44]. During the first SARS epidemic in Guangdong, all patients received Chinese medicine treatments (specific formulations) in the different stages of the disease in addition to western medical treatments, such as *San Ren Tang, Yin Qiao San, Ma Xing Shi Gan Tang, Gan Lu Xiao Du Dan*, and *Qing Ying Tang*, containing mixtures of many different herbs [44]. In Hong Kong, a combination of *Sang Ju Yin* and *Yu Ping Feng San*, plus two other botanicals, *Isatidis folium* (*Isatis tinctoria* L.) and *Scutellariae radix* (*Scutellaria* spp.), had been used successfully to protect high-risk hospital workers against SARS-CoV infection [45]. In 2007, during the first SARS-CoV crisis in China, Chinese medicine treatment was applied to 40%−60% of the

Table 1
Natural compounds and their actions on SARS-CoV-2.

Origin	Extracts or derivates	Mechanism of action
Ammoides verticillata	c-Terpinene, isothymol, limonene, P-cymene, thymol	Inhibition of ACE-2 receptor for SARS-CoV-2 [64]
Curcuma longa	Curcumin	Act against anti-inflammatory diseases, lung diseases, metabolic diseases, and liver, neurological, cardiovascular diseases, and tumors [84] Interaction with several viral targets thereby triggering cell signaling pathways, such as apoptosis and inflammation: DNApol thioredoxin reductase, focal adhesion kinase, protein kinase, tubulin, LOX [84] Limitation of viral multiplication (interfering in viral replication cycle, viral genome replication, viral attachment) [85-89] Modification of the viral surface protein, block of viral entry and viral budding [84] Action on membrane proteins by modulation of the host lipid bilayer structure [107] Bind to SARS-CoV-2 protease, spike glycoprotein-RBD [35] Inhibition of ACE2 suppressing SARS-CoV-2 entry to the cell [35] Inhibition of COVID-19 M^{pro} (viral main protease that impede immune response) [76] Scavenge of several small oxidative molecules [99] Up-regulation of glutathione (GSH) expression and inhibition of reactive oxygen species (ROS) generation [100] Antithrombotic properties useful [101]
Marine algal	Sulfated polysaccharides	Rich source of many antioxydant agents promising for the development of drugs for the prevention and treatment of various chronic and acute human disease [97]
Marine algal	Polyphenolic compounds (flavonoids, cinnamic acid, benzoic acid, gallic acid, quercetin)	High antioxidant activity and potential antiviral molecules [96]
Brown macroalgae or diatoms	Phlorotannins	Antioxidant and anti-inflammatory properties [96]
Tannins	Proanthocyanidins (syn. condensed tannins), hydrolysable tannins (syn. gallotannins), Lamiaceae tannins (depsides)	Inhibition of the functionality of viral envelope proteins [44] Interaction with salivary proteins and surface proteins of epithelial cells with inhibition of an incoming virus from adhering to host cells [83]
Natural oil	Laurel oil	Antiviral potential against enveloped viruses [81,82] *In vitro* activity of laurel oil against SARS-CoV [44] with inhibition of viral replication [81]
Salvia officinalis L.	Sage oils/leaves	Topical application as gargle solutions [44]
Phytoestrogens from *Cicer arietinum*	Daidzein, genistein, formononetin, biochanin A	
Palm oil	Palmitic acid	
Vegetable oils like canola, soybean, flaxseed/linseed, olive, some nuts	Linolenic acid	
Coffee	Chlorogenic acid	Binding to HSPA5 with the inhibition of coronavirus S protein interaction [68]
Extravirgin olive oil	Hydroxytyrosol	
Berries, herbs, mushrooms, coffee beans	Caffeic acid	
Honeybee hive propolis	Caffeic acid phenethyl ester	
Fungi, peanuts, tomatoes, garlic	*Cis-p*-coumaric acid	
Cinnamomum verum	Cinnamaldehyde	
Seeds of *Nigella sativa*	Thymoquinone	
Allium sativum L. or garlic	Garlic essential oil	Strong interaction with ACE2 protein [63] Good inhibition of PDB6LU7 protein (M^{pro}) [63]
Crocus sativus L.	Crocin	
Nerium oleander	Digitoxigenin	Inhibitor of SARS-CoV-2 M^{pro} [70]
Lauris nobilis L.	*β*-Eudesmol	
Psorothamnus arborescens	5,7,3′,4′-Tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone	
Mymirica cerifera	Myricitrin	
Hyptis atrorubens Poit	Methyl rosmarinate	
Phaseolus vulgaris	3,5,7,30,40,50-Hexahydroxy flavanone-3-*O*-*β*-*D*-glucopyranoside	Inhibition of SARS-CoV-2 $3CL^{pro}$ activity and replication [74]
Phyllanthus emblica	(2*S*)-eriodictyol 7-*O*-(600-ogalloyl)-*β*-*D*-glucopyranoside	
Fraxinus sieboldiana	Calceolarioside B	
Camellia sinensis	Myricetin 3-*O*-*β*-*D*-glucopyranoside	
Camellia sinensin	Theaflavin	Binding to RdRp [78] Anti-IL-6 action [94]
Glycyrrhiza uralensis	Licoleafol	Inhibition of SARS-CoV-2 $3CL^{pro}$ activity and replication [74]
Amaranthus tricolor	Amaranthin	
Polygonum cuspidatum, grapes, wine	Resveratrol	Upregolation of circulating ACE2 with reductive effect on SARS-CoV-2 severity [66] Reduction of IL-6 production [66]
Pligonum cuspidatum	Polydatin	Antioxidant properties [95]

Table 1 (*Continued*)

Origin	Extracts or derivates	Mechanism of action
Scutellaria baicalensis Georgi	Baicalin	ACE2 inhibition [65]
Erigeron breviscapus (Vant.) Hand Mazz	Scutellarin	Reduction the ACE expression and activity in brain tissue [65]
Citrus auarantium, Citri Reticulatae Pericarpium	Hesperitin	Inhibition of cleavage of the $3CL^{pro}$ [65]
Soybean	Nicotiamine	Potent inhibitor of ACE2 [65]
Herb licorice root (*Glycyrrhiza radix*)	Glycyrrhizin	Inhibition of viral adsorption and penetration (blocking ACE2 receptor) [65]
Citrus Sp.	Tangeretin, hesperidin, nobiletin, naringenin	
Caesalpinia sappan	Brazilein, brazilin	Inhibition of RBD-S, PD-ACE2, SARS-CoV-2 Main protease [35]
Alpinia galanga	Galangin	
Betula pubescens	Betulinic	
Rauwolfia canescens	Desmethoxyreserpine	Inhibition of replication and $3CL^{pro}$ [69]
Linum usitatissium	Lignan	
Metasequoia glyptostroboides	Sugiol	
Tinospora cordifolia	Coumaroyltyramine	
Salvia miotiorrhiza Bunge	Cryptotanshinone	
Pteridophyta	Kaempferol	
Piper caninum Blume	*N-cis*-feruloyltyramine	Inhibition of PL^{pro} and $3CL^{pro}$ [69]
Apples, barks, berries, brassica vegetables, capers, flowers, *Ginkgo biloba*, grapes, *Hypericum perforatum*, leaves, nuts, onions, red onions, *Sambucus canadensis*, seeds, shallots, tea, tomatoes	Quercetin	
Salvia miltiorrhiza	Tanshinone IIa	
Pinus sylvestris, *Cedrus deodara*, *Larix decidua*, *Abies grandis*, *Cupressus sempervirens*	Dihomo-c-linolenic	Inhibition of $3CL^{pro}$ [69]
Salvia miltiorrhiza Bunge	Dihydrotanshinone	Inhibition of entry and spike protein [69]
Piper nigru	Moupinamide	Inhibition of PL^{pro} [69]
Nigella sativa	DTQ, TQ, Thymol, THQ, P-cymene, 4-terpineol,T-anethole	ACE2 inhibition [67]
Clerodendrum spp.	Taraxerol, friedelin, stigmasterol	Inhibition of main protease enzyme M^{pro}, spike protein, and RdRp [77]

infected patients received beyond standard modern medicine treatment [46], even if the positive results are still not conclusive about the real efficacy of the combined treatments with Chinese medicine as an adjuvant [46]. During the recent SARS-CoV-2 infections, TCM has been again widely applied in China [44]. A recent study pointed out that than 85% of SARS-CoV-2 infected patients received TCM treatment in China [47]. Luo et al. [48] reported that *Astragalus membranaceus* (*Astragalus mongholicus* Bunge), *Glycyrrhizae uralensis* Fisch. ex DC., *Saposhnikovia divaricata* (Turcz. ex Ledeb.) *Schischk*., *Atractylodis macrocephalae* Koidz. (rhizome), *Lonicerae japonica* Thunb. (flower), *Forsythia suspensa* (Thunb.) *Vahl* (fruit), *Atractylodes lancea* (Thunb.) *DC.* (rhizome), *Platycodon grandiflorus* (Jacq.) *A.DC.* (root), *Agastache rugosa* (Fisch. & C.A.Mey.) *Kuntze*, and *Cyrtomium fortunei J. e rugosa* (Fisch. & C.A.Mey.) *Kuntze*, and *Cyrtomium fortunei* J. Sm. were the ten most used Chinese medicinal plants in the treatment of COVID-19.

Before the introduction of vaccination protocols, the only really effective weapon against SARS-CoV-2 together with the monoclonal antibodies, none drug has been approved against CoVs and some potential natural therapeutic strategies have been proposed (Table 1).

Possible ways to block/reduce the actions of SARS-CoV-2 and other viruses can be several: 1) inhibiting the adhesion of viruses to host cells; 2) inhibiting the viral enzymes; 3) stimulating the host immune system, reducing oxidative stress and inflammatory response.

3.1 Virus adhesion to host cells and natural compounds

Enveloped viruses have a lipid bilayer which is originated from host cell membrane. This layer often contains (glyco)proteins, that can protrude out the cell [49]. In several cases, these proteins are involved in the specific mechanisms of host cell recognition promoting viral adhesion and penetration [50]. Well-known proteins involved in these processes are influenza virus haemagglutinin [51] or coronavirus S protein [52]. Naturally different coronavirus use different host cell receptors such as heparan sulfate proteoglycans, angiotensin-converting enzyme 2 (ACE2), aminopeptidase N, heat shock protein A5 (HSPA5), furin, and *O*-acetylated sialic acid [7,53-57].

Several natural products can have anti-adhesive action and modify the receptor-mediated recognition and early viral interaction with the host cells, with a subsequent reduction of the viral internalization and reduced infections [44].

Researches showed that ACE2 is the receptor used by SARS-CoV-2 in order to infect human cells [58,59]. Recent studies pointed out that ACE2 is highly expressed in the oral cavity [59], so virus may predominantly enter in the human body via the oral mucosa [60]. In fact, SARS-CoV-2 is very infective for its high adhesion capacity on the oral cell surface [7] and for its ability to penetrate into host lung cells through the ACE2 receptor (stage 1 of the viral infection) [8]. Coronavirus uses its spike glycoproteins to bind host receptors. Its RBD (receptor-binding domain) binds strongly to human ACE2

receptors. Also, S1domain of spike glycoprotein is able to interact with the human CD26, an immunoregulatory factor important for hijacking and virulence [61]. CD26 is present both as a soluble form in plasma and on the cell surface of various immune and nonimmune cell types and it is involved with inflammatory processes [62].

A recent study showed that isothymol, thymol, limonene, P-cymene, c-terpinene and garlic essential oil, obtained from *Ammoides verticillate*, is able to bind ACE2 protein, inducing the virus to lose the host receptor [63,64].

Another study highlighted the action of several natural compounds in the prevention of SARS-CoV-2 infection, inhibiting the viral spike protein adhesion to the ACE2 enzyme; indeed, baicalin, scutellarin, nicotianamine and glycyrrhizin are able to bind strongly ACE2 receptor [65]. Chen et al. [65] have carried out molecular docking studies demonstrating how these molecules are able to strongly bind the ACE2 receptor. Based on this concept and on the necessity for SARS-CoV-2 to bind ACE2 in order to penetrate host cells, the authors suggest that these molecules are potential candidates for 2019-nCoV treatment/prevention. However, their efficacy on anti-2019-nCoV is worth further investigation.

Also Tangeretin, Hesperidin, Nobiletin, Naringenin, Brazilein, Brazilin and Galangin are able to to bind RBD-S and PD-ACE2, blocking the adesion of SARS-CoV-2 to host cells [35].

Nicotiamine, extracted from soybean, is a potent inhibitor of ACE2 [65].

In the same way baicalin inhibits ACE2 enzyme, while *Scutellarin* only causes reduction of ACE expression and activity in brain tissue [65].

Curcumin causes inhibition of ACE2 suppressing SARS-CoV-2 entry to the cell [35].

Resveratrol, extracted from *Polygonum cuspidatum* or grapes or wine, reduces/blocks the binding of SARS-CoV-2 with ACE2 present on cells membrane in a different way compared to the compounds previously seen: it causes upregulation of circulating ACE2 with reduction of SARS-CoV-2 illness severity [66].

Dithymoquinone (DTQ), thymoquinone (TQ), thymol, thymohydroquinone (THQ), P-cymene, 4-terpineol, T-anethole, all these derived from *Nigella sativa*, are able to inhibit ACE2 receptor too [67].

Glycyrrhizin, extracted from Herb licorice root (*Glycyrrhiza radix*), is used to treat chronic hepatitis and it has not toxic effect [65]. *In vitro* study glycyrrhizin has anti-SARS-CoV-2 actions inhibiting viral adsorption and penetration, due to ACE2 receptor block [65].

Cell-surface heat shock protein A5 (HSPA5), also termed GRP78 or BiP, can be a receptor for Coronavirus. During viral infection, HSPA5 is overexpressed, translocates to the cell membrane where it is recognized by the SARS-CoV-2 spike protein [68]. Different natural products can block the recognition site of cell-surface HSPA5 and compete for the viral Spike recognition [68]. The principal way of this interaction are the H-bonding and the hydrophobic interaction [68]. Some studies showed high binding affinity phytoestrogens (Diadiazin, Genistein, Formontein, and Biochanin A), chlorogenic acid, linolenic acid, palmitic acid, caffeic acid, caffeic acid phenethyl ester, hydroxytyrosol, *cis-p*-coumaric acid, cinnamaldehyde and thymoquinone for HSPA5 blocking coronavirus S protein interaction [68].

Even dihydrotanshinone, extracted from *Salvia miltiorrhiza* Bunge, could block SARS-CoV-2 penetration into the host cell inhibiting bond between spike protein and ACE2 receptor: this natural compound binds the S protein [69].

Other compounds able to determine inhibition of RBD-Sprotein are tangeretin, hesperidin, nobiletin and naringenin (extrated from *Citrus* Sp.), brazilein and brazilin (extracted from *Caesalpinia sappan*), galangin (extracted from *Alpinia galanga*) [35].

3.2 Inhibition of viral enzymes by natural compounds

Some natural compounds can inhibit the action of viral enzymes. Coronavirus uses protease to cleave the structural protein used during viral formation in the host cells. Crocin, digitoxigenin and *β*-eudesmol inhibit SARS-CoV-2 by blocking the main protease (M^{pro} or $3CL^{pro}$) [70]. M^{pro} has been proposed as a therapeutic target in anti-coronavirus drug [71-73]. The $3CL^{pro}$ regulates virus replication and it is important for viral life cycle, so that these compounds would be able to inhibit virus replication [74].

A study screened the $3CL^{pro}$ sequence in 3D homology model using a medicinal plant library with 32.297 potential phytochemical traditional Chinese medicinal compounds and 9 of these (5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, myricitrin, methyl rosmarinate, 3,5,7,30,40,50-hexahydroxy flavanone-3-*O*-*β*-*D*-glucopyranoside, (2*S*)-eriodictyol-7-*O*-(600-ogalloyl)-*β*-*D*-glucopyranoside, calceolarioside B, myricetin 3-*O*-*β*-*D*-glucopyranoside, licoleafol, amaranthin) seem to be able to inhibit SARS-CoV-2 viral $3CL^{pro}$ enzime activity [74]. Also, *Hesperetin* can inhibit, dose-dependently, cleavage activity of the $3CL^{pro}$ [75]. Betulinic, desmethoxyreserpin, lignan, sugiol and dihomo-c-linolenic cause inhibition of replication and $3CL^{pro}$ [69]. Also tangeretin, hesperidin, nobiletin, naringenin, brazilein, brazilin and galangin are able to to bind SARS-CoV-2 main protease (M^{pro}) [35].

Moreover, coumaroyltyramine, cryptotanshinone, kaempferol, *N-cis*-feruloyltyramine, quercetin and tanshinone IIa are able to inhibit PL^{pro}, in addition to $3CL^{pro}$ [69]. Another compound that causes inhibition of PL^{pro} is moupinamide, extract from *Piper nigrum* [69]. Garlic essential oil, derived from *Allium sativum* L., determines a good inhibition of PDB6LU7 protein (M^{pro}) [63]. Even curcumin (*Curcuma longa*) determines inhibition of COVID-19 M^{pro} (viral main protease that impede immune response) [76]. Taraxerol, friedelin and stigmasterol, derived from *Clerodendrum* spp., cause inhibition of the main protease enzyme (M^{pro}) as well as Spike protein and RdRp [77]. From *C. longa* is extracted curcumin, that is able to bind SARS-CoV-2 spike glycoprotein-RBD, blocking the penetration of virus into host cell [35]. Instead, theaflavin, extracted from *Camellia sinensin*, could bind RdRp of SARS-CoV-2 [78]. Tannins have not specific antimicrobic action, but are able to inhibit the functionality of viral envelope proteins [44]. Condensed tannins or extracts containing tannins have inhibitory actions on the influenza virus or RSV [79-82]. There is a very heterogeneous group of natural substances including proanthocyanidins (syn. condensed tannins), hydrolysable tannins (syn. gallotannins), and the so-called Lamiaceae tannins (depsides) [44]. Tannins also interact with salivary proteins and with epithelial surface proteins [83]. The tannins are naturally immobilized on the epithelia, where they can be present for long time, offering new perspectives in preventing infection [44].

A study showed *in vitro* activity of Laurel oil against SARS-CoV [44], acting against enveloped viruses [81,82]. Essential oil from the aerial parts of the laurel tree (*Laurus nobilis*) was able to inhibit viral replication *in vitro* [81]. Laurel oil has amounts of the monoterpenes 1,8-cineol and *β*-ocimen and the sesquiterpene dehydrocostus lactone [81].

However, Sage oil, rich in 1,8-cineol, showed poor effects [81]. Inhalative administrations of laurel oil would therefore be useful, but a considerable allergenic potential has emerged [44]. Sage leaves (*Salvia officinalis* L.) contain tannins (depsides), useful for topical administration in gargle solutions [44].

Curcumin interacts with several molecular virus targets activating cellular signaling pathways (apoptosis and inflammation): DNApol thioredoxin reductase, focal adhesion kinase, protein kinase, tubulin and LOX [84]. Also, this natural compound limit viral multiplication, interfering in viral replication cycle, viral genome replication and viral attachment [85-89] and modify the viral surface proteins, preventing viral penetration and viral budding [84].

3.3 Host immune system, inflammatory response, oxidative stress and natural compounds

The third possible way is the action of these natural compounds regulating immune system. The immune response against COVID-19 is similar to that for other coronaviruses [84]. The regulation of the immune system activity may be a promising approach in order to prevent viral infections [90]. However, since the pathology of late-stage SARS is linked to an excessive reaction of the immune system with subsequent cytokine storm [91,92], a not specific stimulation of immune system may also be a risk [44].

When SARS-CoV-2 involves the upper and lower respiratory tract it determines a mild or severe acute respiratory syndrome with subsequent release of pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-6 [93]. The binding of virus to the toll like receptor (TLR) determines the production and release of pro-IL-1β that is cleaved by caspase-1, with subsequent inflammasome activation and production of active mature IL-1β which is an important mediator of lung disesase, fever and fibrosis [93]. One of the mechanisms involved in the lethality of coronavirus is the realization of interstitial pneumonia due to an excessive production of IL-6.

Some natural products seem to be useful for their anti-IL-6 action, such as curcumin [94], resveratrol [94], epigallocatechin-3-gallate [(2*R*,3*R*)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2*H*-chromen-3-yl]3,4,5-trihydroxybenzoate (EGCG), an ingredient of green tea, *Camellia sinensis* (Theaceae) [94]. Resveratrol, (3,4′,5-*trans*-tri-hydroxy-stilbene), a stilbene of plant origin belonging to the class of phytoalexins, is a molecule capable of interacting with biological structures and activating repair processes and defensive actions against biotic stresses due to infections and abiotic stresses such as oxidative ones.

Polydatin (3,5,4′-dihydroxystylbene-3-*O*-*β*-*D*-glucopyranoside) is a glucoside derived by resveratrol for the presence of the glycosidic group bound in position C-3, where it replaces an hydroxy group. The substitution of the glycosidic group leads to conformational changes in polydatin which are reflected in changes in biological properties. In resveratrol, the most reactive hydroxyl group for its "scavenger" activity of free radicals, is the group placed in position 4′. This group remains in the polydatin preserving its antioxidant properties, in fact, the hydroxyl in C-3 which in this compound is replaced by the glycosidic group is the least reactive as regards the "scavenger" activity [95]. This causes polydatin to maintain the biological activities of resveratrol but present in more remarkable advantages that can be exploited in the pharmacological field. Polydatin is more resistant than resveratrol to enzymatic oxidation, it is able to penetrate cell through an active transport mechanism that uses glucose transporters, and, thanks to its solubility in water, it is absorbed more efficiently by the intestine. These properties give polydatin the characteristics of a compound with greater bioavailability and greater stability. Furthermore, being polydatin soluble in water, it can also be administered parenterally, lending itself to a better pharmacological use.

The biological activities of resveratrol and its glucosidic derivatives, such as polydatin, protective for human health can be summarized in antioxidant activity; reduction of deleterious effects due to oxidative stress on cells and on different tissues and a strong protective action on the cardiovascular system; anti-inflammatory activity, due to their ability to regulate the production of nitric oxide (NO) and the production of pro-inflammatory cytokines; modulation of lipids synthesis by preventing accumulation of cholesterol and fats in the liver; inhibition of platelet aggregation; immunomodulatory action on immune cells; antiviral and antibacterial action; strong anti-aging and neuro-protective activities; strong anti-mutagenic and anti-cancer action by the inhibition of cellular events linked to the stages of initiation, promotion and progression of the cancerization.

Polyphenolic compounds (flavonoids, cinnamic acid, benzoic acid, gallic acid, quercetin), derived from Marine algal, have high antioxidant activity and potential antiviral molecules[96].

From marine algal derive sulfated polysaccharides too [97]. These compounds have several antioxydant agents useful for the development of drugs able to prevent and treat various chronic and acute human disease [97].

Also phlorotannins, extracted from brown macroalgae (or Diatoms), has antioxidant and anti-inflammatory properties [96].

Curcumin, extracted from *Curcuma longa*, showed antiviral activities against different viruses so it can be useful for the management of COVID-19 infection [84]. It is evident the inhibitory actions of curcumin on inflammatory cytokines in fact, it is able to inhibit the signals involved in the regulation of various pro-inflammatory cytokines expression, such as NF-κB and MAPK pathways [98]; it reduces crucial chemokines and cytokines involved in lung infection (e.g. IFNγ, MCP-1, IL-6 and IL-10) [84]. Curcumin acts as a scavenger of various small oxidative molecules [99] and induces an up-regulation of glutathione (GSH) expression and inhibition of reactive oxygen species (ROS) generation [100]. Antithrombotic properties of curcumin are useful for COVID-19 patients because some reported thrombotic events [101].

4. Discussion

Currently, there are not available specific anti-virus drugs useful for this lethal disease. The supportive care and non-specific treatment useful for the symptoms are actually the only options [102]. Tocilizumab seems to be a new therapeutic possibility for COVID-19. In fact, guidelines by China's National Health Commission considered Tocilizumab after a small study for its immunosuppressant action and its ability to reduce interleukin-6 production. This drug cannot be used for the preventive treatment.

TCM, for example, is supported by the China government in its action to contain and eradiate SARS-CoV-2 [102]. Health Commission of 26 provinces promoted the use of TCM in combination with conventional medicine for the therapy strategies against COVID-19 [102]. On 17 February, 2020, National Health Commission (NHC) of the People's Republic of China declared that TCM was used on the treatment of 60 107 COVID-19 patients [103]. To March 1, 2020, there were 303 ongoing clinical trials in order to evaluate the efficacy and safety of several therapeutic strategies for COVID-19 patients in China [102]. 50 of these trials (16.5%) are concerning the utility of TCM, including 14 trials (4.6%) to examine the efficacy of combined treatment with traditional medicine and TCM [102].

For all these reasons, it is necessary to provide complementary and alternative treatments for the therapy of COVID-19 patients, or in preventing infection [104-106]. To date, this current pandemic event is a valid opportunity to test the real value of natural products or nutraceutics in preventing/treating new emerging contagious pathologies. Randomized, double-blind and placebo-controlled studies are the best opportunity in order to verify the most reliable evidence for the prophylaxis or therapy. For this reason, a natural compound can be a useful preventive instrument for workers professionally exposed to the contagion and/or positive patients not in intensive care. Naturally, it is necessary to organize trials on large number of subjects.

It would be quite conceivable to use therapeutic formulation of new natural compounds, such as concentrated tanning extracts, for topical use in the oral cavity for prophylaxis and adjuvant therapy. It could be useful the prescription of chewing gums, gargle or mouthwash solutions containing these natural extracts in order to offer novel opportunities.

5. Conclusions

COVID-19 pandemic is the most important health problem worldwide. COVID-19 is an infectious disease characterized by severe acute respiratory syndrome and, to date, no specific there are not available anti-virus drugs or vaccines useful for its treatment. A natural compound can be useful for the prevention of this disease particularly for workers professionally exposed to the risk of contagion, and/or positive patients not in intensive care. For this reason, every possible hypothesis must be tested, none can be discarded a priori.

Conflicts of interest

The authors declare no conflict of interest.

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