Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Antiviral activity of bioactive phytocompounds against coronavirus: An update

Riya Bhattacharya, Kamal Dev, Anuradha Sourirajan *

Faculty of Applied Sciences and Biotechnology, Shoolini University of Biotechnology and Management Sciences, Bajhol, PO Sultanpur, District Solan, 173229, Himachal Pradesh, India

ARTICLE INFO

Keywords:
Phytocompounds
SARS-CoV
MERS-CoV
Antiviral
SARS-CoV-2
COVID-19, mechanism

ABSTRACT

Viral infections are one of the main cause of diseases worldwide due to the rising trends of migration, urbanization and global mobility of humans. The outbreak of corona virus diseases caused by SARS-CoV (year 2003), MERS-CoV (year 2012) and SARS-CoV-2 (year 2019) raised global health concerns. The side effects associated with the conventional drugs and increase in cases of anti-microbial resistance have led the researchers to switch to natural sources, especially plants, as they have immense potential to be used as antiviral agents. The aim of the article is to summarize the evidences of the bioactive phytocompounds from different plants as an effective alternative for the treatment of infections caused by coronaviruses. However, the use of most plant compounds succumbs to limitations due to lack of experimental evidences and safety studies. Therefore, further research and studies are required to validate their therapeutic uses for wide application of plant-based medicine, including anti-virals.

1. Introduction

The emerging trends in migration, urbanization and global travel have made viral outbreaks as an alarming threat for human health. Viral infections are of serious concern due to their complexity, diversity and limited availability of vaccines and antiviral therapies. As a result, they commonly lead to epidemic and pandemic events (Drexler, 2010; Neiderud, 2015). The treatment and control of viral infections largely depends on the availability of antiviral drugs, which are few in number and most of them do not act directly on virus, rather prevent their replication in the host. Viruses consist of a genome (either RNA or DNA) surrounded by a protein or lipid-containing envelope, and the latter facilitates the viral entry into host cells resulting in several ailments like warts, colds, fever, or even death (Tapparel et al., 2013).

Viruses survive and replicate in the host by hijacking the metabolic pathways of the host cells. Therefore, it is difficult to design an appropriate drug to attack the virus without triggering any adverse effects on the host. Consequently, the unique features of viruses (specificity, affinity, and self-defense mechanisms), and the limitations of antiviral chemotherapy necessitate the dire need to develop new antiviral agents, which possess efficient selectivity, strength, in vivo stability and safety profiles (Akram et al., 2018).

The Coronaviridae family comprises of enveloped single-stranded RNA viruses that are generally causative agents of common cold, upper respiratory disorders and lower respiratory infections, especially in elderly persons and children, who have weak immune system. Currently, there is an outbreak caused by a novel subtype of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has resulted in a pandemic with millions of infections and deaths worldwide in humans. The novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has become a global health concern since December 2019 till date. In this context, it is extremely important to understand the mechanism of the SARS-CoV-2 viral pathogenesis to develop specific and effective drugs. Currently, it has been reported that SARS-CoV-2 shows sequence homology with the SARS-CoV and a bat coronavirus (Gorbalenya et al., 2020). Despite its similarity to SARS-CoV, its transmission efficiency and diagnostic methods are very different, and SARS-CoV-2 is much more virulent compared to SARS-CoV-1. This could possibly be due to the nucleotide changes in the spike (S) protein and its receptor-binding domain (RBD) (Kannan et al., 2020; Coutard et al., 2020; Wan et al., 2020). Therefore, scientists worldwide are exploring the preventive methods and treatment for
COVID-19, until a vaccine will be available (Balachandar et al., 2020).

As the world is awaiting curative remedies for COVID-19, there have been several attempts in the recent past towards repositioning of existing drugs to combat the spread of COVID-19. The World Health Organization (WHO) estimates that about 80% of global population rely on traditional medicine to treat infectious diseases (Pan et al., 2013). Several in vitro and in vivo studies carried out on plants and their derived products have helped to develop effective antibiotic, antimitotic, and antiviral activities. In addition, the pharmaceutical companies began to develop new antimicrobial drugs from natural plant sources (Barreca et al., 2017). The evaluation of several medicinal plants revealed their potential to be used as therapeutic agents against different viruses (Akrum et al., 2018). The available antiviral drugs act on specific enzymes involved in targeting the viral structure or in the replication cycle, making them effective targets. But the failure of several conventional drugs against viral infections and the rise in incidence of specific viral resistance has led to an interest in plants as an alternative source of effective antiviral agents (Irwin et al., 2016). Different plant components including essential oils and phytocompounds, such as phenolic acids, flavonoids, terpenes, lignans, coumarins, and alkaloids exhibit potential activity against viruses (Duglia, 2012). Thus, medicinal plants are a promising source for treatment viral diseases (Gomathi et al., 2020).

With the onset of COVID-19 pandemic, research has been initiated to screen the potential of several plant secondary metabolites in inhibiting the SARS-CoV-2 main protease (Mpro®)/chymotrypsin-like protease (3CLpro®) using molecular docking analysis to examine binding affinity. However, screening a large number of medicinal plants for phyto-compounds with antiviral activity against SARS-CoV-2 will be a challenge in very short period of time. Drug discovery is a time consuming, slow and challenging process (Shaikh et al., 2013; Eweas et al., 2014). Thus, it is necessary to exploit computational tools for new drug development, which has made the process of drug discovery rapid and cost effective in the past (Eweas et al., 2014). For screening and searching phyto-compounds, the ligand-based virtual screening tool/molecular docking is very effective to identify most probable molecule with pharmacological activity (Guo et al., 2014; Banegas et al., 2018).

The aim of this review is to provide an update on the antiviral activity of different medicinal plants and their isolated bioactive phyto-compounds, their mechanism of action and potential interactions with conventional drugs. The review focuses on the literature available on structure, immunological influence, mechanism of action of the phyto-compounds, ongoing clinical trials, recent diagnostics and the potential use of certain medicinal herbs for the effective treatment of coronavirus. Based on the review of literature, we suggest that the traditional medicinal plants can be used as a beneficial and effective means to combat viruses like the SARS-CoV-1, MERS-CoV and SARS-CoV-2.

2. Overview of coronaviruses

There are total 39 species of coronaviruses under the realm of Riboviria, which belong to the family Coronaviridae, suborder Coronovirinae and order Nidovirales (Gorbalenya et al., 2020). All the SARS-CoV viruses fall under the species severe acute respiratory syndrome-related coronavirus and genus Beta-coronavirus. Most of the species are enzootic and only few species infect humans (Schoeman and Fielding, 2019). So far, seven human CoVs (HCoVs) have been reported, which include, human coronavirus NL63 (HCoV-NL63) and human coronavirus 229E (HCoV-229E) of the alpha-coronavirus genus, and human coronavirus OC43 (HCoV-OC43), human coronavirus (HCoV-HKU1), SARS-CoV, SARS-CoV-2 and middle east respiratory syndrome coronavirus (MERS-CoV) of the beta-coronavirus genus. Human coronaviruses are mostly associated with upper respiratory tract infection, which ranges from mild to moderate, including common cold. It is believed that most of the people might have been infected with one of these viruses at some point in their lifetime (Killerby et al., 2018).

The SARS-CoV and MERS-CoV are the two major viruses that are responsible for severe pneumonia in humans (Song et al., 2019). The emergence of SARS-CoV was first reported in 2003, which led to more than 8000 infections and 774 deaths spread across 37 countries (Peiris et al., 2004). This was followed by the emergence of MERS-CoV in Saudi Arabia in 2012, which was responsible for 858 deaths out of 2494 infections (Zaki et al., 2012). Subsequently, an outbreak of SARS-CoV-2 emerged in December 2019 in the city of Wuhan, China from animal source and transmitted to human population, resulting in the COVID-19 pandemic with lakhs of deaths and millions of infected cases all over the world. As of October 11, 2020, the World Health Organization (WHO) has reported 37,109,851 infections in humans and 1,070,355 deaths worldwide due to COVID-19, and its spread to 214 countries and territories (World Health Organization (WHO), 2020a,b). To combat the battle against this dreadful virus, the WHO has strategized the following measures: to avoid human to human contact, maintaining social distancing and isolate patients at early stages, identify and stop its transmission from the animal source, finding out crucial aspects of the virus and speed up research activities for its prevention and cure, dissemination of appropriate directions to the public and minimize the social and economic impact.

The SARS-CoV-2 is a zoonotic virus that belongs to the coronaviridae family and can infect humans and several other animal species (Lu et al., 2020). The SARS-CoV-2 belongs to the subgenus sarbecovirus and mostly similar to bat coronavirus, with 96.2% sequence homology (Chan et al., 2020a). The appearance of symptoms due to SARS-CoV-2 infection occurs slowly over an incubation period of around 2 weeks. During this incubation period, the virus replicates in the upper and lower respiratory tract, forming lesions (Chan et al., 2020b). The common symptoms reported in the infected individuals are loss of taste, fever, cough, dyspnea and lesion in the lungs (Huang et al., 2020). The key proteases of the SARS-CoV namely 3C-like Protease (3CLpro®) and the Papain-like protease (PLpro®) are potential targets for the development of inhibitors against SARS-CoV (Chou et al., 2003; Zhang and Yap, 2004; Anand et al., 2005). The 3CLpro® and PLpro® are the key enzymes involved in the processing of the non-structural proteins of the virus (nsps) required for the viral replication (Baez et al., 2015; Cascella et al., 2020). The surface of SARS-CoV is coated with the S proteins, which possess the potential to attach to human angiotensin converting enzyme 2 receptors (ACE2). ACE2 receptors are expressed in the lungs, kidney, endothe- lium, heart, and intestine (Zhang et al., 2020). An alternative way to block the activity of the SARS-CoV is to target its S protein or blocking the human ACE2 from binding to the S protein.

3. Structural and genomic organization of coronaviruses

The morphology of coronaviruses varies from spherical to pleomorphic shape, with a diameter of 80–120 nm (Masters, 2006). Coronavi- ruses possess the ability to form double membrane vesicles (DMVs) in the infected cells. They also exhibit recombination, high rates of muta- tion, and propensity to cross species. The coronavirus genome consists of 6–7 open reading frames (ORFs), as described below.

3.1. SARS-CoV

The genome of SARS-CoV encodes the structural spike (S) glyco- protein, membrane (M) glycoprotein, small envelope (E) protein and nucleocapsid (N) protein in 5’-3’ direction within the 3’ proximal 1/3rd region of the genome. All the SARS-CoV genomes harbor an extremely large gene 1 (separated into ORFs 1a and 1b and extending over two-thirds of the genome) encoding nonstructural proteins responsible for proteolytic processing of the gene 1 polyprotein products, virus genome replication, and sub-genomic (sg) mRNA synthesis (Fig. 1). A variable number of ORFs appearing to be virus- or group-specific, encoding nonstructural proteins (nsps) are also present in the genome. These include ORF 3a (7.7 kDa protein), ORF 3b (27.7 kDa protein), and...
ORF 7 [0.7 kDa hydrophobic protein (HP)] in TGEV (Transmissible gastroenteritis coronavirus); ORF 3 (25.3 kDa protein) in PEDV (Porcine epidemic diarrhea coronavirus); ORF 4a (15.3 kDa protein) and ORF 4b (10.2 kDa protein) in HCoV-229E; ORF 2a (32 kDa protein), ORF 2b (65 kDa complete or 34.6 kDa truncated hemagglutinin esterase (HE) protein, depending on the strain), ORF 4 (17.8 kDa protein), ORF 5a (13.1 kDa protein), and an ORF internal to gene 7 (23 kDa internal (I) protein) in MHV (Mouse hepatitis coronavirus); ORF 2a (32 kDa protein), ORF 2b (65 kDa HE protein), ORF 4a (4.9 kDa protein), ORF 4b (4.8 kDa protein), ORF 5 (12.7 kDa protein), and an ORF internal to gene 7 (23 kDa I protein) in BCoV (Bovine coronavirus); and ORF 3a (6.7 kDa protein), ORF 3b (7.4 kDa protein), ORF 5a (7.5 kDa protein), and ORF 5b (9.5 kDa protein) in IBV (Avian coronavirus) (Fig. 1).

The 5′-untranslated region (UTRs) ranges in length from 209 to 528 nt and contains a similarly positioned short, AUG-initiated open reading frame (ORF) relative to the 5′ end (Morris and Geballe, 2000).

The 3′ UTRs vary in length from 288 to 506 nt, with some strains of IBV having 3′ UTRs of greater length because of internal sequence duplications (Williams et al., 1993). They possess an octameric sequence of GGAAGAGC upstream of the 3′-terminal poly(A) tail.

### 3.2. MERS-CoV

The genome of MERS-CoV strain was reported to be 30,114 nucleotides (nt), including the 3′ and 5′ UTRs. The MERS-CoV exhibits structural genomic organization of betacoronavirus with the following components: 5′-untranslated region (UTR) (nt 1–272), replicase complex ORF1ab (nt 273–21508), S gene (nt 21450–25511), ORF3 (nt 25526–25837), ORF4a (nt 25846–26175), ORF4b (nt 26087–26827), ORF5 (nt26834 to 27,508), E gene (nt 27584–27832), M gene (nt 27847–28506), N gene (nt 28560–29801), ORF8b (nt 28756–29094), and 3′ UTR (nt 29094–30114) (Fig. 2). The two essential poly-proteins namely pp1ab and pp1a are cleaved into 15/16 non-structural proteins (nsp) by 3CLpro and PLpro. The nsp14 protein functions as proofreading enzyme, thereby curtailing the mutation rates during replication of the genomic RNA of coronavirus (Ziebuhr et al., 2000; Snijder et al., 2003; Gorbalenya et al., 2006; Smith et al., 2013; Raj et al., 2014; Durai et al., 2015). Studies have revealed that the accessory ORF proteins play an important role in MERS-CoV infection and pathogenesis (Menachery et al., 2017).

The MERS-CoV has the potential to adjust and survive in new environments by acquiring various virulence factors and their transfer from one person to other during outbreak (Zumla et al., 2015).
phylogenetic analysis revealed that human and camel MERS-CoV were homologous to each other.

3.3. SARS-CoV-2

SARS-CoV-2 are spherical positive single-stranded RNA viruses that are identified by the presence of S proteins projecting from the virion surface (Neuman et al., 2006; Barcena et al., 2009). The spherical shape of SARS-CoV-2 along with the spike projections led to the name coronavirus from the Latin word “corona” which means “crown”, because of the appearance of the virus as a royal crown under the electron microscope (Neuman et al., 2006; Barcena et al., 2009).

Recent studies have demonstrated that SARS-CoV-2 has a similar genomic organization to other beta-coronaviruses, containing 5′ UTR (265 nt), gene encoding a replicase complex (orf1ab), genes encoding non-structural proteins (nsp), S protein gene, E protein gene, M protein gene, N protein gene, 3′-UTR (229 nt), and other non-structural ORFs (Fig. 3) (Zhu et al., 2020). The S, ORF3a, E, M, and N genes of SARS-CoV-2 comprise 3822, 828, 228, 669, and 1260 nucleotides, respectively (Fig. 3). Similar to SARS-CoV, SARS-CoV-2 carries a predicted ORF8 gene (366 nt in length) found between the M and N ORF genes (Wu et al., 2020a,b). However, SARS-CoV-2 is more diverse from MERS-CoV and SARS-CoV. Recent studies highlighted that SARS-CoV-2 genes share < 80 % nucleotide identity and 89.10 % nucleotide homology with their corresponding genes of SARS-CoV (Zhou et al., 2020; Wu et al., 2020a,b).

The S, M, and E proteins are located in the viral envelope but the N protein interacts with the viral RNA and is present in the core of the viral particle, forming the nucleocapsid (Fehr and Perlman, 2015).

The S protein is a glycosylated protein that is responsible for homotrimeric spikes on the surface of the viral particle and mediates viral entry into host (Bosch et al., 2003). S protein exists as two subunits (S1 and S2) on the viral particle due to cleavage of S protein by host furin-like proteases during viral replication (Bosch et al., 2003; Izaguirre, 2019). The N protein binds with the viral RNA and is involved in packaging of viral RNA into the viral particle during viral assembly (Chang et al., 2006; Hurst et al., 2009). The M protein is one of the most important proteins in the virion structure. It is present in higher quantities than any other protein in the viral particle, while E protein is found in small quantities within the virion (Nal et al., 2005).

Although the source of transmission of SARS-CoV-2 is as yet unclear, it is believed that humans were infected through an unidentified

Fig. 3. SARS-CoV-2 structural and genomic organization. S, M, and E proteins are located in the viral envelope but the N protein interacts with the viral RNA and is present in the core of the viral particle, forming the nucleocapsid. S protein exists as two subunits (S1 and S2) on the viral particle due to cleavage of S protein by host furin-like proteases during viral replication. The SARS-CoV-2 genome has the following genes from 5′ to 3′: replicase open reading frame (ORF) 1ab, S, envelope (E); membrane (M); and N. The figure was made with the help of Biorender.com.
intermediary animal host (possibly bats) followed by intense and rapid spread from human-to humans (Fig. 3 and 4). It is also believed that animals such as dogs, pigs might have served as intermediate host for SARS-CoV-2 (Fig. 4). In the advanced stages, the SARS-CoV-2 virus manifests the symptoms of pneumonia in the patients, which progresses to acute respiratory distress syndrome (ARDS), resulting in the need for life-support to sustain the patient’s life (Gatera and Pavarini, 2020). The current pandemic caused by SARS-CoV-2 is maintaining a sustained progression throughout the world, thus calling for an emergency international alarm for finding an effective cure and vaccine for this infection.

4. Current diagnostics and treatment for coronavirus infections

During SARS-CoV and MERS-CoV outbreaks, diagnostic tools were developed for their accurate detection but they are not effective for detection of SARS-CoV-2. The nucleic acid detection of the viral particle is primarily used in SARS-CoV-2 diagnosis (Wang et al., 2020a, 2020b, 2020c). The collection of upper respiratory nasopharyngeal (NP) swabs for the diagnostic tests has been recommended (Centers for Disease Prevention and Control (CDC, 2020). The Charité algorithm has two steps: the first step involves two reverse transcriptase PCR (RT-PCR) assays for genes encoding E protein and RNA-dependent RNA polymerase (RdRp) of Sarbecovirus subfamily; if both the tests are positive, the sample proceeds to the second step, wherein it is tested for SARS-CoV-2 specific RdRp by RT-PCR (Loeffelholz and Tang, 2020). However, these methods are cost-intensive, and thus cheaper alternatives have been developed to track the symptoms of COVID-19 such as smart-phone surveillance (Dorigatti et al., 2020). Imaging techniques are also used as a diagnostic method in COVID-19, including chest CT scans, which have been commonly used to detect lung abnormalities caused by SARS-CoV-2 infection (Shi et al., 2020; Xu et al., 2020a, b).

The strategies used to halt the propagation of RNA viruses in host cells or tissues include inhibition of RNA transcription, RNA modification, virus packaging enzymes, and the capsid or surface proteins assisting the viral diffusion into the host cells (Dinesh et al., 2020). The current treatment regimen for COVID-19 includes drugs such as remdesivir, chloroquine, arbidol, favipiravir, anti-inflammatory drugs, anti-HIV drugs, and approaches such as interferon therapy, and monoclonal antibodies (Dinesh et al., 2020; Dong et al., 2020). However, there are no specific and completely effective medications against SARS-CoV-2. Although vaccine development against SARS-CoV-2 has been initiated, they are not available yet at the global level. Therefore, researchers are exploring the pool of natural and chemicals compounds that could inhibit the major proteases of the virus or downregulate the rate of propagation of the SARS-CoV-2 virus in the cells.

4.1. Current ongoing trials

Different research institutes and companies worldwide have been working on clinical trials to repurpose existing drugs as well as to develop vaccines and drugs to combat the fast spreading and fatal SARS-CoV-2 (Rudra et al., 2017). For repurposing the existing drugs, randomized controlled trials (RCTs) are being undertaken by various biotechnological companies and research organizations such as National Institutes of Health (NIH), USA to identify disease specific drugs. Clinical trials are underway for major drugs that have the potential to treat COVID-19. Research on traditional medicine is also being undertaken to utilize them in the treatment of COVID-19. Plants provide a natural source of anti-viral inhibitors that can be extended for treatment of diseases caused by SARS-CoV-2. Hence, by repurposing the compounds and extracts from medicinal plants, more innovative and effective drug options can be unveiled for eliminating this viral transmission.
5. Plants with antiviral properties for the treatment of SARS diseases

The Earth is a hub of more than 500,000 plant species, of which 10 % are utilized as food source and 10–15 % as source of drugs (Borris, 1996). Since ancient times, phytomedicine of ethnic communities used to be the basic method of treatment in China (Chang and But, 2014), India (Dev, 1999), Africa and many other countries (Schultes and Rafnaf, 1990). Globally, a major proportion of the world’s populations rely on plant-based medications for primary health care and phyto-compounds as ingredients of drugs (Farnsworth, 1990).

Plants can serve as a wide source of viral protein inhibitors for the treatment of SARS. Plants produce a wide array of secondary metabolites that can possess inhibitory effect on the enzymes, proteins and the propagation of viruses. Secondary metabolites are expressed in response to biotic and abiotic stresses. Some examples include plant active compounds such as flavonoids, carotenoids, and diarylheptanoids. Over centuries, medicinal herbs have been used as a treatment and preventive strategy for several diseases, including respiratory viral infections (Park et al., 2016; Kiran et al., 2020; ul Qamar et al., 2020). The benefit of using these herbs in viral respiratory infections is due to their immune stimulating and inflammation modulating effects to manage the immune system. Although numerous studies have focused on the SARS-CoV and MERS-CoV, there are few studies on cure for COVID-19 disease, which are limited to in silico studies of the phyto-compounds (Mohammadi and Shaghaghi, 2020; ul Qamar et al., 2020).

5.1. Antiviral activity of phyto-compounds against SARS-CoV, MERS-CoV and SARS-CoV-2

Natural medicine is a valuable field of research to extract and establish curative properties. However, limited number of phytochemicals have been systemically reported for their therapeutic potential (De Clercq, 2005; Hostettmann et al., 2000). The antiviral properties of phyto-compounds on SARS-CoV, MERS-CoV and SARS-CoV-2 are summarized below (Table 1): Glycyrrhizin, a bioactive compound of Chinese liquorice (Glycyrrhiza uralensis Fisch), and lycorine isolated from Lycoris radiata L. showed strong anti-SARS-CoV activity (Li et al., 2005). Subsequently, Fiore et al. (2008) extracted glycyrrhizin from Glycyrrhiza glabra and reported that glycyrrhizin is a potent inhibitor of SARS-CoV virus replication, and adsorption and penetration of virus during the early steps of the replicative cycle. The caffeine beverages like green and black tea from Camellia sinensis have bioflavonoids with several medicinal properties. A study reported that water soluble tannic acid and theflavin-3, 3’-digallate inhibit 3CLpro protease of SARS-CoV (Chen et al., 2005). Similarly, the phyto-compounds namely hesperetin, sinigrin, beta-sitosterol, indigo and aloe emodin extracted from Isatis indigotica were found to have an inhibitory effect on the SARS-CoV 3CLpro (Lin et al., 2005).

Quercetin is a flavonoid that is abundant in several plants and food products with a multitude of medicinal and pharmacological properties (Massi et al., 2017). Both quercetin and quercetin 3-β-glucoside possess the ability to inhibit the activity of 3CLpro protease of SARS-CoV in vitro (Chen et al., 2006). Wen et al. (2007) screened 221 phyto-compounds isolated from Chamaecyparis obtusa, Juniperus formosana and Cryptomeria japonica against SARS-CoV and found that certain abietane type di-terpenoids and lignoids have best anti-viral effects. Similarly, bioactive compounds isolated from six herbal extracts namely, Gentiana scabra (dried rhizome), Dioscorea batata (tuber), Cassia tora (dried seed), Taxillus chinensis (leaf), and Cibotium barometz isolated (dried rhizome) exhibited anti-SARS-CoV activity in a cell-based assay on infected Vero E6 cells at concentrations between 25 and 200 μg/mL (Wen et al., 2011). Several independent studies have shown that the compounds such as curcumin, caffeic acid, chalcones, cinnamic acid and betulinic acid isolated from different medicinal plants are potent inhibitors of 3CLpro protease of SARS-CoV (Table 1). Similarly, Jo et al. (2019) showed that flavonoids of Livistona chinensis and herbaceticin isolated and Linum usitatissimum showed inhibition of 3CLpro in MERS-CoV.

Urtica dioica (Stinging nettle) has been used in different countries as traditional medicine for years owing to its therapeutic effects on cardiovascular, immune, nervous and digestive systems (Dhobiabi et al., 2020). Interestingly, lectins extracted from Nicotiana tabacum (tobacco agglutinin; NICTABA), Nicotiana benthamiana, and Urtica dioica exhibit strong inhibitory potential against proliferation of the SARS-CoV (Keyaerts et al., 2007; Zheng et al., 2009; Demurts et al., 2016). Li et al. (2005) showed that extracts of Lycoris radiata possess anti-SARS-CoV activity with a significantly lower dose of effectiveness (about 2.1–2.4 μ g/ml). The antiviral activity of the extracts was attributed to the presence of lycorine in L. radiata (Li et al., 2005).

Phyto-compounds targeting the second major protease PLpro include flavonoids (tomentins) from Paulownia tomentosa (Cho et al., 2013), chalcones from Angelica keiskei (Park et al., 2016), and diarylheptanoids extracted from Alnus japonica (Park et al., 2012), which were reported as potent inhibitors of PLpro of SARS-CoV (Fig. 5). An alternative way to block the activity of the SARS-CoV is to target the spike protein (S) of SARS-CoV S proteins or blocking the human ACE2 receptor. Yi et al. (2004) reported that tetra-O-galloyl β-glucose from Gallia chinensis and luteolin from Veronica linearifolia exhibit strong binding affinity to spike (S) protein of SARS-CoV. Emodin (1,3,8-trihydroxy-6-methylanthraquinone), rhein (1,8-dihydroxy-3-carboxyl-910-anaoltriaquinone), and chrysirin (5,7-dihydroxylavone) are produced in high levels in plants of genus Rheum and Polygonon; these compounds were responsible for blocking the binding of S protein in SARS-CoV to ACE2 (Ho et al., 2007; Fig. 5). Emodin blocked the binding of S protein to ACE2 in a dose-dependent manner (Ho et al., 2007).

5.2. In silico studies on antiviral activity of phyto-compounds against SARS-CoV-2

Owing to the recent occurrence of COVID-19 pandemic and advances in virtual tools and databases available for drug screening, several research groups worldwide have reported in silico screening of phyto-compounds reported for activity against SARS-CoV and other viral diseases. Zingiber officinalis (ginger) is an herbaceous plant native to South Asia belonging to the Zingiberaceae family and has been used in various countries as traditional medicine for years. The phyto-compounds of ginger have been screened for binding the proteins of SARS-CoV-2 (Rathinavel et al., 2020). The phyto-compound 6-gingerol showed the highest binding affinity (-15.7591 kJ/mol) with 5R7Y SARS-CoV-2 main protease, which is essential for replication and propagation of SARS-CoV-2 (Rathinavel et al., 2020). Moreover, 6-gingerol possesses excellent drug likeness with zero violations and very good pharmacokinetic properties, indicating its potential for treating COVID-19.

Organosulfur compounds are found in the plants of the Allium genus such as onions (e.g. Allium cepa), and garlic (Allium sativum). In a recent in silico study, the organosulfur materials such as allyl disulfide and allyl trisulfide from Allium sativum showed significant potential in binding to human ACE2, the target of SARS-CoV-2 (Thuy et al., 2020).

In another study ul Qamar et al. (2020) screened the Chinese medicinal plants library of 32,297 phyto-compounds for potential binding with 3CLpro of SARS-CoV-2 generated by homology modeling. The iso-flavone namely 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone extracted from Pseorotamamus arborescens showed the highest binding affinity with 3CLpro of SARS-CoV-2 (Table 1; ul Qamar et al., 2020). Sampanji-Ramiah et al. (2020) explored the in-silico binding of 27 phyto-compounds (present in spices and condiments used in Indian and other cuisines) to SARS-CoV-2 6LU7 protease (3CLpro) and 6Y2E protease, both of which are required for viral replication. Out of the 27 compounds, 15 showed binding affinity above threshold values for both
Table 1

List of medicinal plants, their habitat, target virus, the constituent antiviral phytocompounds, their classification, and mode of action (if reported) against coronaviruses.

| S No. | Plant | Habitat/ (wild/ cultivated) | Virus | Phyto-Compounds | Classification | Mode of action | References |
|-------|-------|-----------------------------|-------|-----------------|---------------|---------------|------------|
| 1.    | *Zingiber officinale* | Asia, Hawaii, Europe (cultivated) | SARS-CoV-2 | 6-gingerol | Phenolics | *In silico* binding affinity to 5R7Y protease | Rathinavel et al. (2020) |
| 2.    | *Psorothamnus arborescens* | Southwestern North America, desert and dry mountainous habitats (wild) | SARS-CoV-2 | 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone | Flavonoids | Inhibition of 3CLpro | ul Qamar et al. (2020) |
| 3.    | *Lycoris radiata* | China, Korea, Nepal, Japan, United States (cultivated) | SARS-CoV | Lycorine | Alkaloids | Inhibition of virus replication and cellular entry | Li et al. (2005) |
| 4.    | a) *Gentiana scabra* (dried rhizome) b) *Dioscorea batatas* (tuber) c) *Cassia tora* (dried seed) d) *Taxillus chinensis* (leaf) | Found in an apparently wild situation in valleys and on the slopes of hills in China, sunny slopes (wild) Central America (wild) Cambodia, Indonesia, Laos, Malaysia, Philippines, Thailand, Vietnam (wild + cultivated) | SARS-CoV | —— | —— | —— | —— |
| 5.    | *Glycyrrhiza glabra* | Central and South-Western Asia, as well as to the Mediterranean region (wild) | SARS-CoV | Glycyrrhizin | Saponin | Inhibition of virus replication and cellular entry | Fiore et al. (2008) |
| 6.    | a) *Zingiber officinale* b) *Piper longum* L. c) *Syzygium aromaticum* d) *Trogia involutata* L. e) *Anacyclus pyrethrum* f) *Andrographis paniculata* g) *Hygrophiula auriculata* h) *Terminalia chebula* i) *Justicia adhatoda* L. j) *Plectranthus amboinicus* k) *Sauarea lappa* l) *Tsirumpana cordifolia* m) *Clerodendrum serratum* n) *Sida acuta* Burm. f. o) *Cyperus rotundus* L. | Asia, Europe, India (cultivated) India, Malaysia, Nepal, Sri Lanka and Vietnam (wild) Indonesia, India, Pakistan, Sri Lanka, Comoro Islands, Madagascar, Seychelles, and Tanzania (cultivated) Outer Himalayan ranges eastwards to Assam; southwards to Travancore, throughout warmer regions of India (wild) North Africa, Mediterranean region, Himalayas, North Africa, and certain regions in the Arabian peninsula (wild + cultivated) India and Sri Lanka (wild + cultivated) Tropical Asia and Africa, India, Sri Lanka (cultivated) India and China (Yunnan), Sida L., Malaysia, and Vietnam (wild) Indian subcontinent (Assam, Bangladesh, India, Nepal and Sri Lanka), Laos and Myanmar(wild) Southern and Eastern Africa, from South Africa (KwaZulu-Natal) and Swaziland to Angola and Mozambique and north to Kenya and Tanzania, India and Southeast Asia- (cultivated) North Asia- Kashmir and | SARS-CoV-2 | β-sesquiphellandrene; Piperine Eugenol; β-Caryophyllene Stigmasterol Squalene γ-Sitosterol Andrograpanin; 5-Hydroxy-7,8-dimethoxyflavanone Lupeol; Betulin; Chebulagic acid Vasicinone Carvacrol Luteolin Timospongone Bharangin Magnoflorine Cyperene | Terpenoids Alkaloids Phenolics Terpenoids Lipids Terpenoids Flavonoids Betulin Phenolics Terpenoids Alkaloids Lipids Terpenoids Alkaloids Terpenoids | Kiran et al. (2020) |

(continued on next page)
### Table 1 (continued)

| S No: | Plant | Habitat/ (wild/ cultivated) | Virus | Phyto-Compounds | Classification | Mode of action | References |
|-------|-------|-----------------------------|-------|----------------|---------------|---------------|------------|
| 7     | a) Justicia adathoda L | neighboring Himalaya region and also in Garhwal of Uttar Pradesh (wild) Indigenous to tropical regions of the Indian subcontinent (wild) Tropical and sub-tropical parts particularly in Bengal, Odisha and peninsular India (cultivated) Central America, northern Australia (wild) Africa, southern and central Europe to France and Austria, and southern Asia (wild) | SARS-CoV-2 | Vasicine | Alkaloids | In silico | Kiran et al. (2020) |
| b) Carica Papaya | | | | | | | |
| c) Andrographis paniculata Burm | | | | | | | |
| d) Ocimum tenuiflorum | | | | | | | |
| e) Melia azedarach | | | | | | | |
| 8     | a) Chamaecyparis obtuse | Central Japan in East Asia, northern hemisphere (cultivated) | SARS-CoV | Ferruginol; Dehydroabieta-7-one; Sugiol; 8β-hydroxyabieta-9 (11); 6,7-dehydrooryzaneone; Pinusulic acid; α-cadinol; Hinokinin; Savinin 3β,12-diacetoxyabieta-681,113-Tetraene; Cedrane-312-diol; Betulonic acid; Cryptojaponol; 7p-Hydroxydeoxycryptojaponol; Lectin | Terpenoids | Inhibition of 3CLpro | Wen et al. (2007) |
| b) Juniperus formosana | China (from Tibet in the west to Zhejiang in the east) and in Taiwan (cultivated) Japan, China, India (cultivated) | SARS-CoV | Lactone | Terpenoids | Inhibition of 3CLpro | | |
| c) Cryptomeria japonica | Central Japan in East Asia, northern hemisphere (cultivated) | SARS-CoV | Lactone | Terpenoids | Inhibition of 3CLpro | | |
| 9     | Utrica dioica | Europe, Asia and western North Africa, it is now found worldwide, including New Zealand and North America (wild + cultivated) | SARS-CoV | Allyl disulfide; Allyl trisulfide | Organosulfur | Inhibition of Spike (S) protein | Keyaerts et al. (2007); Van der Meer et al. (2007), Kumaki et al. (2011) |
| 10    | Allium sativum | Central Asia and northeastern Iran (wild + cultivated) | SARS-CoV | Chalcone | Flavonoids | Inhibition of ACE2 receptor | Thuy et al. (2020) |
| 11    | Angelica keiskei | Japan, where it is found on the Pacific Coast (wild) | SARS-CoV | Betulinic acid | Terpenoids | Inhibition of 3CLpro and PLpro | Park et al. (2016) |
| 12    | Betula pubescens | Northern Europe and northern Asia (wild) | SARS-CoV | Tetra-O-galloyl β-D-glucose | Phenolics | Inhibition of S protein | Wen et al. (2007) |
| 13    | Galla chinensis | Asia (China) (wild) | SARS-CoV | Hirsutene; Hirsutanol; Oregonin; Rubrocan; | Diarylheptanoids/ Phenolics | Inhibition of PLpro | Yi et al. (2004) |
| 14    | Alnus japonica | Japan, Korea, Taiwan, eastern China, and Russia (cultivated) | SARS-CoV | Hirsutene | Terpenoids | | Park et al. (2012) |
| S No | Plant                      | Habitat/ (wild/ cultivated) | Virus     | Phyto-Compounds          | Classification | Mode of action | References                |
|------|----------------------------|-----------------------------|-----------|--------------------------|----------------|----------------|---------------------------|
| 14   | Curcuma longa             | Southern Asia especially    | SARS-CoV  | Rubranside B; Rubranside A | Phenolics      | Inhibition of 3CLpro | Wen et al. (2007)         |
|      | latais                    | India (cultivated)          |           | Curcumin                 |                |                |                           |
| 15   | Camellia sinensis         | East Asia, and probably in  | SARS-CoV  | Theaflavin-3,3’-digallate | Phenolics      | Inhibition of 3CLpro | Chen et al. (2005)        |
| (Black tea) | in the borderlands of north |           |           |                          |                |                |                           |
|       | Burma and southwestern    |                               |           |                          |                |                |                           |
|       | China (cultivated)        |                               |           |                          |                |                |                           |
| 16   | Nicotiana benthamiana     | Australia (cultivated)      | SARS-CoV  | NiCTABA; Lectin          | Viral growth   | Inhibition of 3CLpro | Zheng et al. (2009);     |
|      |                           |                               |           |                          | inhibitor      |                | Demursus et al. (2016)    |
| 17   | Houttuynia cordata        | Southeast Asia (cultivated) | SARS-CoV  | –                        | Phenolics      | Inhibition of 3CLpro | Lau et al. (2008); Fung   |
|      | (cultivated)              |                               |           |                          |                |                | et al. (2011)             |
| 18   | Litchi chinensis          | Native to the Guangdong     | MERS-CoV  | Flavonoids               | Inhibition of 3CLpro | Kim et al., 2019 |
|       | and Fujian, India, other  |           |           |                          |                |                |                           |
|       | countries in Southeast    |                               |           |                          |                |                |                           |
|       | Asia (cultivated)         |                               |           |                          |                |                |                           |
| 19   | Rhizoma Cibotii           | China (wild)                | SARS-CoV  | –                        | Phenolics      | Inhibition of 3CLpro | Wen et al. (2011)         |
| 20   | Polygonum multiflorum     | Central and southern China, | SARS-CoV  | Emodin                    | Phenolics      | Inhibition of ACE2  | Ho et al. (2007)          |
| Thunb. | Eastern Asia and the Russian |           |           |                          |                | receptor,         |                           |
|       | Far East, Europe and North |                               |           |                          |                | inhibition of S   |                           |
|       | America (wild)            |                               |           |                          |                | protein          |                           |
| 21   | Rheum officinale          | China (wild-cultivated)     | SARS-CoV  | Emodin                    | Phenolics      | Inhibition of ACE2  | Ho et al. (2007)          |
|      | (cultivated)              |                               |           |                          |                | receptor,         |                           |
|       |                           |                               |           |                          |                | inhibition of S   |                           |
|       |                           |                               |           |                          |                | protein          |                           |
| 22   | Veronica litorifolia      | Northern Hemisphere, though | SARS-CoV  | Luteolin                 | Flavonoids     | Inhibition of S   | Yi et al. (2004)          |
|      |                           | with some species from the   |           |                          |                | protein          |                           |
|       |                           | Southern Hemisphere         |           |                          |                |                |                           |
|       |                           | (cultivated)                |           |                          |                |                |                           |
| 23   | Paulownia tomentosa      | Central and western China,  | SARS-CoV  | Tomentin A; Tomentin B;  | Flavonoids     | Inhibition of PL   | Cho et al. (2013)         |
|      |                           | North America, Eastern USA  |           | Tomentin C; Tomentin D; |                |                 |                           |
|       | (wild)                    | (wild)                      |           | Tomentin E                |                |                 |                           |
| 24   | Stephanos cepharaanthra  | Eastern and southern Asia    | SARS-CoV  | Cepharanthine             | Alkaloids      | Viral Growth     | Chattopadhyay (2006)      |
| Hayata | and Australia (wild)      |                               |           |                          |                | inhibitor        |                           |
| 25   | Myrica faya               | Macaronesia (the Azores,    | SARS-CoV  | Myricetin                 | Flavonoids     | Inhibition of Helicace,| Yu et al. (2012)          |
|       |                           | Madeira, and the Canary      |           |                          |                | nsp13            |                           |
|       |                           | Islands), western coastal   |           |                          |                |                |                           |
|       |                           | mainland Portugal (         |           |                          |                |                |                           |
|       |                           | cultivated)                 |           |                          |                |                |                           |
| 26   | Scutellaria laeviflora    | North America (wild)        | SARS-CoV  | Scutellarein              | Flavonoids     | Inhibition of Helicace,| Yu et al. (2012)          |
|      |                           |                             |           |                          |                | nsp13            |                           |
| 27   | Ixora indica              | Europe, especially in        | SARS-CoV  | Hesperetin; Sinigrin;    | Flavonoids     | Inhibition of 3CLpro | Lin et al. (2005)         |
|      |                           | Western and Southern Europe,|           | Beta-sitosterol;         | Glucosinolates |                 |                           |
|       |                           | China, England, Germany      |           | Aloeemodin                | Lipids         |                 |                           |
|       |                           | and France (wild)           |           |                          | Phenolics      |                 |                           |
| 28   | Torreya xucifera          | Southern Japan and to South  | SARS-CoV  | Amentoflavone             | Flavonoids     | Inhibition of 3CLpro | Ryu et al. (2010)         |
|       |                           | Korea’s Jeju Island (wild-   |           |                          |                |                 |                           |
|       |                           | cultivated)                 |           |                          |                |                 |                           |
| 29   | Cinnamomum cassia         | Southern China, South and    | SARS-CoV  | Procyanidin A2; Procyanidin B1; | Flavonoids     | Viral growth     | Zhuang et al. (2009)      |
|       |                           | Southeast Asia (India,      |           | Cinnamomum cassia (       |                | inhibitor        |                           |
|       |                           | Indonesia, Laos, Malaysia,  |           | (cultivated)             |                |                 |                           |
|       |                           | Thailand, and Vietnam) (     |           |                          |                |                 |                           |
|       |                           | (cultivated)                |           |                          |                |                 |                           |
| 30   | Linum usitatissimum       | Syria, Switzerland and      | MERS-CoV  | Herbacetin                | Flavonoids     | Inhibition of 3CLpro | Kim et al., 2019          |
|       |                           | Germany, India, China       |           |                          |                |                 |                           |
|       |                           | (cultivated)                |           |                          |                |                 |                           |
| 31   | Laurus nobilis           | Mediterranean region         | SARS-CoV  | β-elemene; 1,8-cineole;  | Terpenoids     | Viral Growth      | Loizzo et al. (2008)      |
|       |                           | (cultivated)                |           | α-pinene; β-pinene       |                | inhibitor        |                           |
| 32   | Nicotiana tabacum         | Caribbean, tropical and     | SARS-CoV  | Viral growth              | Viral growth   | Zheng et al. (2009);|                           |
|       |                           | subtropical America         |           | inhibitor                 | inhibitor      | Wang et al. (2005);|                           |
|       | (cultivated)              | (cultivated)                |           |                          |                | Franco et al. (2016);|                           |
|       |                           |                               |           |                          |                | Sampangi-Ramaiah et al. (2020) |                   |
| 33   | Thymus vulgaris           | Southern Europe from the    | SARS-CoV  | Ursolic acid              | Terpenoids     | In silico binding |                           |
|       |                           | western Mediterranean to    |           |                          |                | affinity to 6LU7 and|                           |
|       |                           | southern Italy (cultivated) |           |                          |                | 6TY2E proteases  |                           |

(continued on next page)
the proteases. The key compounds with high binding affinity to 6LU7 and 6Y2E proteases include coriandrin (component of the essential oil of *Coriandrum sativum* widely in Indian cuisines across both north and south India), ursolic acid of *Thymus vulgaris*, rosmarinic acid of *Rosmarinus officinalis* and glucobrassicin of *Brassica juncea* (Sampangi-Ramaiah et al., 2020).

Siddha medicine is widely used in Southern India, which prescribes a concoction called Kabasura kudineer chooranam for cold, cough, and fever (Kiran et al., 2020). Molecular docking studies were performed for 32 phytochemical constituents of herbs present in Kabasura kudineer chooranam and 05 phytochemical constituents of herbal formulation named JACOM against spike protein (S) of SARS-CoV-2 (PDB ID: 6VSB) to observe the molecular interactions between target protein and ligands. All the phytochemical analogs were successfully docked with S protein of SARS-CoV-2 (Kiran et al., 2020; Table 1).

Recently, Rolta et al. (2020) reported molecular docking studies of 100 major phytocompounds of ten selected medicinal plants (*Rheum emodi*, *Thymus serpyllum*, *Cymbopogon citratus*, *Moringa oleifera*, *Thalictrum foliolosum*, *Berberis aristata*, *Piper nigrum*, *Allium sativum*, *Myristica fragrans* and *Zanthoxylum armatum*) for interaction with RNA binding domain (N-terminal Domain/ NTD; PDB 6VYO) of nucleocapsid phosphoprotein of SARS-CoV-2. The molecular docking study revealed that five phytocompounds namely emodin, anthrarufin, alizarine, aloe-emodin and dantron of *Rheum emodi* showed effective binding affinity and pharmacokinetic properties with NTD of RNA binding domain of nucleocapsid phosphoprotein of SARS-CoV. The figure was made with the help of Biorender.com.

| S No: | Plant | Habitat/ (wild/ cultivated) | Virus | Phyto-Compounds | Classification | Mode of action | References |
|-------|-------|-----------------------------|-------|----------------|---------------|---------------|------------|
| 34.   | *Coriandrum sativum* | Southern Europe and Northern Africa to Southwestern Asia(wild and cultivated) | SARS-CoV-2 | Coriandrin | Phenolics | In silico binding affinity to 6LU7 and 6Y2E proteases | Sampangi-Ramaiah et al. (2020) |
| 35.   | *Rosmarinus officinalis* | Mediterranean region (wild and cultivated) | SARS-CoV-2 | Rosmarinic acid | Phenolics | In silico binding affinity to 6LU7 and 6Y2E proteases | Sampangi-Ramaiah et al. (2020) |
| 36.   | *Brassica juncea* | Northwest Eastern Island, Midway Atoll, Hawaii, USA, India (wild and cultivated) | SARS-CoV-2 | Glucobrassicin | Glucosinolates | In silico binding affinity to 6LU7 and 6Y2E proteases | Sampangi-Ramaiah et al. (2020) |

Fig. 5. Summary of phytocompounds and their mode of action on coronaviruses. The targets of different phytocompounds is depicted as follows: a. Emodin, allyl disulfide, allyl trisulfide, and tetra-O-galloyl β-D-glucose inhibit ACE2 receptor binding to spike protein; b. Ferruginol, 3β,12-diacetoxyabieta-6(8),11(13)-tetraene, and cryptojaponol inhibit virus replication; c. Flavonoids, caffeic acid, cinnamic acid, herbacetin, and hesperetin, and ursolic acid inhibit 3CLpro; d. Flavonoids, chalcones, and diarylheptanoids inhibit PLpro; e. Tetra-O-galloyl β-D-glucose, luteolin, terpenoids, carotenoids, ursolic acid and phytosterols target coronavirus spike protein; f. Quercetin and glycyrrhizin inhibit the cellular entry of SARS-CoV. The figure was made with the help of Biorender.com.
Fig. 6. Structure of various classes of phytocompounds with anti-viral potential against coronaviruses studied by *in vitro*, *in vivo*, and *in silico* approaches. The PubChem CID of each compound is indicated in parenthesis. A: Alkaloids; B: Terpenoids; C: Flavonoids; D: Phenolics; E: Phytosterols; F: Glucosinolates; G: Organosulfur compounds; H: Saponins (Source: Table 1). Structures were obtained from pubchem.ncbi.nlm.nih.gov.
treating other ailments in humans, revealing their multi-dimensional pharmacological properties. Analysis of the targets and mechanism of action of the phytocompounds indicates a broad spectrum of targets on both coronaviruses and the host receptors (Fig. 5). These include blocking of ACE2 receptor binding by spike protein, inhibition of viral proteases, inhibition of viral replication, targeting coronavirus spike protein, and blocking viral entry into host (Fig. 5; Table 1). With ongoing research for COVID-19 therapeutics, the list of anti-viral phytocompounds is certainly dynamic with more anticipated updates.

6. Conclusions

Over the past few decades, there has been a huge demand to decipher the root of coronavirus infections not only in animals but also in humans. As a complementary approach, the search for new antiviral drugs of natural origin has gained momentum. Currently, COVID-19 has emerged as the most intense and petrifying viral infectious disease all over the world to be handled by the human race.

Based on the high degree of homology of the genome (> 96 %) and the receptors of SARS-CoV and SARS-CoV-2, this review was attempted to summarize the plant species and their bioactive compounds with antiviral potential against coronaviruses, which can be used as anti-SARS-CoV-2 agents. The literature review suggested more than 70 compounds from 62 plant species with anti-viral activity against coronaviruses that might exhibit treatment potential for COVID-19 disease. Several of these anti-viral activities have been predicted from studies on molecular docking of bioactive compounds of different medicinal plants with proteases and spike protein of SARS-CoV-2. Moreover, the anti-viral phytocompounds identified from in-silico studies also showed good drug-likeliness properties. Thus, the phytocompounds identified from in-silico studies can be validated by in vitro, in vivo and clinical studies against SARS-CoV-2. To assure public safety and control of infection in the event of a re-emergence of COVID-19, effective anti-SARS-CoV agents and treatments are highly desirable and imminent in the immediate and near future. The findings of this review will provide a reservoir of natural compounds for researchers world-wide focusing on drug discovery for COVID-19. The literature on anti-viral potential of phytocompounds will also pave way for

![Fig. 6.](continued)
experimental affirmation of several traditional and natural medicine in use for centuries in several sections of the world.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgement

We acknowledge Prem Kumar Khosla, Vice Chancellor, Shoolini University, and Yeast Biology lab for support and encouragement.

References

Akram, M., Tahir, I.M., Shah, S.M.A., Mahmood, Z., Afza, A., Ahmad, K., Mehboob, H., 2018. Antiviral potential of medicinal plants against HIV, HSV, influenza, hepatitis, and coxsackievirus: a systematic review. Phytother. Res. 32 (5), 811–822.

Anand, K., Yang, H., Bartlam, M., Rao, Z., Hilgenfeld, R., 2005. Coronavirus main protease: target for antiviral drug therapy. Coronaviruses With Special Emphasis on First Insights Concerning SARS. Birkhauser Basel, pp. 173–199.

Bier-Santos, Y.M., John, S.E.S., Mesecar, A.D., 2015. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. Antiviral Res. 115, 21–38.

Balachandar, V., Mahalaxmi, I., Kaavya, J., Vivekanandhan, G., Ajithkumar, S., Arul, N., 2020. Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific SARS-CoV-2 spike protein ligand docking programs by fitness accuracy. Front. Plant Sci. 7, 54.

Banegas, A.J., Cerón-Carrasco, J.M., Perez-Sánchez, H., 2018. A review of ligand-based virtual screening web tools and screening algorithms in large molecular databases in the age of big data. Future Med. Chem. 10 (22), 2641–2658.

Bércena, M., Ostergotel, G.T., Bartelink, W., Faas, F.G., Verkleij, A., Rottier, P.J., 2009. Cryo-electron tomography of mouse hepatitis virus: insights into the structure of the coronavirus. Proc. Natl. Acad. Sci. U.S.A. 106 (2), 582–587.

Barraza, D., Gattuso, G., Bellocco, E., Calderaro, A., Trombetta, D., Smeriglio, A., Naiberi, S.M., 2017. Flavanones: Citrus phytochemicals with health-promoting properties. BioFactors 43 (4), 495–506.

Borris, R.P., 1996. Natural products research: perspectives from a major pharmaceutical company. J. Ethnopharmacol. 51 (1–3), 29–38.

Bosch, B.J., van der Zeijl, E., De Haan, C.A., Rottier, P.J., 2003. The coronavirus spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 176, 104742.

Bosch, B.J., 2009. Cryo-electron tomography of mouse hepatitis virus: insights into the age of big data. Future Med. Chem. 10 (22), 2641–2658.

Bosch, B.J., 2003. The coronavirus spike glycoprotein with ligands and its implication to drug design against SARS. Biochem. Biophys. Res. Commun. 308 (1), 148–151.

Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N.G., Decroly, E., 2020. The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Res. 176, 104742.

Dalgia, M., 2012. Polyphenols as antimicrobial agents. Curr. Opin. Biotechnol. 23 (2), 174–181.

De Clercq, E., 2005. Recent highlights in the development of new antiviral drugs. Curr. Opin. Microbiol. 8 (5), 552–560.
