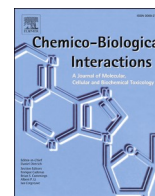




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Role of phytoconstituents in the management of COVID-19

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ABSTRACT

Background: COVID-19, a severe global pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has emerged as one of the most threatening transmissible disease. As a great threat to global public health, the development of treatment options has become vital, and a rush to find a cure has mobilized researchers globally from all areas.

Scope and approach: This review focuses on deciphering the potential of different secondary metabolites from medicinal plants as therapeutic options either as inhibitors of therapeutic targets of SARS-CoV-2 or as blockers of viral particles entry through host cell receptors. The use of medicinal plants containing specific phytoconstituents could be seen in providing a safer and long-term solution for the population with lesser side effects.

Key Findings and Conclusions: Considering the high cost and time-consuming drug discovery process, therapeutic repositioning of existing drugs was explored as treatment option in COVID-19, however several molecules have been retracted as therapeutics either due to no positive outcomes or the severe side effects. These effects call for exploring the alternate treatment options which are therapeutically effective as well as safe. Keeping this in mind, phytopharmaceuticals derived from medicinal plants could be explored as important resources in the development of COVID-19 treatment, as their role in the past for treatment of viral diseases like HIV, MERS-CoV, and influenza has been well reported. Considering this fact, different phytoconstituents such as flavonoids, alkaloids, tannins and glycosides etc. Possessing antiviral properties against coronaviruses and possessing potential against SARS-CoV-2 have been reviewed in the present work.

1. Introduction

The ongoing global COVID-19 pandemic still remains a major challenge for scientific communities since its outbreak in December 2019 and has become one of the major causes of mortality and morbidity in large populations. As of June 19, 2020, the World Health Organization (WHO) reported that 213 countries and territories have been affected from this deadly infectious disease originated from Wuhan, China with 8,585,194 infected and 456,439 death cases confirmed worldwide Fig. 3 [1]. COVID-19 has not only affected the global health care system but also hampered the economic growth of the countries along with changes in the normal lifestyle and habits [2,3]. COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is recognized

as a communicable and deadly respiratory illness, which begins with normal common cold symptoms and become adverse with course of time leading to fever, dry cough and shortness of breath [4,5]. Certain morbidity factors such as hypertension, cardiovascular diseases, diabetes mellitus, pollution and age increase the risk of COVID-19 [6,7].

Coronavirus was first discovered in animals and birds commonly in bats and cats in mid-1960s and found to spread to human by zoonotic transmission [8,9]. The coronaviruses went unrecognised globally until the SARS-CoV pandemic emerged in 2002–03 in Guangdong China, which caused severe acute respiratory syndrome (SARS) infecting more than 8000 people with 800 deaths, followed by Middle east respiratory syndrome (MERS-CoV) which emerged in 2012 in Saudi Arabia infecting nearly 2300 people with 850 deaths [10,11]. At the end of December

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Table 1
Comparative data of SARS-CoV, MERS-CoV and SARS-CoV-2 [14,17,18].

	SARS-CoV	MERS-CoV	SARS-CoV-2
Origin	Southern China	Saudi Arabia	Wuhan, China
Host	Palm civets	Camel	Not known
Transmission	Through close contacts between human to human	Touching infected camels or consuming their milk or meat	Human to human transmission through close contacts
Symptoms (major)	Fever, dry cough, headache, difficulty in breathing, muscle aches, loss of appetite, diarrhoea	Fever, chills, diarrhoea, nausea, vomiting, sneezing, congestion, sore throat	Fever, fatigue, cough, shortness of breath
Incubation Period	2-7 days	5-6 days	2-14 days
Recovery Treatment	5-6 weeks No vaccines available, antiviral medicines	6-7 weeks No vaccines available, only drugs for symptoms are available	2-8 weeks No vaccines available, only existing drugs are in use for symptoms
Countries effected	29	26	>140
Fatality Rate	9.5%	34.4%	2.3%

2019, a novel coronavirus infected several numbers of people in Wuhan, China. On January 2020, this novel virus was named as 2019-nCoV officially by WHO and in the same month, several countries became the victim of this deadly infectious virus [12]. Therefore, we can say that

coronavirus mediated infections occur periodically in different areas of the world. The 2019 novel coronavirus shows 88% sequence similarity with bat derived SARS-CoV and 50% similarity with MERS-CoV [13]. WHO estimated the reproductive number (R_0) for SARS-CoV-2 between 2 and 2.5 higher than the SARS-CoV which is 1.7-1.9 and MERS with <1 , thus a higher potential of spreading with mortality rate of COVID-19 is 2.3% which is less than that of SARS (~9.5%) and MERS (34.4%). According to various genomic and in vitro analyses, it is clear that SARS-CoV-2 shares same host cell entry receptor as SARS-CoV, i.e., angiotensin converting enzyme-2 (ACE-2) while MERS-CoV uses dipeptidyl peptidase (DPP4). Similar to earlier SARS-CoV and MERS-CoV, the novel SARS-CoV-2 infects part of lungs and thus causes bilateral peripheral pneumonia with multiple organ failures and thus has been declared more contagious than earlier SARS and alveolar MERS [14-16]. Table 1 includes the comparative data between SARS-CoV, MERS-CoV and SARS-CoV-2 in terms of their origin, host, transmission, symptoms, incubation period, recovery, etc.

1.1. Family of coronaviruses

According to International Committee on Taxonomy of Viruses, coronaviruses come under subfamily of Coronavirinae from the family Coronaviridae and order Nidovirales (Fig. 1) [19]. The Coronavirinae subfamily is further divided into four genera, i.e., alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus [20]. First two infect only mammals and rest infect birds and in some case mammals too. The alpha-coronaviruses include human coronavirus NL63 (HCoV-NL63), porcine transmissible gastroenteritis coronavirus

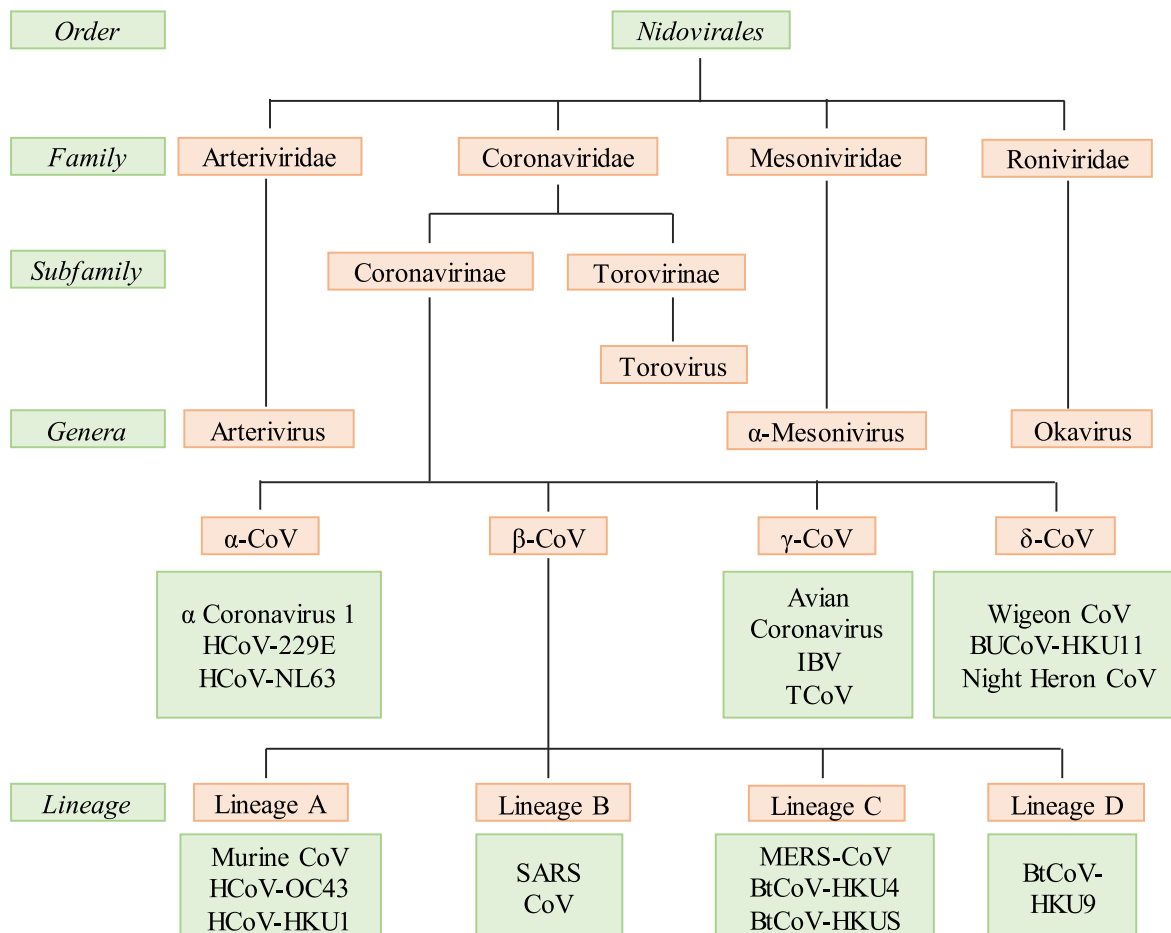


Fig. 1. Family of coronaviruses.

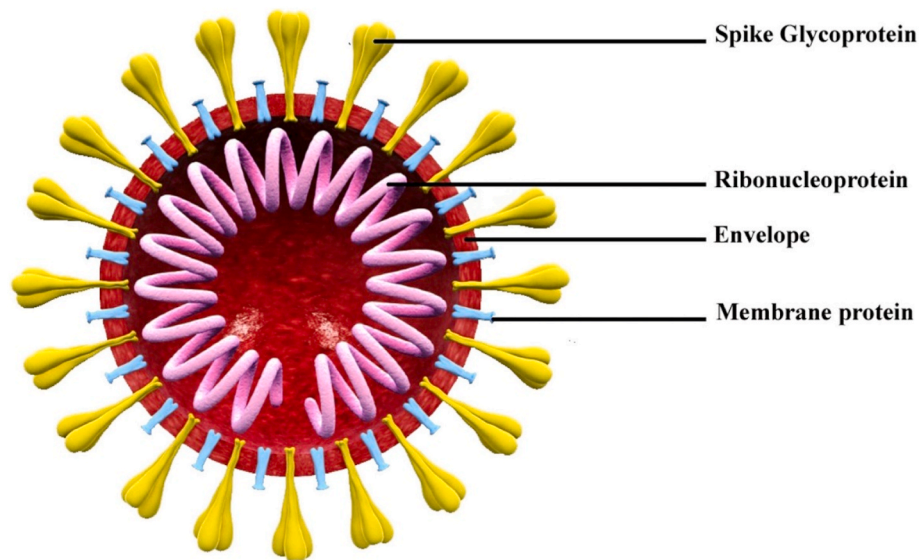


Fig. 2. Schematic diagram of SARS-CoV-2 structure. Reproduced from Ref. [29] with permission from Elsevier.

(TGEV), PEDV, and porcine respiratory coronavirus (PRCV), whereas the beta-coronaviruses include SARS-CoV, MERS-CoV, bat coronavirus HKU4, mouse hepatitis coronavirus (MHV), bovine coronavirus (BCoV), and human coronavirus OC43. The gamma-and delta-coronaviruses include avian infectious bronchitis coronavirus (IBV) and porcine delta-coronavirus (PdCV), respectively [21]. The alpha-coronaviruses and beta-coronaviruses result into pulmonary illness in humans and cholera infantum in animals [22]. MERS-CoVs are deadly pathogenic viruses causing serious respiratory problem in humans, while other viruses like SARS-CoV and HCoV- NL63, HCoV-229E, HCoV-OC43 and HKU1 do not result into critical conditions compared with the earlier. Domestic animals are the sources for transmission of these viruses from natural host to humans [23]. Data collected from various databases show that all the human coronaviruses originated from animals such as SARS-CoV, MERS-CoV, HCoV-NL63 and HCoV-229E originated from bats [24]. These studies concluded that bats are mainly responsible for transmission of these. SARS-CoV-2 also has been found to be originated

from bats and further spread to human by zoonotic transmission according to reports published [25].

The SARS-CoV-2 is a single stranded, enveloped, large positive sense RNA virus with a size of nearly 125 nm and genome size of 27–32 kb [17]. The virus contains four structural proteins i.e., envelope protein (E), membrane protein (M), spike protein (S) and nucleocapsid protein (N) (Fig. 2). Viral genome is packed within nucleocapsid (N) with a shell of envelope outside [26]. This envelope is associated with other three structural proteins (M, S, and E) having different functions; the membrane protein is a transmembrane glycoprotein which helps the virus in developing capsid and structure assembly whereas envelope protein is involved in virus packaging and spike protein helps entry into host cells [27]. The spikes are responsible for the formation of large protrusion and thus gives them the shape of crown and hence the name corona meaning crown in Latin [28].

Currently there is no specific treatment for this deadly infectious disease except quarantine and symptomatic treatment protocol for

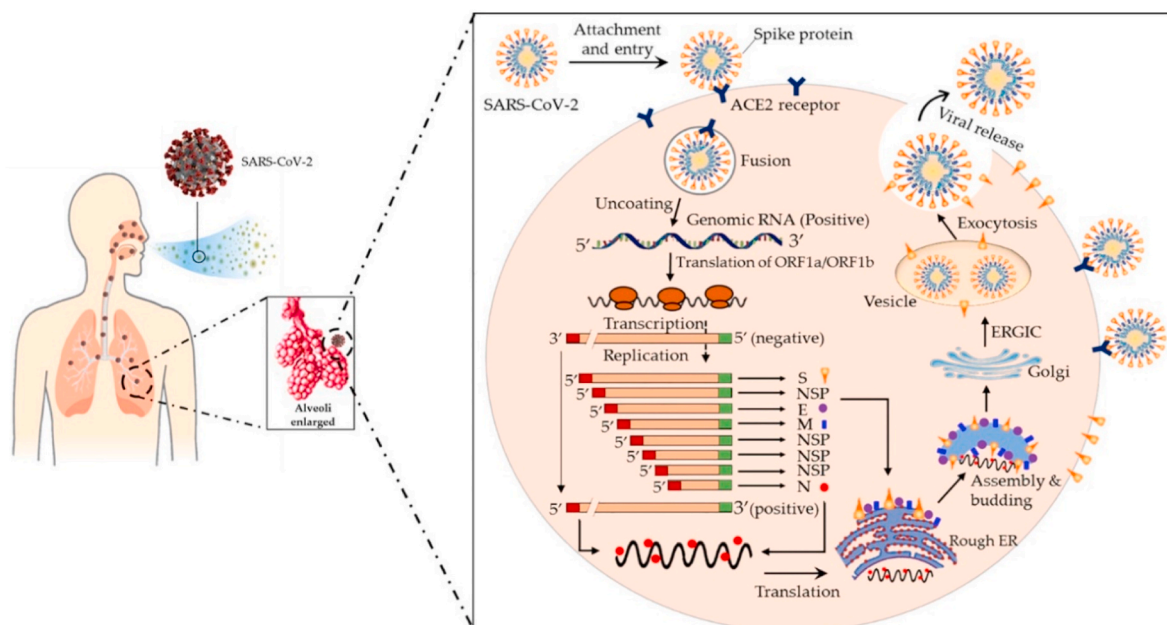


Fig. 3. Schematic diagram of coronavirus infection. Reproduced from Ref. [12] with permission from Elsevier.

disease management [29]. As it is clear from different reports that the sequence homology of SARS-CoV and SARS-CoV-2 is nearly similar but the transmission efficiencies are different which are probably due to changes in the nucleotide sequences in spike protein (S) and receptor binding domain [30]. Medical practitioners are using existing drugs for controlling the symptoms and a community of researchers globally are involved in developing new drug modalities and vaccines since past 8 months, however no success has been met so far and it may still take months to years in developing the same [31]. Considering the high virulence of SARS-CoV-2, it is imperative to develop new preventive or therapeutic agents at the earliest to control the current pandemic situation. Bioactive molecules from plants have served as invaluable sources of different therapeutic drugs and are being used in the treatment of various diseases around the world. Medicinal plants are also being explored in management of COVID-19 pandemic in two ways, i.e., either as immunomodulators or viral target inhibitors based on their established roles in managing other viral diseases. The secondary metabolites and other chemical compounds from plants could prove as promising therapeutic agents as antiviral either by inhibiting the viral replication or viral cell entry and/or otherwise treating the underlying infection caused by SARS-CoV-2 and thus could prove a safer and innovative treatment for this viral infectious disease [32–35].

This review has thus been planned to list the potential phytochemicals and their plant sources which can be used as inhibitor molecules targeting either the host cell or SARS-CoV-2 therapeutic receptors in providing a safer and long-term solution for the population with lesser side effects.

1.2. Coronavirus infection mechanism

The SARS-CoV-2 share some sequence homology with SARS-CoV but show different transmission potential and infection range [36]. The ongoing COVID-19 disease is seen as more treacherous with still no treatment and could be potentially due to certain functional mutations occurring in the SARS-CoV-2. The major differences observed in SARS-CoV-2 are absent 8a, longer 8b and shorter 3b segments and different Nsp-2 and -3 proteins. Along with these, the open reading frames are also different in some places like in orf8 and orf10 [17]. The process of infection is totally dependent on the interaction between virus and the host cell and begins when the viral particles get attached to the cell surface receptor of the host cell and it delivers the nucleocapsid inside the target cell membrane. The main function is provided by S-protein in binding and fusion with the host cell membrane. SARS-CoV-2 binds with the same receptor ACE-2 present in respiratory epithelium and alveoli of lungs, as SARS-CoV. Fusion takes place because of gain of conformational changes by the spike protein and the process depends upon two factors i.e., pH acidification and proteolytic activation [36–39] (Fig. 3). The S-protein is homotrimeric with each subunit having two domains S1; the receptor binding domain and S2; the membrane fusion domain enabling the virus to enter the host cell. After fusion, the cleavage of fusion protein is the prime event for further process of infection and it is the main characteristic of class I viral fusion proteins [40].

S protein is cleaved by proteases into two domain S1 and S2, of which S2 domain is responsible for entering fusion protein inside the membrane of host cell and ultimately facilitating the entry of virus into the cell [17,36]. Unlike SARS-CoV-2, some coronaviruses like MHV-2 and SARS-CoV do not need cleavage of spike protein for entering purpose, they can directly enter inside the cell with the presence of exogenous proteases and this process is 100–1000 fold efficient than the endosomal pathway. Proteases like transmembrane protease/serine family (TMPRSS) and human airway trypsin like protease (HAT) both induce the fusion of SARS-CoV-2 [41,42]. Once the fusion occurs and fusion protein enters the host cell, ACE-2 gets cleaved and it is covered by ADAM17 in extra membranous space which convert angiotensin I to angiotensin II, a negative regulator of renin angiotensin pathway and

this reduced ACE-2 is responsible for respiratory injury and illness [43]. Once viral protein gets translated into the cell, various pathways gets activated and are associated with spreading of infection. An ORF3a protein code for Ca^{+2} ion channel and activates transcription of NF- κ B pathway by interacting TRAF3. The ORF8b protein activates the inflammasome pathway through NLRP3. All these pathways result in overproduction of cytokines and thus cause respiratory problems. JNK pathway is also activated by ORF3a, ORF3b and ORF7a which is responsible for lung disorders [17,44,45]. The viral infection can be minimized if the virions do not bind to the cell and this can be done by inactivating the virus. SARS-CoV-2 binds more strongly to the receptor ACE-2 than the SARS-CoV and therefore infection transmission rate and virulence is much higher than the SARS-CoV [46]. TMPRSS2 associated with ACE-2 is responsible for spreading the infection at initial stages and thus could be another therapeutic target for the new drug discovery [47].

1.3. Therapeutic targets

Currently there are no approved specific treatments or drugs to treat COVID-19 except the clinical management such as infection prevention, control measures and life supportive care [48]. The prevailing conditions of current pandemic such as re-emergence of infection cases, uncontrolled transmission and morbidity associated with the disease are crippling the healthcare systems with grave effects on the global economies and posing a challenging situation for health practitioners and scientists to identify the therapeutic strategies to handle this problem [49]. Therapeutic repurposing of existing drugs like anti-malarials, antivirals, and NSAIDs etc., has been used as an effective approach in management of COVID-19 with drugs inhibiting either the different viral receptors/enzymes or the host cell receptors. Identification of drug targets (viral or host cell) remains one of the important criteria for the discovery of new molecules as well as to check the therapeutic efficacy of existing drug molecules [13,50]. The below section briefly enlists the potential therapeutic targets along with the current drugs repurposed towards these targets.

1.4. Angiotensin converting enzyme-2 (ACE-2)

ACE-2 is the functional receptor of SARS-CoV-2 and is a negative regulator of renin angiotensin system (RAS) [51]. The S-proteins of SARS-CoV-2 get attached with ACE-2 receptor of the host cell in a much stronger manner compared to the SARS-CoV thus producing higher pathogenicity [52]. Many reports have suggested that ACE-2 could be one of the possible COVID-19 targets as it can block the binding of the virus with the host cell and thus blocking the viral cell entry. Therapeutic options for blocking the viral entry utilizing neutralizing antibodies such as soluble receptor binding domain that could occupy ACE-2 and soluble ACE-2 are envisaged as possible viral trap and thus inactivators of SARS-CoV-2 [53]. Despite the initial controversy on use of ACE inhibitors and angiotensin receptor blockers (ARBs) in hypertensive COVID-19 patients, several clinical findings have recommended their continued use during infection treatment as these drugs possess anti-inflammatory activities as well as inhibit platelets aggregation and thus preventing clot formation seen in COVID-19. Besides synthetic products, some natural products such as amentoflavone, chrysanthemin, and biovobin have shown good binding affinity towards ACE-2 [54,55].

Choroquine (CQ), a well-known anti-malarial drug has been explored for prophylactic and therapeutic treatment in current pandemic due to multiple roles in inhibiting the viral life cycle [56]. CQ inhibits the viral infection by increasing the endosomal pH value required for the fusion of virus and host cell. Treatment with CQ has shown improved pulmonary abrasion with healthy outcomes. It is also reported that high dose of CQ will cause cardiac risks and its safety and effectiveness is not investigated till now [57–59]. Hydroxychloroquine (HCQ) shares the similar structure and antiviral activity with CQ and

was looked upon as a better and safer treatment for COVID-19. Both are responsible for inhibiting the spike protein attachment with ACE-2 receptor in the host cell and also interfere with the glycosylation process of ACE-2 of host cell. CQ and HCQ decreased the cytokine storm, in COVID 19 patients. It disrupts the DNA/RNA interaction and reduces the expression of pro inflammatory genes [60,61]. However, WHO halted the use of combination of HCQ and lopinavir/ritonavir after their failure to reduce the mortality rate [62,63].

1.5. Transmembrane protease serine 2 (TMPRSS2)

Along with ACE-2, TMPRSS2 is also responsible for virus entry into the host cells by activating the viral S-proteins [36]. TMPRSS2 cuts the S-glycoprotein into two-part S1 and S2. Both subunits function differently; S1 binds with host cell surface receptor and S2 helps in fusion of host and viral cell. It is pertinent to note that spike protein activity is one of the main reasons for the viral pathogenicity and virulence [64]. Various studies have shown that inactivating the TMPRSS2 could facilitate inhibition of the viral infection. Camostat mesylate is an example of FDA approved serine TMPRSS2 inhibitor used in other diseases, and is under clinical trials for COVID-19 and will take several months for clinical validation [65].

1.6. RNA dependent RNA polymerase (RdRp)

Nsp12 or RdRp is the main conserved protein present in coronavirus which is responsible for viral replication and transcription. It is a complex machinery, where Nsp12 binds with nsp7 and nsp8 (cofactors) to produce viral genomic RNA [66]. SARS-CoV shares the same structure of Nsp12 with the SARS-CoV-2. It was observed that Nsp12 was the potential drug target with much safer profile and less toxicity for SARS-CoV and MERS-CoV [52]. Currently, remdesivir (antiviral drug) that targets RdRp activity is under clinical trial and also been used in severely ill-terminal COVID19 patients [67]. Docking-based screening studies have found some natural compounds targeting RdRp including nymphenolide A, viniferin and theaflavin [55,68].

1.7. 3CL protease

Main protease Nsp5, is also known as 3C like protease which first auto cleaved from the poly proteins and then thereafter cleaves the nsp5 at 11 sites, i.e., nsp4-nsp16, an essential step in the mechanism of viral infection [69]. This is the main protease hence sometimes called as Mpro and it shares almost 96% homology with SARS-CoV. Difference in structure arises in the dimer interface where polar amino group is replaced with nonpolar groups and hence catalytic activity of dimer increases [70]. Mpro is responsible for viral replication and transcription and considered as an important therapeutic target for COVID-19 [71]. A combination strategy using lopinavir-ritonavir; the protease inhibitors was tested against COVID-19, however no benefits was observed and it was observed to cause several side effects like diarrhoea, nausea, asthenia etc., but in some regions of South Korea, this combination was found to be effective, however the testing was done only in one patient [72,73]. Thus, clinical study with large cohort of population is needed to establish the importance of this protease as drug target for COVID19.

1.8. Papain-like proteinase (PLpro)

PLpro is a 213 kDa multidomain polypeptide which cleaves the N-terminal region of polyprotein and releases nsp1, nsp2 and nsp3 required for correction of viral replication. Along with having role in viral replication, it has other important functions of stripping ubiquitin, deISGylation from proteins of host cell for viral immune evasion processes [74]. It is also considered as a promising therapeutic target that not only inhibits viral replication but also saves other cells from being

Table 2

List of repurposed drugs under clinical trial for COVID-19.

Drugs	Type	Target	Status	Refs.
Camostat mesylate	Serine protease inhibitor	TMPRSS2	Under phase 1 and 2 of clinical trials	[73]
Nafamostat mesylate	Serine protease inhibitor	TMPRSS2	Under phase 2 and 3 of clinical trials	[73]
Chloroquine phosphate	Antimalarial	ACE-2	Under phase 2 of clinical trials	[73]
Hydroxy-chloroquine	Antimalarial	Endosome, pH elevation	Still in Controversy	[73]
Remdesivir	Antiviral	RdRp	Under clinical trials	[73]
Umifenovir	Antiviral	Membrane fusion, clathrin-mediated endocytosis	Under phase 4 of clinical trials	[73]
Favipiravir	Antiviral	RdRp	Inconsistent results in clinical trials	[73]
Lopinavir	Protease inhibitor	3clpro, plpro	Inconsistent results in clinical trials	[63]
Ribavirin	Antiviral	RdRp	Under phase 3 of clinical trials	[63]
Arbidol	Antiviral	ACE2	Under clinical trials	[63]
Baricitinib	Rheumatoid arthritis	JAK kinase	Under clinical trials	[63]
Ritonavir	Antiviral	Protease inhibitor	Inconsistent results in completed clinical trials	[61]
EIDD-2801	Antiviral	Viral replication	Prepared for clinical trials	[61]
Tocilizumab	mAb	IL-6 pathway	Under phase 3 of clinical trials	[61]
Sarilumab	mAb	IL-6 pathway	Under phase 3 of clinical trials	[61]
Bevacizumab	mAb	VEGF pathway	Under clinical trials	[61]
Vitamin C	Dietary supplements	Boost immunity	Under phase 2 of clinical trials	[61]
Vitamin D	Dietary supplements	Boost immunity	Under phase 2 of clinical trials	[61]
Azithromycin	Antibiotic	mRNA translation	Under phase 4 of clinical trials	[61]
Corticosteroids	Corticosteroids	Dampen pro-inflammatory cytokines and possess antifibrotic property	Still in controversy	[61]
Clevudine	Antiviral	Blocks DNA supply of virus to nucleus	Under phase 2 of clinical trials	[13]
Isotretinoin	Retinoid	Against PLPro	Under phase 3 of clinical trials	[13]
Ivermectin and Nitazoxanide	Antiparasitic	Inhibit import in alpha/beta receptor	Under phase 2 and 3 of clinical trials	[13]
Deferoxamine	Chelating agents	Inhibit IL6 synthesis through decreasing NF-Kb.	Under phase 1 and 2 of clinical trials	[13]
Dexamethasone	Steroid			[13]

(continued on next page)

Table 2 (continued)

Drugs	Type	Target	Status	Refs.
Piclidenoson	A3 adenosine receptor agonist	Anti-inflammatory action Inhibit cytokine storm	Under phase 4 of clinical trials Under phase 2 of clinical trials	[13]
Tranexamic acid	Antifibrinolytics	Inhibit conversion of plasminogen to plasmin	Under phase 2 of clinical trials	[13]
BLD-2660	Antiviral	Targets IL6	Under phase 2 of clinical trials	[13]
Sildenafil citrate	Phosphodiesterase inhibitor	Dilates blood vessels	Under phase 3 of clinical trials	[13]
Losartan	Angiotensin II receptor antagonist	Targets ACE2	Under phase 1 of clinical trials	[13]
Telmisartan	Antifibrotic	Angiotensin receptor blocker	Under phase 2 of clinical trials	[13]
Atorvastatin	Statin	Target NF-kB	Under phase 2 of clinical trials	[13]
Prazosin	Alpha-blockers	Prevent cytokine storm	Under phase 2 of clinical trials	[13]
Chlorpromazine	Antipsychotics	Inhibit viral replication	Under phase 3 of clinical trials	[13]
Lenalidomide	Antiangiogenic agent	For multiple myeloma patients	Under phase 4 of clinical trials	[13]
Ruxolitinib	Anti-inflammatory	Targets cytokine storm	Under phase 3 of clinical trials	[13]

infected by dysregulation of signalling cascades in the infected cells. There is a list of FDA approved drugs for various other diseases that specifically binds with viral PLpro effectively, as observed by virtual screening, however needs *in vitro*, *in vivo* and clinical validation to establish their effectiveness and clinical use [75,76].

1.9. Cathepsin

Like viral protein processing, cellular machinery of virus is also very important and could be a potential therapeutic target [77]. Keeping in view that SARS-CoV-2 shares similar viral entry mechanism with SARS-CoV, hence similarities in their cellular machinery such as endocytic mechanism for entering into cell could be visaged. Cathepsin is the lysosomal protease that has role in cellular protein turnover [78]. According to various studies, cathepsin B has important role in life cycles of coronavirus, Nipah virus, Ebola virus, influenza virus etc., and helps the virus to enter into cytoplasm through endosomes by fusing with viral envelope and endosomal membrane [79]. The most common pathway of viral internalization is clathrin mediated endocytosis as seen in the life cycles of various viruses including coronavirus [80,81]. Cathepsin L is also a promising target in coronavirus as proved by different studies, and therefore it could be a beneficial target for inhibiting SARS-CoV-2. Drug chlorpromazine is used to inhibit clathrin mediated endocytosis in Ebola virus and is being tested for SARS-CoV-2 too [82]. There are several other drugs available to target cathepsin but so far, all are under clinical trials [83].

Table 2 summarizes the various repurposed drugs alongwith their SARS-CoV-2 therapeutic targets.

1.10. Therapeutic potential of phytoconstituents against coronaviruses

During this pervasive situation, world is facing unhealthy circumstances impeding the normal lifestyle. It is very much necessary to develop drugs or vaccine for this current deadly infectious disease at the earliest, but unfortunately there are no FDA approved drugs available in the market and development of new therapeutic moieties and vaccine remains a costly and time-consuming affair with high failure chances too [12]. Keeping that in mind it is very crucial to use alternate options to combat the current situation. Medicinal plants offer the most common treatment options since ancient times against various viral diseases because of their safer, cheaper and less toxicity profile [84]. The National Health Commission of China suggested traditional Chinese medicine as an alternative defence treatment option [85]. From literature studies it was seen that phytoconstituents such as polysaccharides, triterpenes, phenolic acids, alkaloids, proanthocyanidins and anthraquinones etc., possessed anti-viral activity against rabies virus, HIV, Chandipura virus, Japanese Encephalitis Virus, Enterovirus, Influenza A/H1N1 and other influenza viruses, and SARS [86–89]. Table 3 encompasses a list of different phytoconstituents which have shown anti-viral activity against different types of coronaviruses.

2. Various phytoconstituents that are being studied for the treatment of COVID-19 fall under the following classification

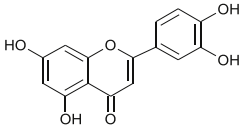
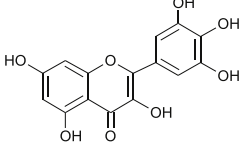
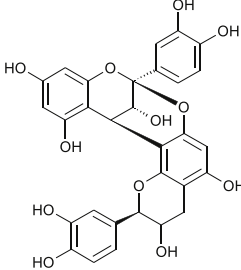
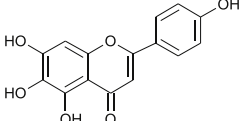
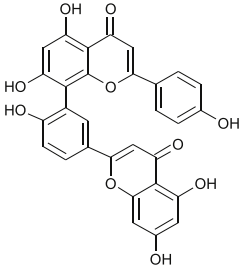
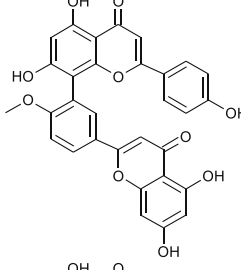
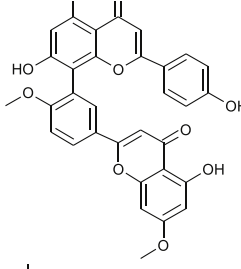
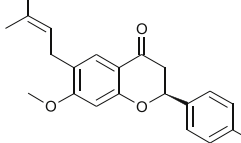

2.1. Flavonoids

Flavonoids are polyphenolic compounds present in plants and possess different biological functions [116]. Many flavonoids are seen having effective role against viral infections especially at the molecular level for inhibiting the growth of virus [117]. Flavonoids block the entry of virus into the cell by blocking the cellular receptors and also interfere with viral replication and translation [118]. Considering the important role played by Mpro enzyme in viral replication and translation, it can be used as one of the potential targets for COVID-19. Different virtual screening studies carried against Mpro enzyme have proposed several flavonoids like azithromycin, mangiferin, procyanidin- β -2,7-dimethoxyflavan-4'-O- β -D-glucopyranoside, amentoflavone, hidrosmin, diosmin, gallic acid, gallic acid gallate, elsamitricin, pectolinarin, quercetin and isochlorogenic acid having high binding affinities and thus could be used to combat the current situation. Along with the Mpro, ACE-2 is also a potential therapeutic target and flavonoids including hesperetin, myricetin, linebacker and caflanone have shown high binding affinity against ACE-2 making them important points of study against SARS-CoV-2 [119,120].

2.2. Alkaloids

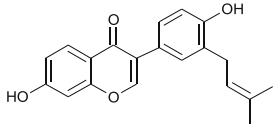
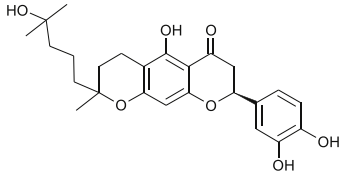
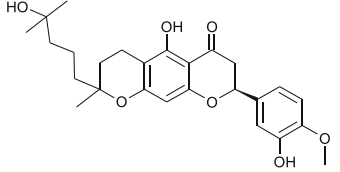
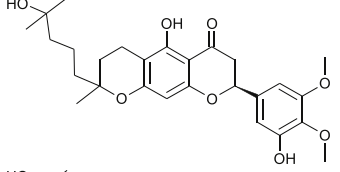
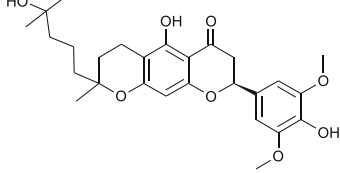
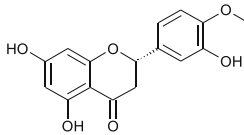
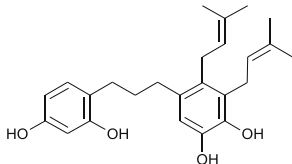
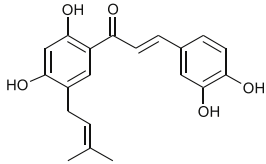
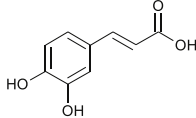
Alkaloids are naturally occurring organic compounds containing basic nitrogen atoms [121]. Alkaloids were found to have key roles in inhibition of viral replication as it blocks the function of viral DNA polymerase [122]. As these plant's secondary metabolites have DNA intercalating properties, they may be effective candidates against viral infection and could lead to development of drug molecules. Resoquinone, synthetic derivative of quinine (alkaloid), an antimalarial drug has been found as an effective therapeutic agent against COVID-19 [123]. Isoquinoline was effective against spike protein and nucleocapsid protein of SARS-CoV-OC43 in human lung cells suggesting that this could serve as a drug candidate against SARS-CoV-2. Some alkaloids which are having DNA intercalating activity are sanguinarine, quinine, cinchonine, hartmine, chelidone, coptisine, berberine, palmatin, tetradine etc., and could be used for development of drug molecules [124,125]. Emetine isolated from ipecacuanha root for induction of vomiting in the poisoning management has been found as effective against COVID-19 [126].

Table 3
Phytoconstituents and their plant sources having antiviral potential against different types of coronaviruses.

Compound (source)	Structure	Strain	Targets	Refs.
Flavonoids				
Luteolin (<i>Galla Chinensis</i>)		SARS-CoV BJ01	Binds with S2 subunit	[90]
Myricetin		SARS-CoV	Inhibit ATPase activity	[91]
Procyanidin A2 (<i>Cinnamomi sp.</i>)		SARS-CoV PUMCO1 F5	Targets clathrin dependent endocytosis pathway	[92]
Scutellarein (<i>Scutellaria barbata</i>)		SARS-CoV	Inhibit ATPase activity	[11]
Amentoflavone (<i>Torreya nucifera</i>)		SARS-CoV	Targets CLPro	[93]
Bilobetin (<i>Torreya nucifera</i>)		SARS-CoV	Targets CLPro	[93]
Ginkgetin (<i>Torreya nucifera</i>)		SARS-CoV	Targets CLPro	[93]
Bavachinin (<i>Psoralea corylifolia</i>)		SARS-CoV	Targets PL Pro	[94]
Neobavaisoflavone (<i>Psoralea corylifolia</i>)		SARS-CoV	Targets PL Pro	[94]

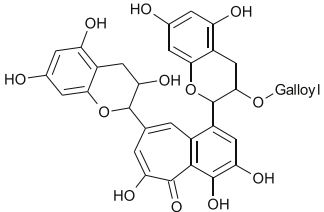
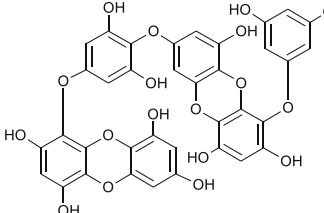
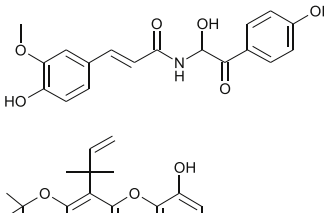
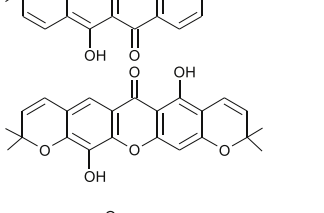
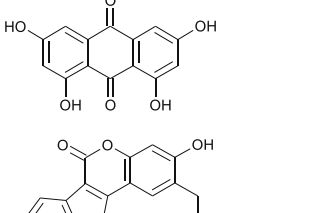
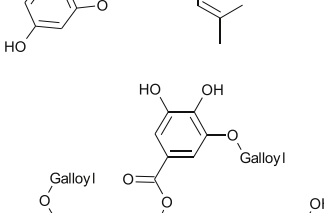
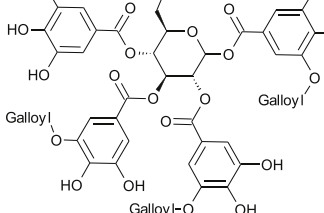
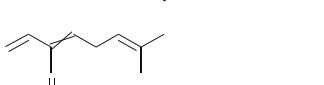


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Table 3 (continued)

Compound (source)	Structure	Strain	Targets	Refs.
Tomentin A (<i>Paulownia tomentosa</i>)		SARS-CoV	Inhibits PL Pro	[95]
Tomentin B (<i>Paulownia tomentosa</i>)		SARS-CoV	Inhibits PL Pro	[95]
Tomentin C (<i>Paulownia tomentosa</i>)		SARS-CoV	Inhibits PL Pro	[95]
Tomentin D (<i>Paulownia tomentosa</i>)		SARS-CoV	Inhibits PL Pro	[95]
Tomentin E (<i>Paulownia tomentosa</i>)		SARS-CoV	Inhibits PL Pro	[95]
Hesperetin		SARS CoV	Against 3CL Pro	[96]
Phenolic compounds				
Kazinol F (<i>Broussonetia papyrifera</i>)		MERS-CoV	Targets PL pro	[97]
Brousochalcone A (<i>Broussonetia papyrifera</i>)		MERS-CoV	Targets PL pro	[97]
Caffeic acid (<i>Sambucus formosana</i>)		HCoV-NL63	Inhibit cell docking	[11]
Isotheaflavin-3-gallate (<i>Camellia sinensis</i>)		SARS-CoV1	Against 3CL Pro	[98]

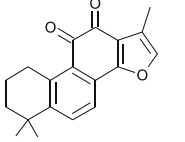
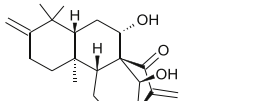
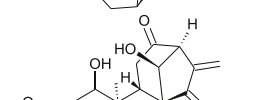
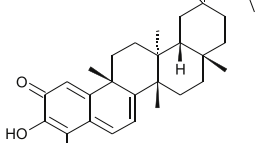
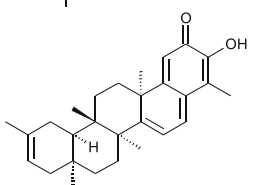
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Table 3 (continued)

Compound (source)	Structure	Strain	Targets	Refs.
Dieckol (<i>Ecklonia cava</i>)		SARS CoV	Against 3CL Pro	[99]
Terrestimine (<i>Tribulus terrestris</i>)		SARS CoV	Against PL Pro	[100]
Xanthones Blanco-xanthone (<i>Calophyllum blancoi</i>)		HCoV 229E	Against Protease	[101]
Pyrano-jacareubin (<i>Calophyllum blancoi</i>)		HCoV 229E	Against Protease	[101]
Anthraquinones Emodin (<i>Rheum officinale</i>)		SARS-CoV	Inhibit binding of S-protein to ACE2	[102]
Coumarins Psoralidin (<i>Cullen corylifolium</i>)		SARS CoV	Against PL Pro	[94]
Tannins Tannic acid (<i>Camellia sinensis</i>)		SARS- CoV1	Against 3CL Pro	[16]
Terpenoids β -Ocimeni (<i>Laurus nobilis</i>)		SARS-CoV FFM1	Inhibit viral replication	[103]
β -Penene (<i>Laurus nobilis</i>)		SARS-CoV FFM1	Inhibit viral replication	[103]
Tanshinone I (<i>Salvia miltiorrhiza</i>)		SARS-CoV	Targets Protease	[104]

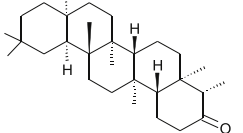
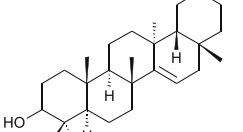
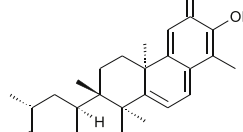
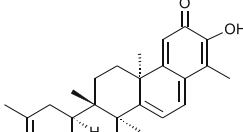
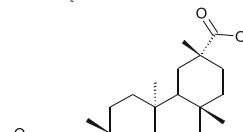
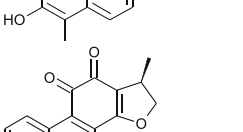
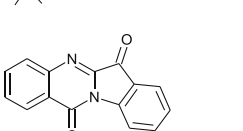
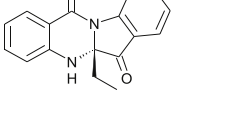
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Table 3 (continued)

Compound (source)	Structure	Strain	Targets	Refs.
Tanshinone IIA (<i>Salvia miltiorrhiza</i>)		SARS-CoV	Targets Protease	[104]
Tanshinone IIB (<i>Salvia miltiorrhiza</i>)		SARS-CoV	Targets Protease	[104]
Celastrol (<i>Tripterygium regelii</i>)		SARS-CoV	Targets protease	[93]
Leukamenin (<i>Lactuca sativa</i>)		SARS-CoV1	Protease inhibitor	[105]
Glaucocalyxin (<i>Lactuca sativa</i>)		SARS-CoV1	Protease inhibitor	[105]
Pseurata (<i>Lactuca sativa</i>)		SARS-CoV1	Protease inhibitor	[105]
Pristimerin (<i>Celastrus orbiculatus</i>)		SARS-CoV1	Targets Protease	[35]
Tingenone (<i>Celastrus orbiculatus</i>)		SARS-CoV1	Targets 3CL Pro	[35]
Iguesterin (<i>Celastrus orbiculatus</i>)		SARS-CoV1	Targets 3CL Pro	[35]
Friedelanol (<i>Euphorbia nerifolia</i>)		HCoV-229E	Antiviral activity	[106]

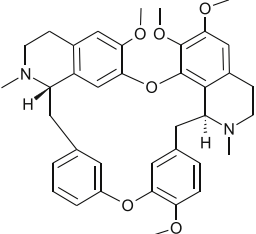
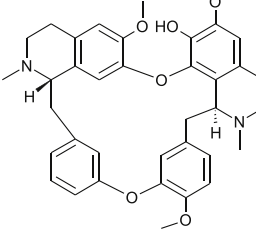
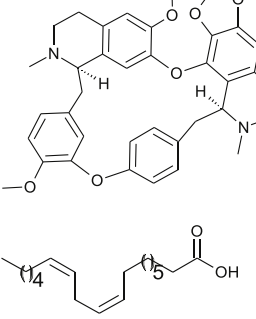
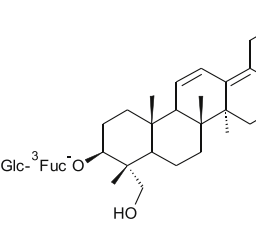
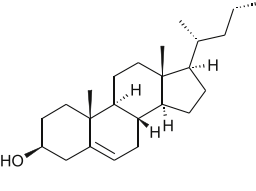
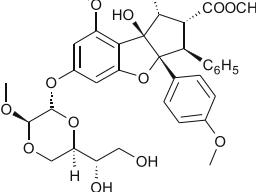
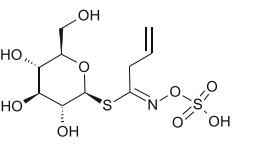

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Table 3 (continued)

Compound (source)	Structure	Strain	Targets	Refs.
Friedelin (<i>Euphorbia nerifolia</i>)		HCoV-229E	Antiviral activity	[106]
Epitaraxerol (<i>Euphorbia nerifolia</i>)		HCoV-229E	Antiviral activity	[106]
Tingenone (<i>Tripterygium regelii</i>)		SARS CoV	Against 3CL Pro	[93]
Iguesterin (<i>Tripterygium regelii</i>)		SARS CoV	Against 3CL Pro	[93]
Pristimererin (<i>Tripterygium regelii</i>)		SARS CoV	Against 3CL Pro	[93]
Dihydrotanshinone 1 (<i>Salvia miltiorrhiza</i>)		SARS CoV	Against 3 CL Pro and PL Pro	[107]
Cryptotanshinone (<i>Salvia miltiorrhiza</i>)		SARS CoV	Against 3 CL Pro and PL Pro	[107]
Alkaloids				
Tryptanthrin (<i>Strobilanthes cusia</i>)		HCoV-NL63	Targets papain like protease	[108]
Indigodole B (<i>Strobilanthes cusia</i>)		HCoV-NL63	Targets papain like protease	[108]
Tetrandrine (<i>Stephania tetrandra</i>)		HCoV-OC43	Inhibit viral replication	[109]

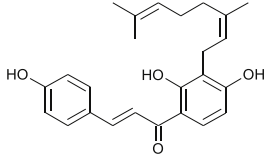
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Table 3 (continued)

Compound (source)	Structure	Strain	Targets	Refs.
Fangchinoline (<i>Stephania tetrandra</i>)		HCoV-OC43	Inhibit viral replication	[109]
Cepharanthine (<i>Stephania tetrandra</i>)		HCoV-OC43	Inhibit viral replication	[109]
Fatty acids Isolinoleic acid (<i>Mucuna pruriens</i>)		SARS-CoV1	Targets Protease	[35]
Steroidal derivatives Saikosaponin B2 (<i>Bupleurum sp.</i>)		HCoV-229E	Targets viral replication	[110]
β -Sitosterol (<i>Isatis indigotica</i>)		SARS CoV	Against 3CL Pro	[107]
Flavaglines Silvestrol (<i>Algalia sp.</i>)		MERS-CoV	Targets RNA helicase	[111]
Glucosides Sinigrin		SARS CoV	Against 3CL Pro	[107]
Chalcones Xanthoangelol (<i>Angelica keiskei</i>)		SARS CoV	Against 3 CL Pro and PL Pro	[112]

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Table 3 (continued)

Compound (source)	Structure	Strain	Targets	Refs.
Diarylheptanoids Hirsutenone (<i>Alnus japonica</i>)		SARS CoV	Against PL Pro	[113]
Lectins Agglutinin (<i>Urtica dioica</i>) Griffithsin (<i>Griffithsia sp.</i>)	- -	SARS-CoV SARS-CoV	Targets viral replication Against glycoprotein spike	[114] [115]

2.3. Phenolics

Phenolics are naturally occurring plant polyphenolic compounds having one or more hydroxyl groups which bind with aromatic hydrocarbon group. They possess the chemical properties where hydroxyl group dissociates under various physiological conditions [127]. Phenolic compounds carrying five or more hydroxyl group along with methoxyl group have antiviral properties [128]. Plants like *Euphorbia spinidens* and *Bombax malabaricum* were tested for anti-HSV and anti-RSV respectively and were effective like ribavirin (antiviral) synthetic drugs [129]. Phenols help in inhibiting the fusion of virus to the host cell by binding with the viral protein present in the viral envelope. Since most of the polyphenols are polar molecules and hence cannot be taken up by the host cells and thus may prove as good candidates against COVID-19 [123,130,131].

2.4. Essential oils

Essential oils are the volatile concentrated hydrophobic liquids extracted from plants. Essential oils are extensive used in phytomedicine and aromatherapy and also in pharmaceuticals. They possess different biological functions like antibacterial, antifungal, antiviral, antioxidant, anti-inflammatory, anticancer etc. [132]. Several reports described the effective antiviral activity of essential oils on influenza virus, herpes simplex virus etc. A mixture of essential oil and oleoresins from medicinal plants was also tested for coronavirus, bronchitis virus etc. [133]. Essential oil easily interacts with phospholipid bilayer of the cell membrane and it disrupts the viral envelope, thus starting their activity prior to host cell attachment.

Lipophilic essential oils work on membrane viral proteins required for fusion but its activity stops once the virus enters inside the cell [134–137]. Recently a team of scientists tested cannabis terpenes for antiviral activity against COVID-19 and the terpenes were found to reduce the severity of SARS virus by interruption with RNA replication proteins thus interfering with viral penetration in healthy cells [124]. Various essential oils have proved to be effective against various types of viruses which includes isoborneol, a monoterpene, having antiviral effect against HSV1. Similarly, eugenol delayed the growth of Herpes virus and also interferes with HSV, while beta-caryophyllene was found to be effective against dengue virus [138,139]. Vanguard Scientific recently launched an effective hand sanitizer having plant derived terpenes [140]. Essential oils thus constitute a major group of phytochemicals which are needed to be investigated thoroughly for the finding of new effective treatment against the COVID-19 severity.

2.5. Stilbenes

Stilbenes are naturally occurring defensive phenolic compounds

found in grapes, berries, bark waste etc., also classified as phytoalexins as they are synthesized by plants in response to UV radiations. Stilbenes have many biological functions like antioxidant, anticancer, anti-inflammatory, antileukemia, anti-HIV, anti-Herpes simplex virus, etc. [141,142]. Different virtual screening studies suggested the use of stilbenes in COVID-19 as they inhibit the complex formed between spike protein and ACE-2 receptor by disrupting the interface of S-ACE-2 complex and thus blocking the entry to the host cell. Stilbenes having high binding affinity to this complex include resveratrol and piceatannol. Some other derivatives of stilbenes like *trans*-resveratrol, pino-sylin, pterostilbene also have antiviral properties but with low binding capacity than mentioned previously [143–145]. Resveratrol has been already tested for MERS-CoV and was found effective as it decreases the cell death [146]. Based on these studies, it is suggested that stilbenes derivatives, especially resveratrol could be very important drug candidate for COVID-19.

2.6. Glycosides

Glycosides are simple sugar molecules having different functional groups. Different drugs and poisons extracted from plants are glycosides and thus useful in various treatments [147]. Antiviral effects of glycosides have been observed in various studies like the cardiac glycosides were seen effective against both DNA and RNA viruses including cytomegalo virus, herpes simplex virus, influenza virus and coronavirus [148]. It targets the cell host protein and thus makes them promising strategy against human viral infections [149]. It was already seen that glycosides are effective for influenza virus as it interferes with the virus attachment and disturbs the release of new viruses by inhibiting the hemagglutinin and sialidase enzymes [150,151]. Iridoid glycosides from *Fructus gardeniae* are very much effective against influenza A as it reduced the cell death by suppressing influenza virus replication [152]. According to a recent report, antiviral activity of Ginsenoside Rb1 class of steroid glycosides was tested and found to be effective against SARS-CoV [153]. Thus, glycosides derivatives need detailed investigation as drug targets for minimising the current pandemic scenario.

2.7. Saponins

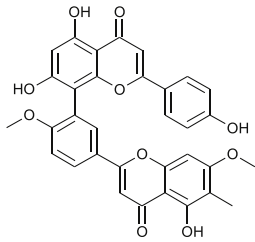
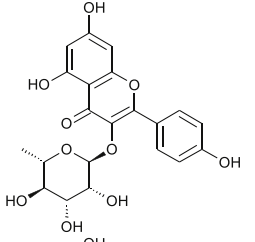
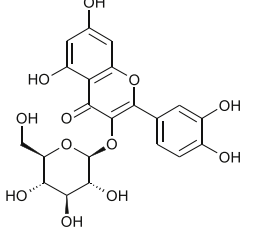
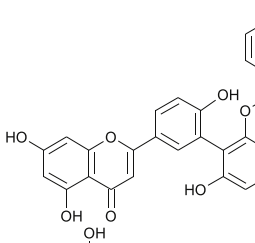
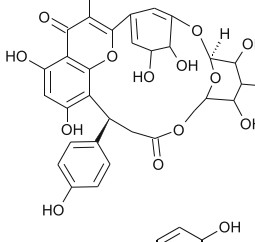
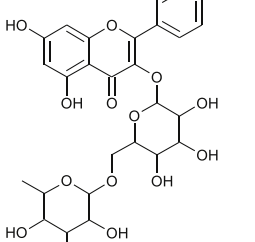
Saponins are non-ionic detergents which possess antifungal, cytotoxic, antibacterial and antiviral properties [154]. Saponins are used in the development of steroidal drugs and thus used in modern medicine [155]. Saponins carries antiviral activity as it can interact with viral envelope and capsid protein which results into disruption of viral particles, also it can interact with host cell membrane which inhibit the viral particle attachment to the host cells thus prevent fusion by coating the cell surface which minimizes the spreading of infections. Some study found that *Quilaja saponaria* extract containing triterpenoid saponins

Table 4
List of phytoconstituents screened via *in silico* studies against targets of SARS-CoV-2.

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Myricitrin		<i>Myrica cerifera</i>	interacts with 3CLPro	[173]
3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-gluco-pyranoside		<i>Phaseolus vulgaris</i>	protease inhibition	[173]
(2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside		<i>Phyllanthus emblica</i>	protease inhibition	[173]
Calceolarioside B		<i>Fraxinus sieboldiana</i>	interact with HIS41 and Cys145	[173]
Kaempferol		<i>Securigera securidaca</i>	PLpro & 3CLpro	[87]
Quercetin		<i>Withania somnifera</i>	PLpro & 3CLpro	[35, 87]
Myricetin 3-O-beta-D-glucopyranoside		<i>Camellia sinensis</i>	3CL Pro inhibition	[173]
Licoleafol		<i>Glycyrrhiza uralensis</i>	3CL Pro inhibition	[173]
Taiwan-homoflavone A		<i>Cephalotaxus wilsoniana</i>	Binds with 3CL pro and ACE2	[55]

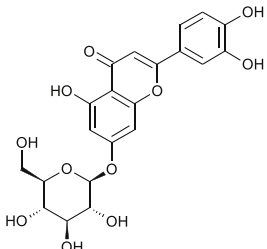
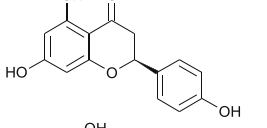
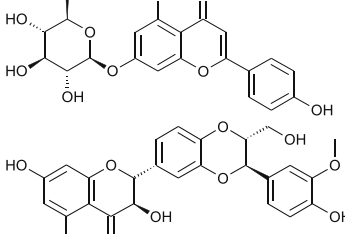
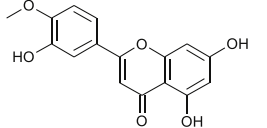
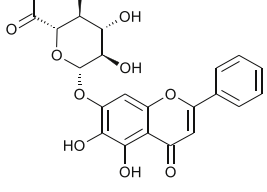
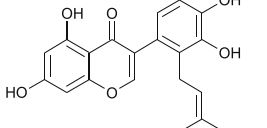
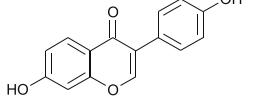
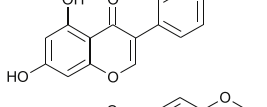
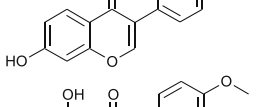
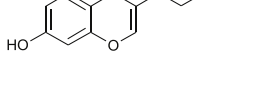

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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Afzelin			3CL Pro inhibition and ACE2	[174]
Isoquercitrin			3CL Pro inhibition and ACE2	[174]
Amentoflavone			3CL Pro inhibition and ACE-2	[174]
Nympholide A		Aquatic plant	M ^{pro} and RdRp	[55]
Biorobin		<i>Acalypha indica</i>	RdRp and hACE-2	[55]
Luteolin-7-glucoside		<i>Olea europaea L.</i>	M ^{pro} inhibitor	[87]

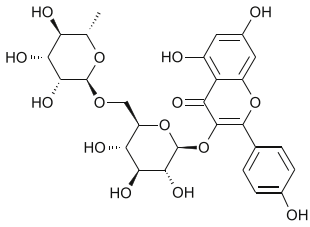
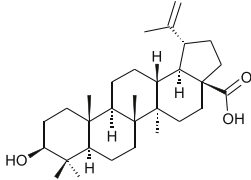
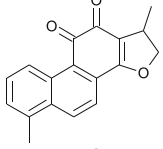
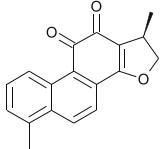
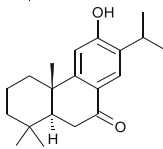
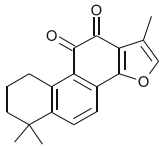
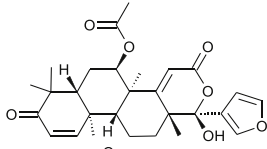
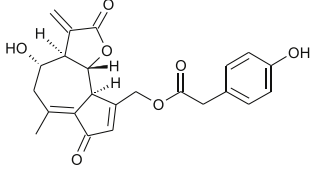
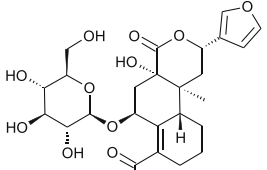
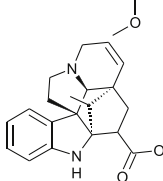
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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Naringenin		<i>Citrus sinensis</i>	Mpro inhibitor	[87]
Apigenine-7-glucoside		<i>Averrhoa belimbi</i>	Mpro inhibitor	[87]
Silybin		<i>Silybum marianum</i>	spike protein inhibition (TMPRSS2)	[175]
5,7-Dimethoxy flavan-4-O-β-D-glucopyranoside			inhibit Mpro	[33]
Baicalin			binds with TMPRSS2	[174]
Isoflavonoids				
5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone		<i>Psoralea sp.</i>	interacts with 3CLPro	[173]
Daidzein		<i>Cicer arietinum</i>	Blocks HSPA5	[68]
Genistein		<i>Cicer arietinum</i>	Blocks HSPA5	[68]
Formononetin		<i>Cicer arietinum</i>	Blocks HSPA5	[68]
Biochanin A		<i>Cicer arietinum</i>	Blocks HSPA5	[68]
Nictoflorin		<i>Nyctanthes arbortristis</i>	interact with protease	[125]


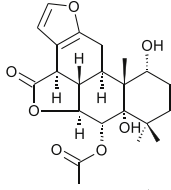
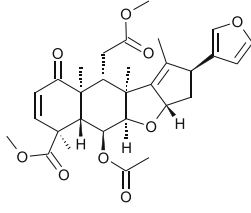
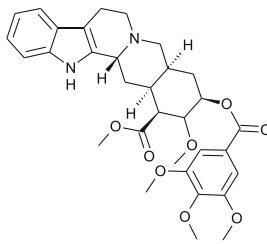
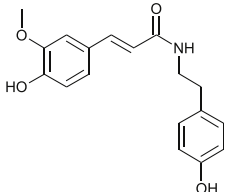
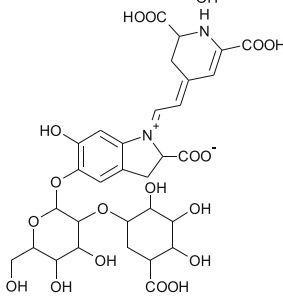
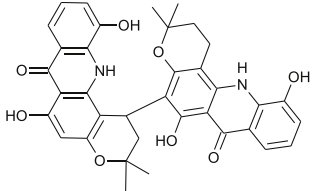
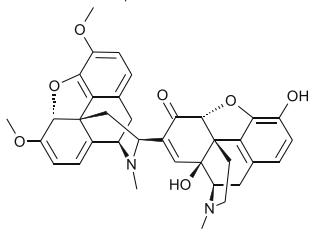

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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
				
Terpenoids				
Betulinic acid		Chinese medicinal plant	replication & 3CLpro	[11]
Crypto-tanshinone		Chinese medicinal Plant	PLpro & 3CLpro	[11]
Dihydro-tanshinone		Chinese medicinal Plant	entry & spike protein	[11]
Sugiol		Chinese medicinal Plant	Replication & 3CLpro	[11]
Tanshinone IIA		Chinese medicinal plant	PLpro & 3CLpro	[11]
Nimolicinol		<i>Azadirachta indica</i>	protease inhibition	[35]
Lactucopicrin		<i>Lactuca virosa</i>	3CL Pro inhibition and ACE2	[55]
Cordioside		<i>Tinospora cordifolia</i>	binds with main protease	[175]
Vindolinine		<i>Catharanthus roseus</i>	binds with NSP15	[35]

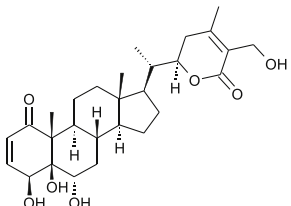
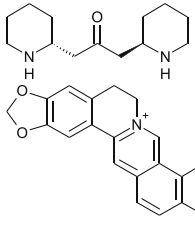
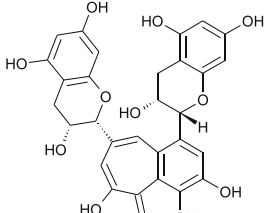
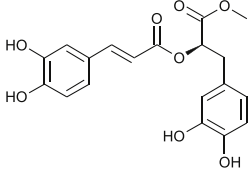
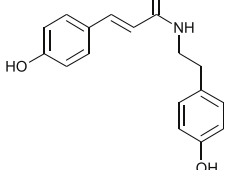
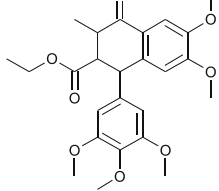
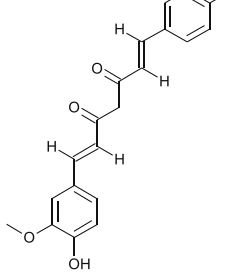

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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Camphorating D		<i>Cinnamomum verum</i>	blocking signalling pathway	[169]
Bonducellpin D			inhibit Mpro	Gurung et al., 2020
Nimbin		<i>Azadirachta indica</i>	Interact with protease	[33]
Alkaloids				
Desmethoxy-reserpine		Chinese medicinal Plant	Replication, 3CLpro & entry	[11]
Moupinamide		<i>Piper nigrum</i>	PLpro	[11]
Amaranthin		<i>Amaranthus tricolor</i>	3CL Pro inhibition	[173]
Oriciacidone F			binds with 3CL and ACE2	[174]
Somniferine		<i>Withania somnifera</i>	binds with NSP15	[35]
2,3-Dehydro-somnifericin		<i>Withania somnifera</i>	binds with NSP3	[35]

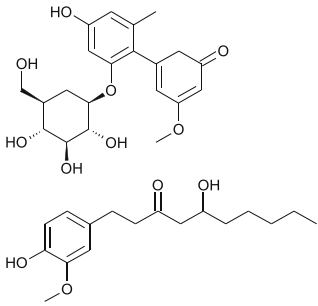
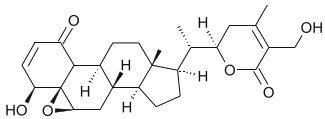
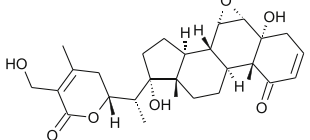
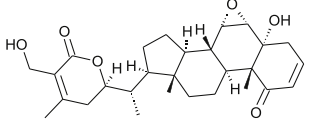
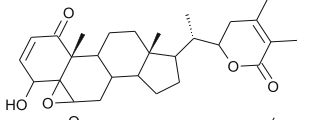
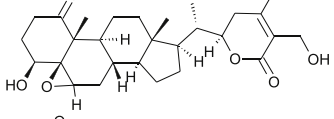
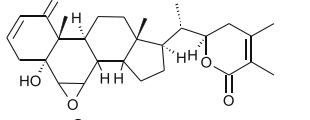
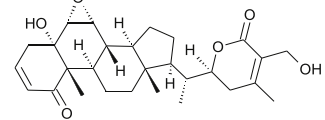
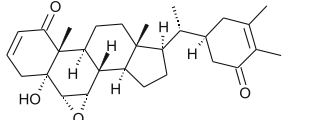
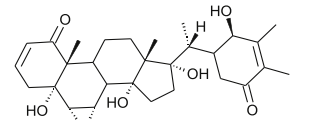
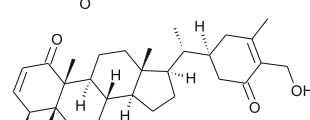

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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Anaferine		<i>Withania somnifera</i>	binds with NSP10, NSP16	[35]
Berberine		<i>Tinospora cordifolia</i>	interact with protease	[125]
Phenolic compounds				
Theaflavin		<i>Camellia sinensis</i>	binds with RdRp	[11]
Methyl rosmarinate		<i>Hyptis atrorubens</i>	interacts with 3CLPro	[173]
Coumaroyl-tyramine		Chinese medicinal Plant	PLpro & 3CLpro	[11]
Lignan		Chinese medicinal Plant	replication & 3CLpro	[11]
Demethoxy-curcumin		<i>Curcuma longa</i>	Mpro inhibitor	[87]
Aloenin		<i>Aloe Vera</i>	interact with protease	[125]

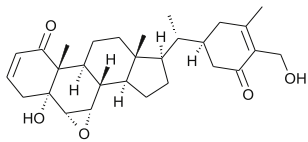
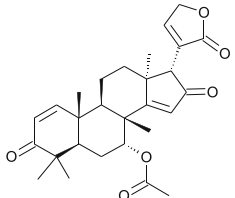
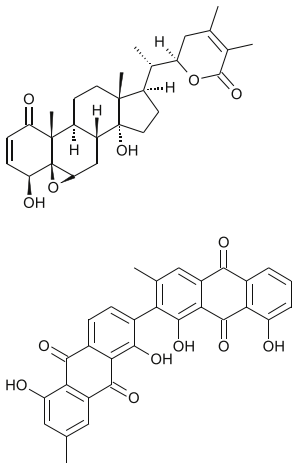
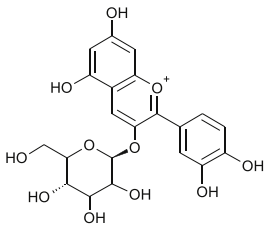
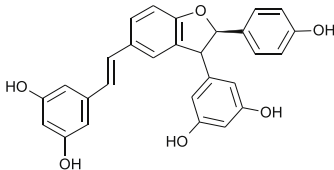
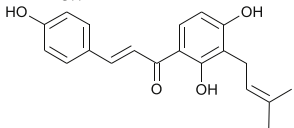
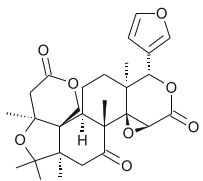
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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Gingerol		<i>Zingiber officinale</i>	Interact with protease	[125]
Steroidal compounds				
27-Deoxy-14- hydroxy withaferin A		<i>Withania somnifera</i>	protease inhibition	[35]
27-Hydroxy withanone		<i>Withania somnifera</i>	interferes with Spike protein	[35]
12-Deoxy witha-stramonolide		<i>Withania somnifera</i>	interferes with Spike protein and binds with NSP9	[35]
27-Deoxy withaferin A		<i>Withania somnifera</i>	interferes with Spike protein	[35]
2,3-Dihydro withaferin A		<i>Withania somnifera</i>	interferes with Spike	[35]
27-Hydroxy withanolide B		<i>Withania somnifera</i>	binds with NSP10	[35]
Witha-stramonolide		<i>Withania somnifera</i>	binds with NSP12 D2	[35]
Withanolide B		<i>Withania somnifera</i>	binds with NSP12 D2 and binds with NSP3	[35]
Withanolide R		<i>Withania somnifera</i>	binds with NSP12 D2	[35]
Withaferin A		<i>Withania somnifera</i>	binds with NSP12 D2	[35]
27-Hydroxy withanolide B		<i>Withania somnifera</i>	binds with NSP9	[35]

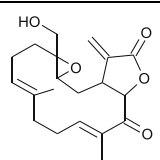
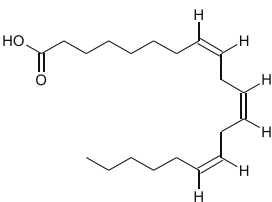
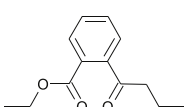
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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
Aza-diradionolide		<i>Azadirachta indica</i>	binds with NSP9	[35]
27-Deoxy-14-hydroxyl withaferin A		<i>Withania somnifera</i>	binds with NSP3	[35]
Anthraquinones Microcarpin			binds with TMPRSS2	[174]
Anthocyanins Chry-santhemin		Black grapes	RdRp and hACE-2	[55]
Stilbenes δ-Viniferin		Grapevine leaves	M ^{Pro} , RdRp and hACE-2	[55]
Iso-gemichalcone			binds with TMPRSS2	[174]
Lactones Limonin		<i>Nigella sativa</i>	binds with NSP16	[35]
Durumolide K			binds with TMPRSS2	[174]

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Table 4 (continued)

Compound	Structure	Source	Mechanism	Refs.
Flavonoids				
				
Fatty acids				
Dihomo-gamma-linolenic acid		Chinese medicinal plant	3CLpro	[11]
Phthalates				
Solvanol		<i>Solanum nigrum</i>	binds with NSP16	[35]

having very strong activity in both human and animal's vaccines. This extract was very effective against HIV-1 and -2 [156,157]. Similarly, triterpene saponin from *Anagallis arvensis* showed antiviral activity against HSV1 and poliovirus 2 [158]. Saikosaponins are triterpene saponin glycosides that have been reported having effective antiviral activity against coronavirus HCoV-229E. Saikosaponins interfere with the early stage of viral replication including adsorption and penetration. Some studies demonstrated the antiviral activity of saikosaponins on other viruses like herpes simplex virus, hepatitis B virus and cytomegalovirus and HIV [110,159]. Thus, this approach of saponins needs attention of scientists for investigation in detail for the development of effective therapeutic candidate against COVID-19.

2.8. Tannins

Tannins are naturally occurring compounds found in plants, seeds, bark, wood and fruits etc. and possess various biological properties and medical uses. The viral infections lead to the overproduction of free radicals and thus oxidative stress triggering the production of reactive oxygen and nitrogen molecules and tannins extracted from plants are very much effective against oxidative stress [160,161]. Several studies confirmed the antioxidant effect as a potential therapy against various viral infections [162]. Antiviral activity of tannins against various viruses like enterovirus, caliciviruses, rotavirus, HIV, herpes simplex virus, and coronaviruses, etc., has been well established [163]. Tannins like pedunculagin, tercatin and punicalin can bind effectively with SARS-CoV-2 which interferes with viral binding site and destroy the protease enzymes such as His41 and Cys145 and this was studied recently by molecular docking methods [164]. A recent study from India suggested the use of tea and haritaki having therapeutic potential against COVID-19 as gallotannin present in tea can interfere with 3CLPro protease activity of coronavirus, but yet clinical trials are not done [165].

2.9. Anthraquinones

Anthraquinones are naturally occurring aromatic compounds having wide range of medicinal applications such as in constipation, arthritis, multiple sclerosis, cancer and others and demonstrate low toxicity with high activity [166,167]. Currently molecular docking studies showed the effect of anthraquinones against SARS-CoV-2. Derivatives such as emodin, aloin A and B, rubiadin, aloe-emodin, pseudohypericin,

damnacanthal, and chrysophanic etc., were found as inhibitors of Mpro of SARS-CoV-2 using docking studies. But the detailed *in vivo* and *in vitro* studies are required to be done to develop promising drug candidate against COVID-19 [168–170]. Emodin extracted from *Rheum officinale* and *Polygonum multiflorum* was also able to block the S-protein binding with ACE-2 receptor in SARS coronavirus [102]. Anthraquinone derivatives such as hypericin are effective against various other viruses like herpes simplex virus, vaccinia virus and parainfluenza virus [171,172].

Various computational tools showed the data of phytoconstituents from different medicinal plants against various therapeutic targets of COVID-19 and thus could be effective against this viral disease. Various types of phytoconstituents investigated through *in silico* docking studies in the SARS-CoV-2 are listed in Table 4.

3. Conclusions

In current adverse conditions of COVID-19 across the world, it is the urgent need of time to develop drugs or therapeutic options at the earliest. Developing new drugs and identifying novel drug targets are indeed time consuming and validation of such novel drugs/targets in clinical trials are mandatory to check their efficacy and effectiveness. Unavailability of the drugs and specific treatments for COVID-19 till date motivate the researchers to look for alternatives for successfully combating the current disease scenario. In this regard, medicinal plants containing specific phytomoieties could provide a wide scope as therapeutic drugs against COVID-19. Furthermore, the low toxicity of herbal medicines and an easy development process provide additional advantages in their fast and wide usage. This study has compiled a data of different types of phytoconstituents possessing antiviral activity against Coronaviruses as well as phytoconstituents showing affinities against therapeutic targets of SARS-CoV-2 like RdRP, 3CLpro, PLpro and the host cell targets like ACE-2 based on the computational screening methods. However, further *in vivo* and *in vitro* studies need to be done to confirm the bioactivity of these compounds against COVID-19. Overall, the development of phytopharmaceuticals as an alternative approach could be seen as a viable treatment option against SARS-CoV-2 in current COVID-19 pandemic.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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