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Molecular scaffolds from mother nature as possible lead compounds in drug design and discovery against coronaviruses: A landscape analysis of published literature and molecular docking studies

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ABSTRACT

The recent outbreak of viral infection and its transmission has highlighted the importance of its slowdown for the safeguard of public health, globally. The identification of novel drugs and efficient therapies against these infectious viruses is need of the hour. The eruption of COVID-19 is caused by a novel acute respiratory syndrome virus SARS-CoV-2 which has taken the whole world by storm as it has transformed into a global pandemic. This lethal syndrome is a global health threat to general public which has already affected millions of people. Despite the development of some potential vaccines and repurposed drugs by some Pharma companies, this health emergency needs more attention due to the less efficacy of these vaccines coupled with the emergence of novel and resistant strains of SARS-CoV-2. Due to enormous structural diversity and biological applications, natural products are considered as a wonderful source of drugs for such diseases. Natural product based drugs constitute a substantial proportion of the pharmaceutical market particularly in the therapeutic areas of infectious diseases and oncology. The naturally occurring bioactive antiviral phytochemicals including alkaloids, flavonoids and peptides have been subjected to virtual screening against COVID-19. Since there is no specific medicine available for the treatment of Covid-19, designing new drugs using in silico methods plays an all important role to find that magic bullet which can target this lethal virus. The in silico method is not only quick but economical also when compared to the other conventional methods which are hit and trial methods. Based on this in silico approach, various natural products have been recently identified which might have a potential to inhibit COVID-19 outbreak. These natural products have been shown by these docking studies to interact with the spike protein of the novel coronavirus. This spike protein has been shown to bind to a transmembrane protein called Angiotensin converting enzyme 2 (ACE2), this protein acts as a receptor for the viral spike protein. This comprehensive review article anticipates providing a summary of the authentic and peer reviewed published literature about the potential of natural metabolites that can be developed into possible lead compounds against this new threat of Covid-19. Main focus of the article will be to highlight natural sources of potential anti-coronavirus molecules, mechanism of action, docking studies and the target proteins as well as their toxicity profiles. This review article intends to provide a starting point for the research endeavors that are needed for the design and development of drugs based on pure natural products, their synthetic or semi-synthetic derivatives and standardized plant extracts. This review article will be highly helpful for scientists who are working or intend to work on antiviral drugs from natural sources.

1. Introduction

Coronaviruses (CoV's) are RNA enveloped family of viruses mostly

found in mammals and birds [1]. The virus infection causes fetal respiratory or enteric disorders and in rare cases hosts develop neurological and liver disorders [2]. Species-specific effects of CoV's are observed in

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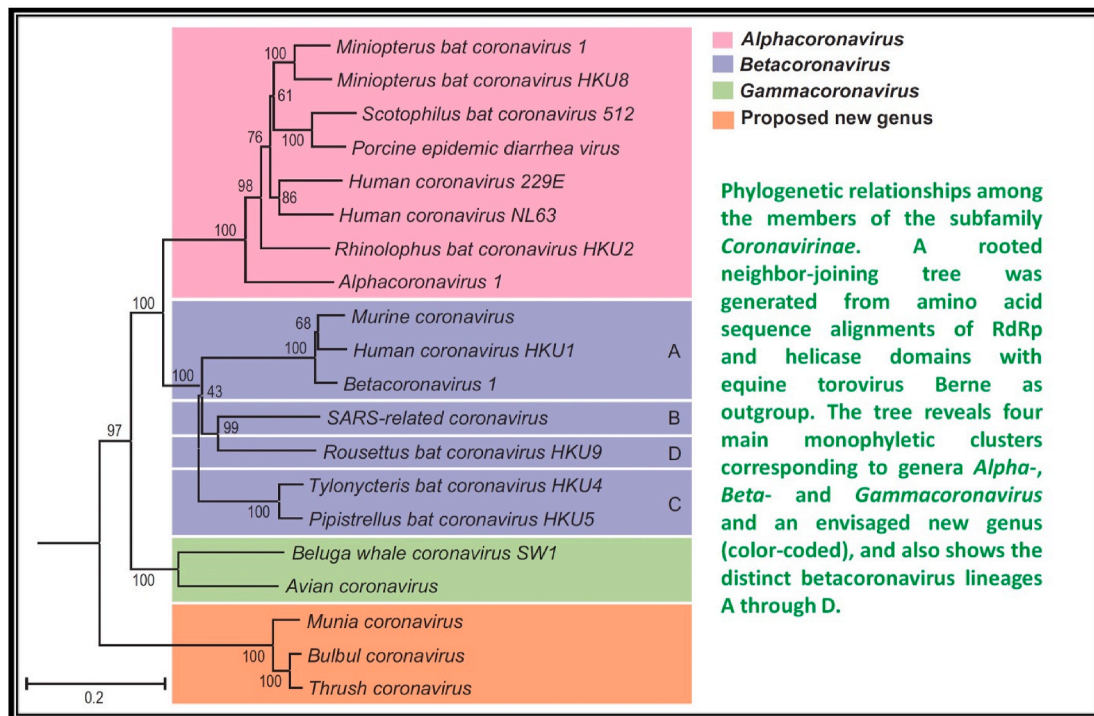


Fig. 1. Phylogenetic relation among the members of the *Coronavirinae* [15].

hosts like some may cause acute or persistent infections. These viruses are highly communicable and transmission may occur through different modes including respiratory and fecal-oral routes. CoV's show distinctive characteristic features in comparison to other viruses like a large genome size even bigger than those viruses having segmented genome [3]. This huge genome size contributes to wealthy and high variety of genetic expressions shown by CoV's and most importantly these expressions are yet to be fully explored and understood. In the year of 1960, CoV's were assembled under a variant class of viruses [4]. Since 1960, various novel viruses have been discovered which affects the respiratory system of humans in a similar fashion as avian infectious bronchitis virus (IBV) and mouse hepatitis virus (MHV) [5]. Study of CoV's under negative-stained electron microscopy reveals characteristic morphological structures. Their external surface was observed with "fringe" like structures later described as "spikes" or "club like" projections [6,7]. Variant density and morphology of these spikes were observed in MHV's in comparison to myxoviruses. The name "coronaviruses" originated on the bases of structure of these spikes as some of them were similar to solar corona [7]. After almost four decades, a novel pathogen with similar viron morphology appeared to harm human respiratory system. It was the lethal and disastrous outbreak of hazardous SARS-CoV causing severe acute respiratory syndrome (SARS) in the year of 2002–2003 [8]. Its sudden and lethal, emergence and spread led to massive eruption of research towards primary and better understanding of CoV's replication mechanism. Several approaches and targets were investigated to control and prophylaxis the lethal virus. CoV's moves into the host cell via interactions among receptors of host cell and S-protein of virus species [9]. Different species of CoV's involve terminus at S1 site of receptor binding domains like SARS-CoV's involve N-terminus and some others involve C-terminus. MERS-CoV enters the host cell via DPP4 (dipeptidyl-peptidase 4) and CEACAM1 (CEA cell adhesion molecule 1) whereas HCoV-NL63 and SARS use ACE2 (angiotensin-converting enzyme 2) [10]. Thereafter, S-protein undergoes cleavage (acid-dependent proteolytic) through serine 2 (TMPRSS2), transmembrane protease, cathepsin, or another protease. Cleavage is followed by fusion at plasma membrane or acidified endosomes within the cell cytol of host. The cleavage of S20 causes an

antiparallel six-helix bundle which permits the collaboration of cellular and viral membranes and leads to the discharge of viral genome into host cell [11]. This review aimed to collect and summarize the published data on coronaviruses and the role of natural products against them.

2. Classification of coronaviruses

Coronaviruses have been listed under a different sub-family (coronavirinae) of family Coronaviridae [12]. The members of the family Coronaviridae, a monophyletic cluster in the order Nidovirales, are enveloped, positive stranded RNA viruses of three classes of vertebrates: fish (bafiniviruses), birds (coronaviruses) and mammals (toro- and coronaviruses) [13]. On the study of unrooted and rooted phylogenetic trees projected for variant genomic regions, four different CoV clusters are eminent. Three clusters correspond to already found unofficial groups 1, 2 and 3 that are now classified officially as genera, Alpha-, Beta- and Gamma-CoV's, respectively [14]. The fourth cluster is different from the former three and found in birds. By all the standards this fourth cluster has been listed under a different genus (unofficial, yet to be approved) tentatively termed as "Delta- CoV's". Moreover, in case of Beta- CoV's further four divergent lineages can be distinguished, assigned as A through D [15], that correspond to former subgroups 2A through D, respectively (Fig. 1).

3. Distinctive characteristic features of coronaviruses

Across Coronavirinae, virions are spherical in shape and a size of 120–160 nm, bacilliform, 170–200 × 75–88 nm (Bafinivirus) or both, having a characteristically bent bacilliform into crescents (Torovirus) [16]. These particles are decked with typically large, petal- or club-shaped surface projections (spikes), creating an image of solar corona under electron microscopy. The CoV's bear helical nucleocapsids and can be released from virion on the application of detergents [17]. The nucleocapsids of coronavirus appear to be loosely-wound and in Torovirinae are characteristically tubular. Coronaviridae are the large size RNA viruses discovered so far in terms of genetic complexity and genome size, except rivaled by okaviruses (belonging to the family of

Table 1
Coronavirus hosts with key binding receptors and factors.

Virus species	Host	Attachment factor	Main receptor
Alphacoronavirus 1			
Canine coronavirus type I	Dog	Unknown	Unclear
Canine coronavirus type II	Dog	Unknown	APN
Feline coronavirus type I	Cat	Unknown	Unclear
Feline coronavirus type II	Cat	Unknown	APN
Transmissible gastroenteritis virus	Pig	Salic acid	APN
Betacoronavirus 1			
Bovine coronavirus	Cow	Unknown	9-O-Ac Sia?
Equine coronavirus	Horse	Unknown	9-O-Ac Sia?
Human coronavirus OC43	Human	Unknown	9-O-Ac Sia?
Porcine hemagglutinating encephalomyelitis virus	Pig	Unknown	9-O-Ac Sia?
Human coronavirus 229E	Human	Unknown	APN
Human coronavirus NL63	Human	Unknown	ACE2
Murine coronavirus	Mouse	4-O- or 9-O-Ac Sia	CEACAM1a
SARS-related coronavirus	Human	Unknown	ACE2

Abbreviations: APN = aminopeptidase N, ACE2 = angiotensin-converting enzyme 2, CEACAM1a = carcinoembryonic antigen adhesion molecule 1.

Roniviridae, okaviruses are large invertebrate nidoviruses) [18].

The replication mechanism in CoV's has been investigated in detail, whereas there is limited data on replication of toroviruses and bafiniviruses, this may be of similar replication mechanism followed by these. Virions enter into the target host cell via surface receptors and their spikes (Table 1). These virions discharge their genome into host cell by fusion of plasma membrane or endocytic vesicles with viral envelope [19]. The complete replication procedure operates within cytoplasm of host cell. It involves the formation of sub-genome sized and full-length minus-strand RNA intermediates with the viral genome serving as both mRNA for template for minus-strand synthesis and replicase polypeptides [20]. Replication-transcription complex (poorly characterized) catalyzes the RNA synthesis, comprising of host and viral proteins associated with interconnected modified network of double and intracellular membrane vesicles. These vesicles are ostensibly derived of endoplasmic reticulum [21–23].

In addition to this all coronavirus members share the following characteristics;

- i. Genome: positive sense RNA, unimolecular, linear, infectious, capped, polyadenylated, 26–32 kb in length, and polycistronic morphology.
- ii. General genomic organization: 5'-UTR-replicase-S-M-N-UTR-3' (genes according to product), with the genome functioning as mRNA for the replicase gene.
- iii. Replicase gene: it constitutes of overlapping ORFs (1a and 1b) that code for the production of giant polyproteins (pp1a and pp1ab), these giant proteins are generated autolytically and generation of pp1ab needs programmed 21 ribosomal frame shift.
- iv. ORFs downstream of the replicase gene: expression from a 3' co-terminal nested set of two or more subgenomic mRNAs that are capped and polyadenylated.
- v. Morphogenesis: virion assembly through budding of preformed nucleocapsids at smooth intracellular membranes of endoplasmic reticulum/early Golgi compartments.

4. Biological role and health disorders caused by coronaviruses

CoV's incorporate pathogens of veterinary, clinical and economic interest, which infect mammals and birds [24]. Viral transmission is species-specific and may occur through fecal-oral or aerogenic and/or fomites. Epithelial cells are the primary targets of CoV's and hence they generally cause respiratory and gastrointestinal infections [25]. These infections may be mild, acute or chronic depends upon the virus species and prolonged infections. In most of the cases, the infections raised by CoV's are generally mild and asymptomatic [26]. However, certain CoV's like SARS-CoV-1 and SARS-CoV-2, cause lethal health disorders and even death. The epidemic of 2002–2003 and the ongoing global pandemic both are the outbreaks of coronaviruses, SARS-CoV-1 and SARS-CoV-2, respectively [27]. Murine coronavirus belongs to the genus Beta-CoV's could raise hazardous neurological and hepatic disorders resulting in demyelination and body paralysis [28]. Alpha-CoV's including ferret, canine and feline CoV's, may cause severe immune-mediated systematic infections in hosts. These infections are presumed of infections to monocyte/macrophage lineage and generate inflammatory lesions within multiple organs. Farmer discovered human CoV's including Alpha-CoV HCoV-229E and Beta-CoV-1 subspecies HCoV-OC43, were considered least hazardous causing common cold and were considered of meek clinical value. CoV's are now identified with adverse health effects like they cause severe LRTI (lower respiratory tract infections) in elderly and infants [29]. Globally, these CoV's are

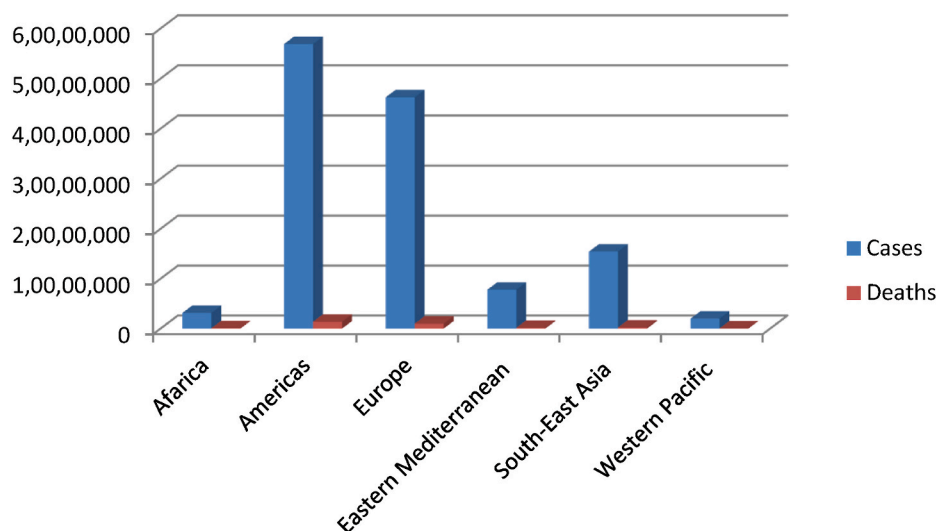


Fig. 2. The number of COVID-19 related cases and deaths reported globally, till April 6, 2021, according to WHO data (Coronavirus disease (COVID-19)), Situation Report April 6, 2021.

Top 10 Worst hit COVID-19 Countries

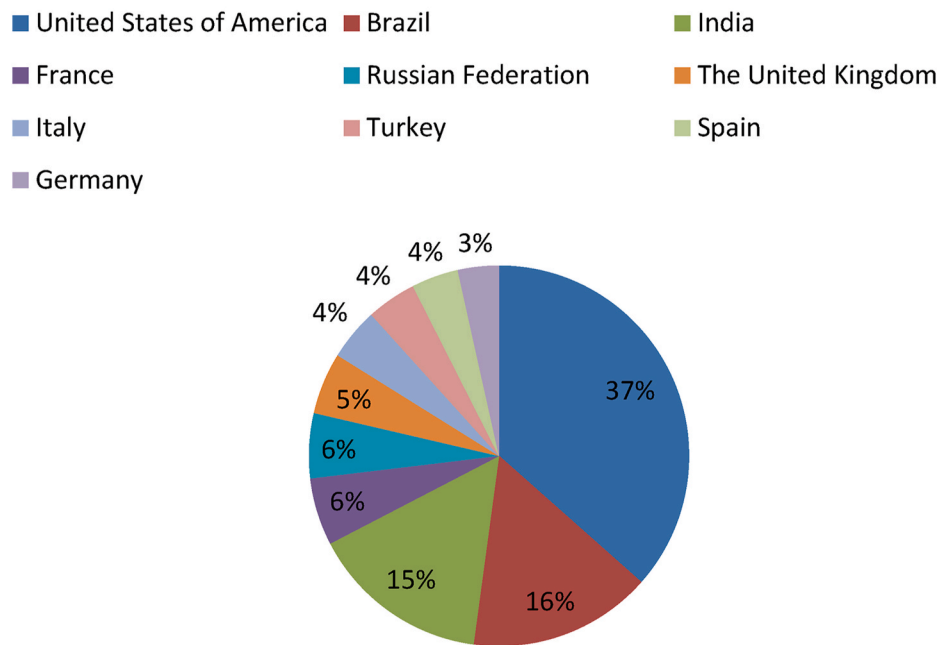


Fig. 3. Pi-chart representation of top 10 worst hit countries by COVID-19, Situation Report; April 6, 2021.

responsible for hospitalization of 5% of infants from LRTI.

In 2002–2003, SARS-CoV-1 (unknown then) caused a serious epidemic of severe pulmonary disorder in human populations which spread to four continents [30]. 8096 persons got infected and it claimed life of 774 victims, creating a 10% mortality rate [31]. On epidemiological surveillance of the disease it was demonstrated that this novel coronavirus originated from bats, spread to raccoon dogs, Chinese ferret badgers and Himalayan palm civets at Guangdong wet markets, China [32]. Later the virus moved into human population via consumption or handling of these infected species. Although, SARS was believed to be vanished till the latest casualties done by SARS-CoV-2, the episode highlighted the pathogenic potency of CoV's and their probability to emerge as novel coronavirus infections through transmission among cross-species. Various similar episodes were observed thereafter though they imposed miniscule epidemiological outcomes like OC43 human coronavirus (cattle to humans, through single cross transmission of bovine coronavirus), 229E human coronavirus (bats origin?) and canine respiratory coronavirus (bovine coronavirus transmission to dogs) [33]. The SARS epidemic has enhanced the research interest in the field of CoV's. Virus discovery and molecular surveillance have found nearly 60 novel CoV's, out of which two effect human respiratory system including HCoV-NL63 and HCoV-HKU1 [34]. The farmer is key agent of causing bronchiolitis and croup among children. Additionally, these studies showed novel lineage of mostly avian viruses including Munia, Bulbul and Thrush coronavirus with close relatives possibly found in mammals like Chinese ferret badger and Asian leopard cat [35]. These novel avian viruses were placed under a different genus (Delta-CoV's) on the basis of rooted phylogeny (Fig. 1). Bats are exceptionally rich harbors of variety of coronaviruses and hence play a key role in coronavirus evolution and ecology [36]. It has been reported that bats may be the original hosts from which lineages for most of the alpha-CoV's and Beta-CoV's were derived. The habitual features of bats like roosting, migration and population densities favor their virus carrier role [37]. This hypothesis has its merits and in recent studies of virus discovery this hypothesis remained truly Herculean proportions. The actual sampling size of the CoV's is limited though the efforts are primarily concentrated on bats, all of our current insights may be biased.

Table 2

Some of the worst hit COVID-19 countries in the world, according to WHO data (Coronavirus disease (COVID-19)), Situation Report; April 6, 2021.

Countries	Number of Cases	Number of Deaths
United States of America	30,412,206	551,769
Brazil	12,984,956	331,433
India	12,686,049	165,547
France	4,757,381	96,260
Russian Federation	4,597,868	101,106
The United Kingdom	4,362,154	126,862
Italy	3,678,944	111,326
Turkey	3,529,601	32,456
Spain	3,311,325	75,783
Germany	2,900,768	77,103
Poland	2,456,709	55,065
Colombia	2,446,219	64,094
Argentina	2,393,492	56,199
Mexico	2,250,458	204,147
Iran (Islamic Republic of)	1,945,964	63,332
Ukraine	1,769,164	35,017
Peru	1,582,367	52,877
Czechia	1,555,245	27,169
South Africa	1,552,416	52,995
Indonesia	1,537,967	41,815
Netherlands	1,307,466	16,629

4.1. Novel coronavirus COVID-19: Epidemiology

The ongoing lethal pandemic of COVID-19, primarily caused by coronavirus SARSCoV-2, originated from Chinese city of Wuhan, in December 2019 [38]. As the month of December is considered among the months of global festival, this lethal infectious virus got freehand and spread at very high frequency. According to World Health Organization, till April 6, 2021 more than 131,487,572 cases and over 2,857,702 deaths have been reported due SARS-CoV-2 infection globally since the onset of the pandemic (Fig. 3). Africa 3,132,143 cases and 78,763 deaths, America 56,880,123 cases, 1,375,139 deaths, Eastern Mediterranean 7,785,717 cases and 161,826 deaths, Europe 46,256,984 cases and 986,342 deaths, South-East Asia 15,438,907 cases and 223,666

deaths and Western Pacific 1,992,953 cases and 31,953 deaths (Fig. 2) [39]. Some of the worst hit countries by SARS-CoV-2 have been listed in Table 2; America tops the list followed by Brazil and India (Fig. 3). SARS-CoV-2 has a minimum incubation period of two weeks or may be longer in some cases. In early stages SARS-CoV-2 mostly may remain asymptomatic and can cause multiple infections in some patients before becoming apparent [40].

The organs adversely affected by SARS-CoV-2 include lungs, kidneys, heart, liver and genitals [41]. Patients with severe COVID-19 infection have been reported in a retrospective investigation to mostly develop ARDS (acute respiratory distress syndrome), abnormal liver functioning, acute cardiac and kidney injury in the proportions of 67.3%, 28.9%, 23.1% and 28.9%, respectively [41]. A mortality rate of 61.5% was observed in patients developing severe COVID-19 infection within four weeks. A great challenge to the medical staff workers not due to the nature of work in ICU's but becoming more vulnerable to the virus and ultimately developing infection. Higher number of medical staff workers has already fallen prey to this deadly virus. SARS-CoV-2 belongs to β -coronaviruses with most likely of animal origin. Recent investigations have demonstrated that SARS-CoV-2 may be a pathogen found in pangolins, snakes and bats. However, on genomic studies it has been revealed that SARS-CoV-2 originated from bats. Genome sequencing has showed that there is a 96% homology between bat coronaviruses and SARS-CoV-2 yet the intermediate host remains unclear [42].

4.2. Transmission

SARS-CoV-2 is transmitted in a number of ways, one of the primary sources is at present hosts and hosts with asymptomatic disease [43]. Close contact and respiratory droplets are the key routes of transmission, and it is better to avoid crowding so that asymptomatic transmission may be stopped. Studies have marked the presence of SARS-CoV-2 in the air of ICU's and prolonged exposure to closed ICU rooms can enhance vulnerability and aerosolic transmission [44]. Moreover, the SARS-CoV-2 has been detected in tears, saliva, urine, and gastrointestinal tract of patients [45]. The diagnosis of a 72 h child positive with COVID-19 has enhanced the possibility of vertical transmission from mother to fetus. Therefore, much higher precautions and preventive measures should be adopted by the medical staff inside hospitals and ICU's as well.

4.3. Pathogenesis

Till date, the mechanism of pathogenesis of SARS-CoV-2 is uncertain and unknown. It is believed that the ACE2 receptor present in alveolar epithelial cells provides passage to the virus by binding to its spike protein via S protein [46,47]. Once bound to these epithelial cells strong immune responses and direct toxicity gets induced. The resultant inflammation leads to strong cytokine storm generating lethal lung injury which causes lung collapse and ultimately death [48]. Pathological studies have demonstrated that SARS-CoV-2 patients develop hyaline membrane and possess diffused alveolar damage. The rest of the features resemble to that of MERS and SARS [49]. ACE2 is also found in epithelial cells of different organs including intestines, heart, and kidneys. Therefore, once SARS-CoV-2 infection develops it can invade to multi-organs and cause multi-organ failure. Tumor necrosis factor, macrophage inflammatory protein 1 α , monocyte chemo-attractant protein-1, interferon gamma-induced protein 10 and levels of IL-2, -6, -7 and -10 granulocyte colony-stimulation factor, all are found highly elevated in case of severe infection and are considered accountable for poor outcomes [50]. In some patients enhancement in pro-inflammatory CCR4+CCR6+Th17 cells and over activation of lymphocytes promote the immune-mediated injury resulting in transformation of mild infection to severe [51]. Predominantly, individuals with reduced immunity and comorbidities are more vulnerable to this infection.

4.4. Diagnosis

Based on recent investigations and data collected from ICU's, COVID-19 patients develop hypoxemia and/or dyspnea within one week of disease onset. Patients with higher viral loads develop even serious complications including acute respiratory distress syndrome, multiple organ dysfunction syndrome, coagulation disorder, metabolic acidosis and septic shock [52]. Patients with SARS-CoV-2 infection may develop cerebral congestion, edema and neuropathy; attention should be paid to neurological symptoms in clinical practice. Some patients have been reported of initial neurological symptoms including myalgia, impaired consciousness, anosmia, headache, and acute cerebrovascular distortion. In future studies, these neurological complexities and their therapeutic modalities should be elucidated. Secondary SARS-CoV-2 infection markers include downregulation of peripheral blood lymphocytes, amplification of blood inflammatory agents like C-reactive protein and IL-6, amplified lactic acid levels and scanning results predicting multi-lobar or bilateral infiltration, short-term lesions and pleural effusion [53]. Stimulatingly, some researchers found that the neutrophil-to-lymphocyte ratio (NLR) is an impelling factor that can be used for initial identification of the prognosis of patients with severe COVID-19. Lastly, it should be pointed out that chest CT plays particularly a decisive role in COVID-19 diagnosis and the disease severity assessment. Chest CT has high diagnostic value in patients who have negative Reverse Transcription-Polymerase Chain Reaction (RT-PCR) results but whose clinical symptoms, auxiliary test results, and epidemiological history make them highly suspected patients [54].

Polymerase chain reaction (PCR) method is considered as the gold standard for disease diagnostics; however, it requires expensive equipment and knowledgeable manpower.

5. Natural products with promising antiviral potential against coronaviruses

Natural products are a rich and valuable gift of Mother Nature to human and other beings on this planet [55]. Since time immemorial, natural products, their derivate and their synthetic analogs have been used to overcome many human ailments including viral infections, ranging from mild to severe. Herbal medicine possesses an enormous scope in nutraceutical market. Most interestingly, the availability, acceptability and rich biological properties have diverted the interest of researchers from synthetic to nature [56]. *Nigella sativa* has been reported with substantial suppressive effects against the hepatitis C virus. Several antiviral natural products induce their antiviral effects via targeting the replication mechanism of virus [57]. Moreover, phytochemicals, marine natural products, and biotechnologically synthesized natural products and analogs have been reported to potentially target different infectious viruses. Natural products acts as a pool of chemical compounds explored and developed as medicine against different diseases and pathogens including antiviral, on daily bases [58]. Till date, there are numerous herbal medicines or their constituting chemical agents which have shown promising antiviral properties. However, there is a scarcity of appropriate research for the development of anti-coronavirus drug linked to natural products. Those potential agents may not only help us to overcome coronavirus but also prevents any future viral attack. In humans beings CoV's predominantly result in common cold but complications like SARS and pneumonia can also occur in some cases [59]. The well-known human effecting CoV's include HCoV-HKU1, -NL63, -OC43, -229E and more widely known SARS-CoV-1 and SARS-CoV-2 which caused epidemic in 2002–2003 and ongoing global pandemic, respectively [60]. In addition to this, in 2012 WHO had signified another type of human coronavirus which resulted in MERS (Middle East Respiratory syndrome) and high mortality [61]. There is no 100% vaccine for CoV's infection and efforts are still on to find potential and preventive treatments. Thus there is an immediate need for potential antiviral drugs that can overcome coronavirus

Table 3
Plant extracts with anti-CoV potential [10].

S. no.	Plant extracts	Virus system	Concentration	Targets	IC ₅₀ /EC ₅₀
1.	<i>Anthemis hyalina</i> , <i>Nigella sativa</i> , and <i>Citrus sinensis</i> extracts	Coronavirus-infected HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule 1a cells inoculated with MHV-A59 (mouse hepatitis virus-A59)	1/50 and 1/100 dilution of ethanolic extract (100 g/200 mL)	Increased IL-8 level. Significantly changed the expression of TRPA1, TRPC4, TRPM6, TRPM7, TRPM8, and TRPV4 genes.	Not defined
2.	Herbal extracts (<i>Gentiana scabra</i> , <i>Dioscorea batatas</i> , <i>Cassia tora</i> , <i>Taxillus chinensis</i> , <i>Cibotium barometz</i>)	SARS-CoV	25–200 µg/mL	3CL protease inhibition.	39 µg/mL and 44 µg/mL (two extracts of <i>Cibotium barometz</i>)
3.	<i>Houttuynia cordata</i> aq. Extract	SARS-CoV	0–400 µg/mL	3CL protease and viral Polymerase inhibition.	Not defined
4.	Extract (<i>Rheum officinale</i> Baill., <i>Polygonum multiflorum</i> Thunb.)	SARS-CoV S spike protein	0–100 µg/mL	Inhibits the interaction of SARS-CoV S protein and ACE2.	1–10 µg/mL
5.	<i>Isatis indigotica</i>	SARS-CoV	1–500 µg/mL	3CL protease inhibition.	Not defined
6.	<i>Lindera aggregata</i>	SARS-CoV	10–1–10–4 mg/mL	Unknown	88.2 ± 7.7 µg/mL
7.	<i>Pyrrosia lingua</i>	SARS-CoV	10–1–10–4 mg/mL	Unknown	43.2 ± 14.1 µg/mL
8.	<i>Artemisia annua</i>	SARS-CoV	10–1–10–4 mg/mL	Unknown	34.5 ± 2.6 µg/mL
9.	<i>Lycoris radiata</i>	SARS-CoV	10–1–10–4 mg/mL	Unknown	2.4 ± 0.2 µg/mL

infections in human beings.

China is extensively using the Traditional Chinese Medicine (TCM) alongside Western medicine against SARS-CoV-2 in accordance with the COVID-19 treatment guidelines issued by National Health Commission (People's Republic of China) [62]. The applications of plant based treatments against SARS-CoV-2 are a major research pool which led to the screening of 125 Chinese herbal medicines against COVID-19 with a direct potential of inhibition [63].

Siakosaponin-A, -B2, C and D have been reported to induce substantial antiviral effects against HCoV-22E9 [64]. These are the naturally occurring triterpene glycosides found and extracted from a number of medicinal plants including *Scrophularia scorodonia*, *Heteromorpha* spp. and *Bupleurum* spp [65]. Siakosaponins effectively targeted the viral attachment and entrance in host thereby preventing primary stage HCoV-22E9 infection. Different extracts of *Lindera aggregata*, *Pyrrosia lingua*, *Artemisia annua* and *Lycoris radiata* have been reported with substantial antiviral effects against SARS-CoV out of hundreds of Chinese medicinal herbs considered for screening [66]. Different natural inhibitors like scutellarein, myricetin and phenolic compound from *Torreya nucifera* and *Isatis indigotica*, of SARS-CoV enzymes such as 3CL protease and nsp13 helicase have shown potential and better results. Other natural medicines for CoV's include the water extract of *Houttuynia cordata* [10]. This water extract has been reported to induce antiviral effects via variant mechanisms including 3CL protease inhibition and inhibition of RNA polymerase activity. Different plant extracts with their modes of action against different CoV's have been listed in Table 3.

6. Compounds of natural origin showing antiviral potency against coronaviruses

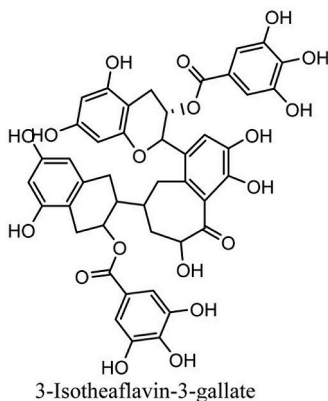
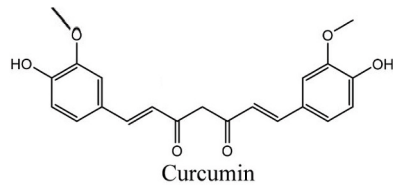
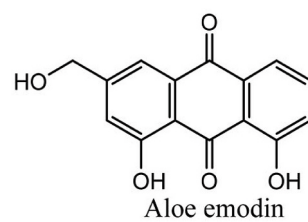
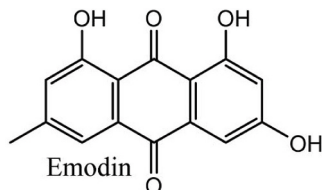
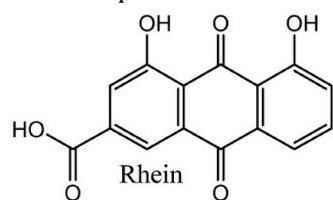
Torreya nucifera-a medicinal plant, is a rich source of flavones and biflavones [67]. These compounds showed potential antiviral activity against SARS-CoV. Out of these compounds, Quercetin, luteolin, apigenin and amentoflavone presented an IC₅₀ value of 23.8, 20.2, 280.8 and 8.3 µM. Three alkaloids including cepharanthine, fangchinoline and tetrandrine, in a recent investigation were shown with inhibitory effects against early stage death stimulated in HCoV-OC43-infected human lung MRC-5 cells with IC₅₀ values of 0.83, 1.01 and 0.33 µM, respectively [68]. The antiviral potency of natural products has inspired many researchers, 221 phytochemicals belonging to different classes were

investigated for antiviral propensity against SARS-CoV's [69]. Out of 221, curcumin, five lignans, two triterpenes, two sesquiterpenes and ten diterpenes revealed anti-SARS-CoV activity. Further, savinin lignin and 8b-hydroxyabieta-9(11),-13-dien-12-one diterpenoid were reported with inhibitory effects on 3CLpro activity in SARS-CoV with SI of greater than 667 [69]. Betulinic acid imposed inhibition of 3CLpro activity and was competitive to savinin against SARS-CoV with Ki value 8.2 µM and 9.1 µM, respectively [69]. Tanhinone I and rosmariquinone are the two tanshinones isolated from *Salvia miltiorrhiza* showed inhibition of replication, PLpro and 3CLpro infections caused by SARS-CoV [70]. Three phenolic compounds; theaflavin-3,3'-digallate, 3-isothaflavin-3-gallate and tannic acid, isolated from black tea were reported with inhibition of SARS-CoV 3CLpro. Furthermore, a number of polyphenolic compounds from *Isatis indigotica*; β-sitosterol, hesperetin, aloe emodin, indigo and singigrin, induced inhibition of SARS-CoV 3CL pro [71]. Research work performed by Yu et al., suggested that scutellarein and myricetin exhibited anti-SARS-CoV 3CLpro activity [72]. Similarly, compounds isolated from *Broussonetia papyrifera* including kazinol J, kazinol F, brousoflavan A, kanizol B, 30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavone, papyriflavonol, 4-hydroxyisolonchocarpin, brousochalcone A and brousochalcone B, all displayed inhibitory effects against SARS-CoV PLpro and 3CLpro [73]. Out of these compounds highest inhibition was exerted by papyriflavonol A with an IC₅₀ of 3.7 µM.

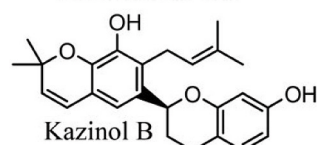
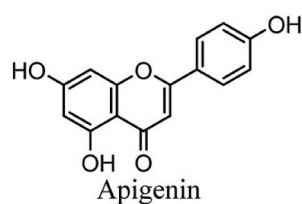
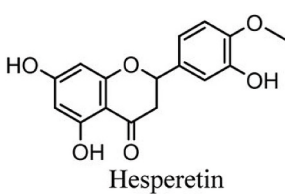
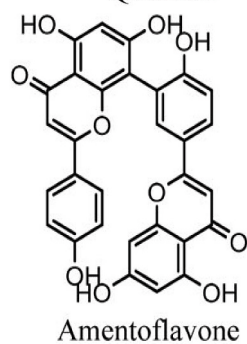
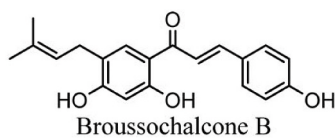
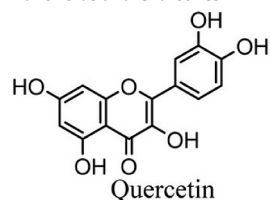
Streptomyces hygroscopicus is rich in hygromycin and showed anti-replicative effects in necrotic liver foci and MHV-A59 (mouse hepatitis virus) in a concentration-reliant fashion [74]. *Bacterium Streptomyces parvulus* antibiotic, actinomycin D suppressed the penetration and attachment of CoV's into host cell. Likewise, ginsenoside Rb1 one of the active members of ginsenosides isolated from *Panax ginseng* showed remarkable antiviral activity [75]. NIH clinical collection investigated 727 compounds for antiviral activities against human and murine CoV's, the most active compound showing promising activity was recorded to be macetaxine alkaloid [76]. *Tylophora indica* is rich in alkaloid content and two alkaloids; 7-methoxycryptopleurine and tylophorine, showed potential inhibition of both S and N protein activity and also inhibited the replication of enteropathogenic coronavirus transmissible gastroenteritis virus [77]. Cepharanthine has been reported to repress the protease enzyme activity in SARS-CoV and recent work performed by Shen et al. showed berbamine substantially inhibited the HCoV-NL63 [78]. The compounds mycophenolate mofetil, emetine and lycorine

Table 4
Molecular structures of some plant based antiviral leads against coronaviruses [10].

Phenolic compounds

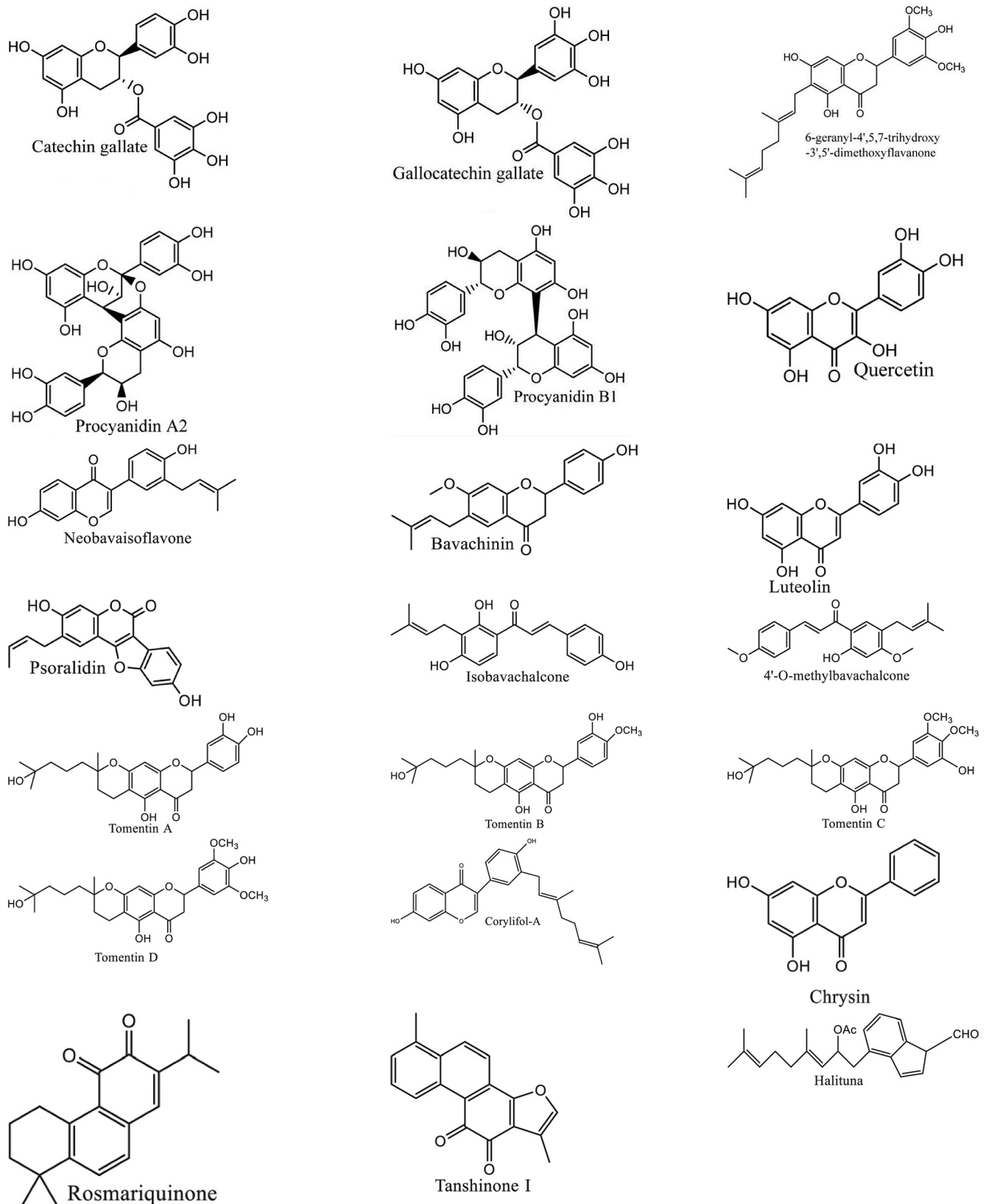


Flavonoids and Chalcones



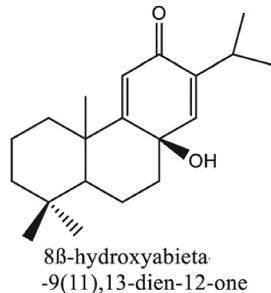
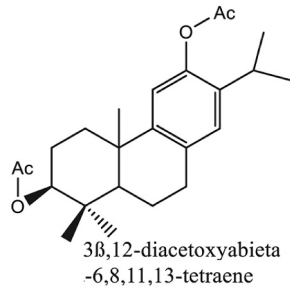
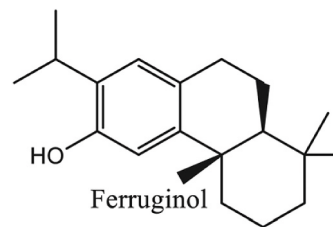
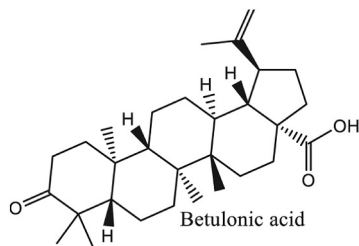
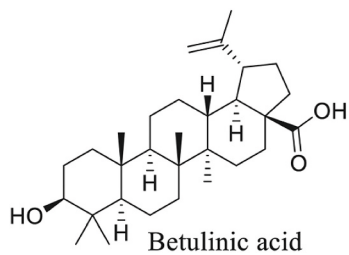
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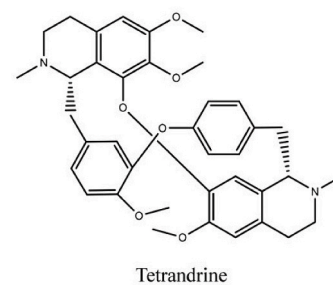
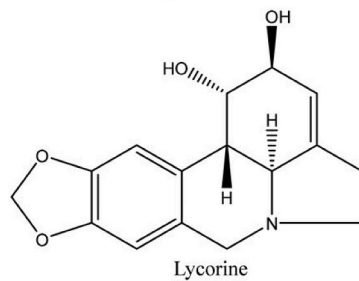
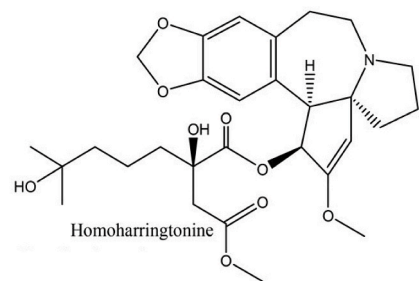
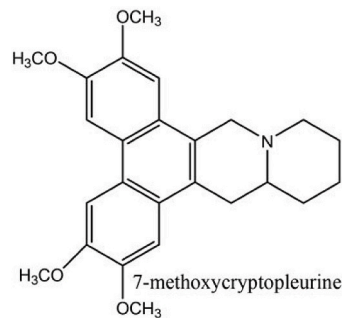
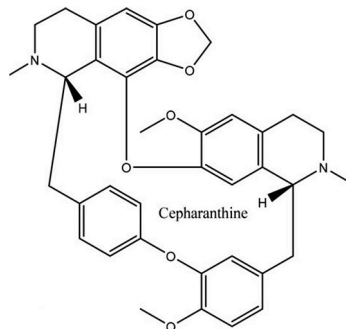
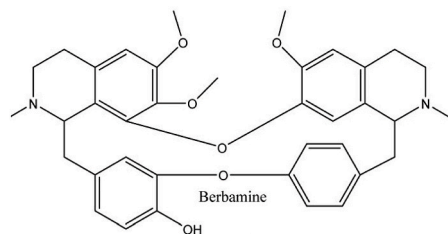
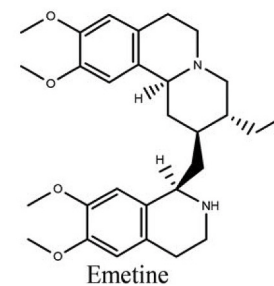
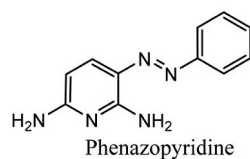
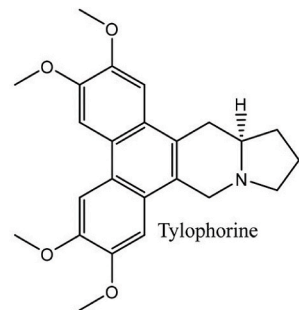


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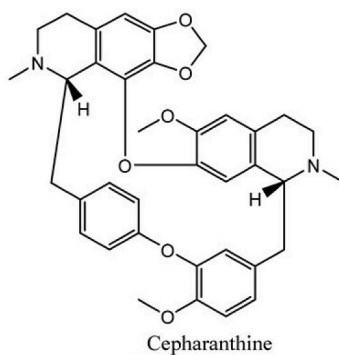
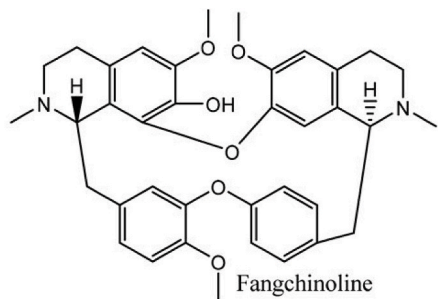


Alkaloids

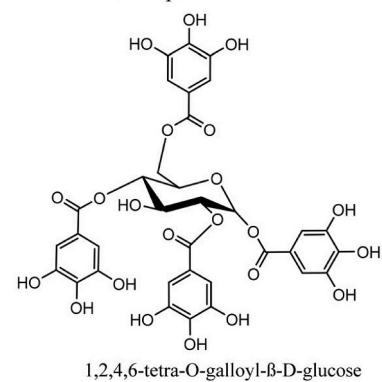
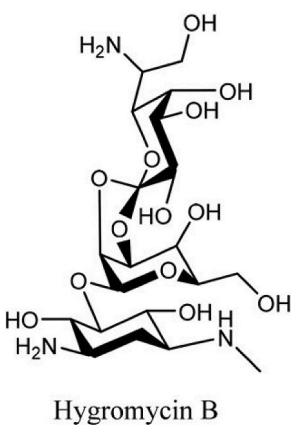
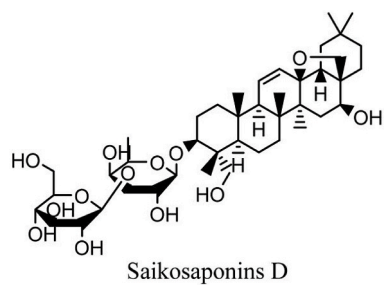
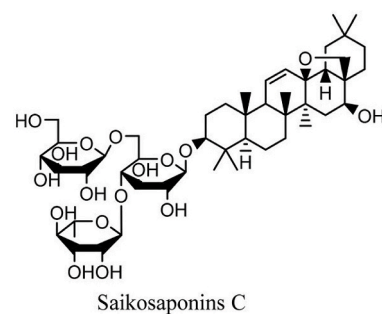
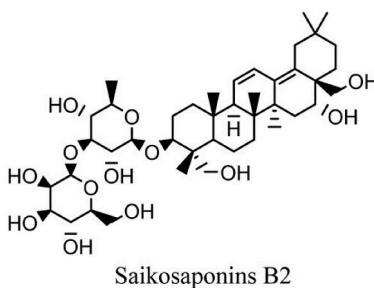
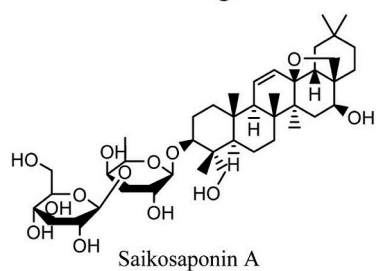
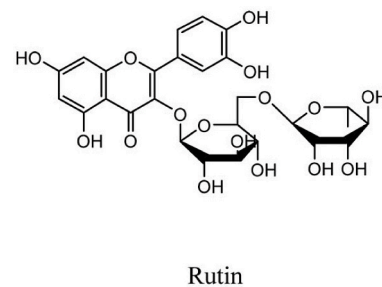
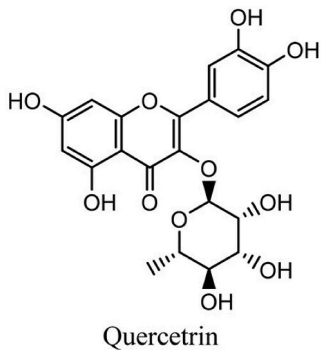
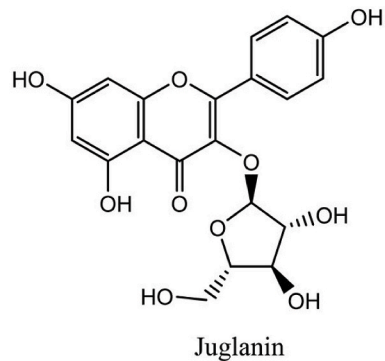


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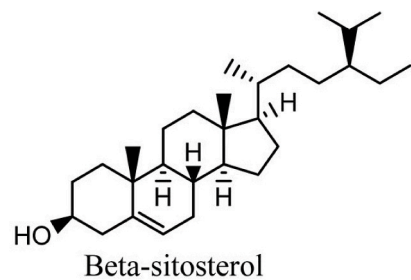
Glycosides



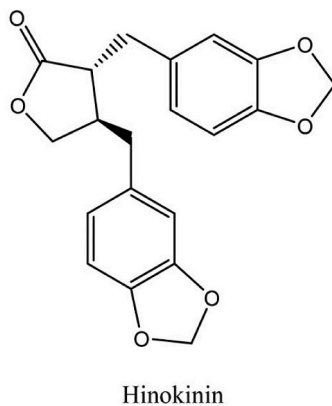
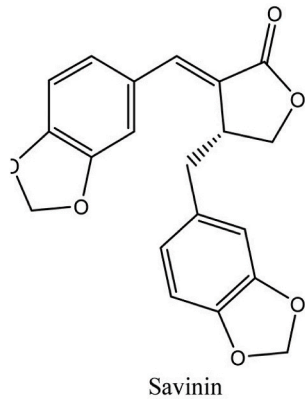
Steroids

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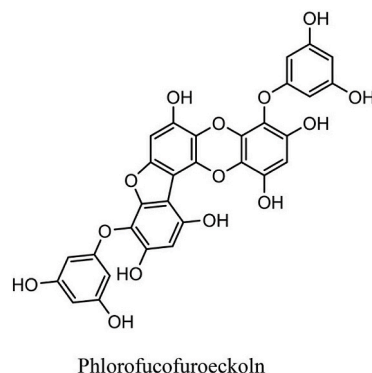
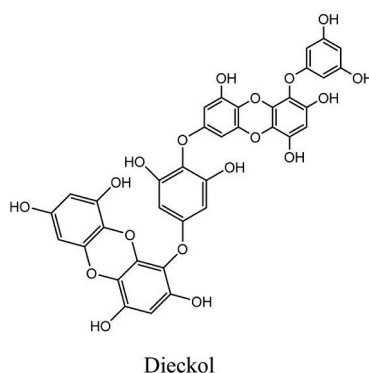
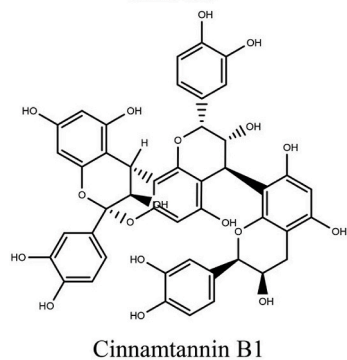
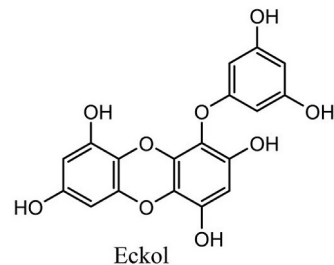
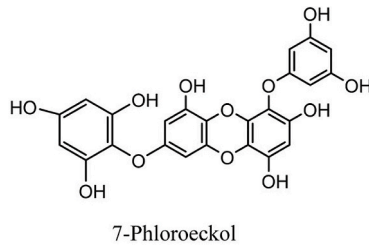
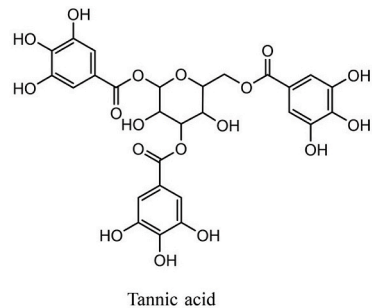
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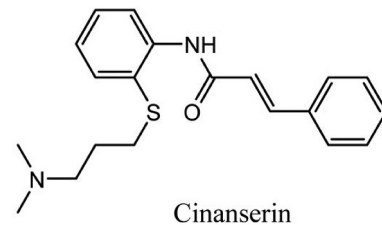
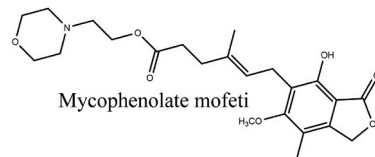
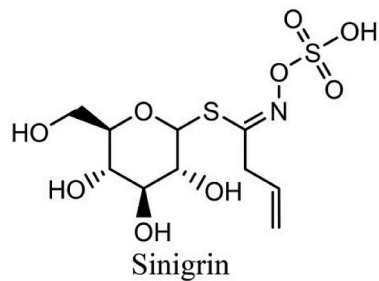
Lignans



Tannins

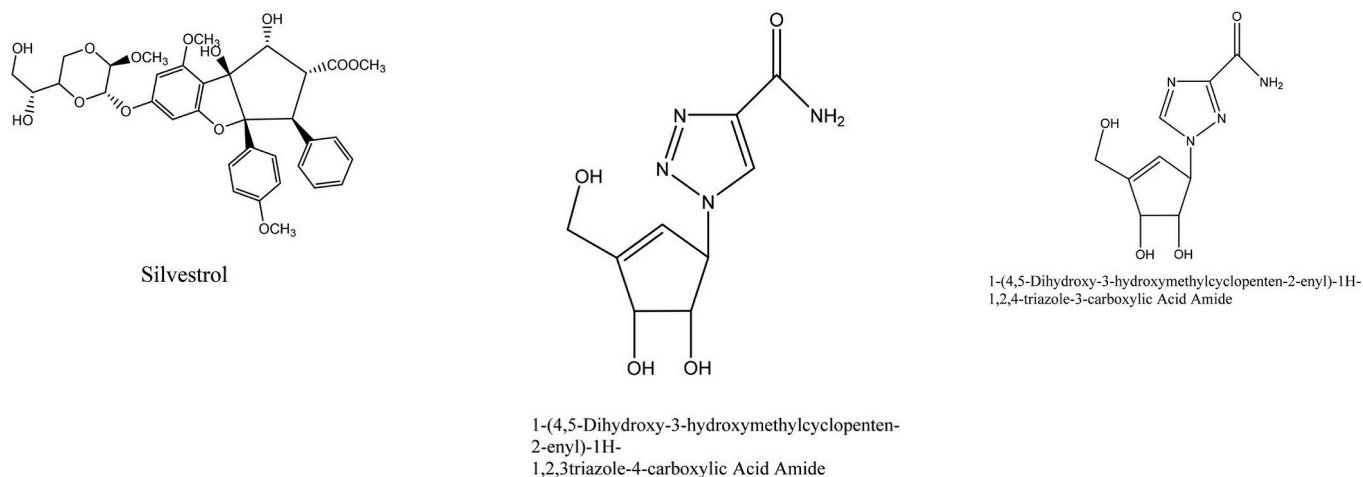


Miscellaneous



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Table 4 (continued)



showed antiviral activities against different human CoV's including MHV-A59, MERS-CoV, HCoV-NL63 and HCoV-OC43. Moreover, emetine and lycorine were observed to arrest cell division, DNA, RNA and protein synthesis whereas mycophenolate mofetil induced immune suppressive effects on mentioned CoV's. Juglanin molecule has been reported with blocking effects on 3a channel in SARS-CoV. In another study, a number of compounds isolated from *Paulownia tomentosa* including 6-geranyl-40-, 5,7-trihydroxy-30,50-dimethoxyflavanone, diplacone, mimulone, 40-O-methyldiplacone, 30-O-methyldiplacone, tomentin A, B, C, D, and E, 40-O-methyldiplacol and 30-O-methyldiplacol were shown with antiviral effects against SARS-CoV PLpro. Likewise, (–)-gallocatechin gallate and (–)-catechin gallate repressed nanoparticle based RNA oligonucleotide against SARS-CoV. On the other hand, quercetin, quercetrin, rutin, cinanserin (1 and 2 dpi) isolated from *Houttuynia cordata* were found to act against murine CoV at 15.63–500 µg/mL [79–81].

Furthermore, 3β,12-diacetoxylabieta-6,8,11,13-tetraene, 8β-hydroxylabieta-9(11),-13-dien-12-one, ferruginol, betulinic acid, curcumin,

savinin, and hinokinin inhibited the replication of SARS-CoV [82]. On the other hand, viral yields as well as viral titers were diminished by ouabain molecule and also declined the viral RNA copies in number. Similarly, the laboratory derivatives; 1-(4,5-dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1H-1,2,3-triazole-4 carboxylic acid amide, 1-(4,5-dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1Himidazole-4-carboxylic acid amide, and 1-(4,5-dihydroxy-3-hydroxymethylcyclopenten-2-enyl)-1H-1,2,4-triazole-3-carboxylic acid amide revealed remarkable anti-SARS-CoV potential [83]. *Tylophora indica* isolated 7-methoxycryptopleurine and tylophorine showed evident inhibition of replication against CoV-infected swine testicular cells [84]. In this study, 7-methoxycryptopleurine (IC₅₀: 20 µM) was extra operative than the tylophorine (IC₅₀: 58 µM). In another study, tylophorine was also found to target viral RNA replication and cellular JAK2-mediated dominant NF-κB activation in CoV at 0–1000 µM [85]. Structure of some of the important antiviral leads from plants against coronaviruses have been listed in Table 4.

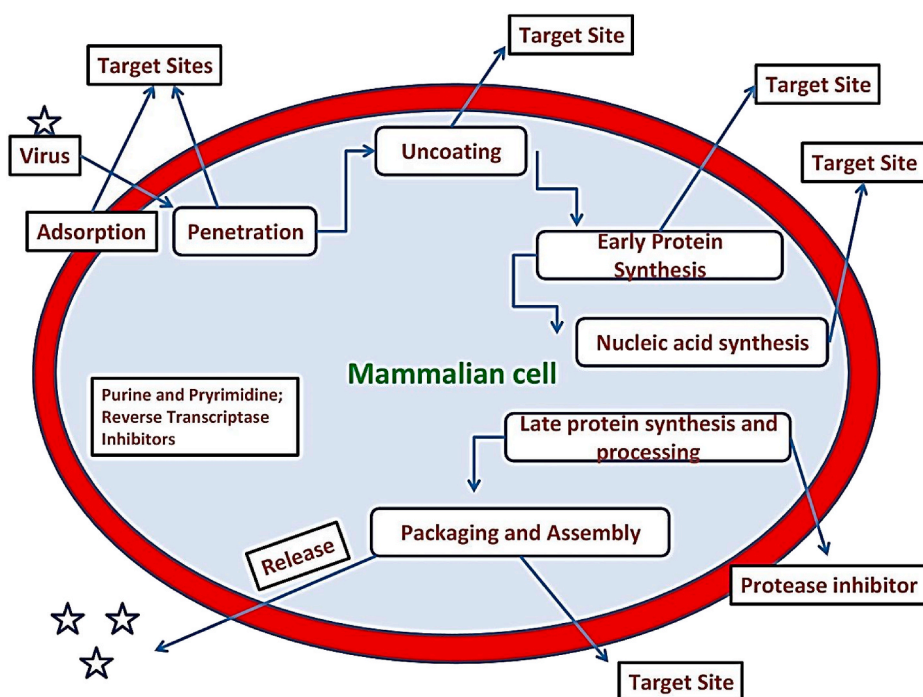


Fig. 4. The virus-host relation and possible target sites during pathogenesis.

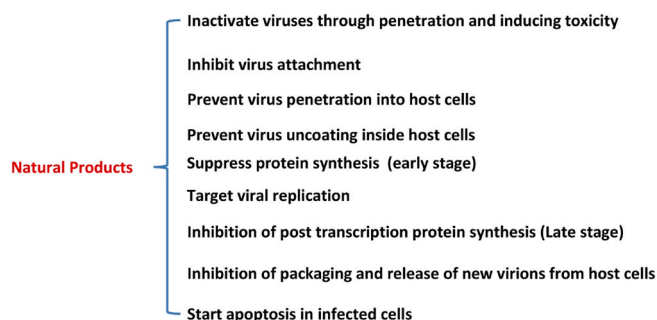


Fig. 5. General mechanism for antiviral activity of different molecular scaffolds from nature.

7. Virus-host interactions and mechanism of antiviral action of natural products

Infectious diseases from time to time have caused serious damages to humanity throughout the world. Viruses are one of the serious agents posing infectious diseases in human beings and have attained resistance to prophylaxis or therapy long before any form of life mainly due to their sole dependence upon the host cells they infect and depend upon for survival and replication. This property of theirs has caused serious issues in drug development and chemotherapy. There are only a handful of antiviral agents available to act upon these infectious diseases caused by viruses included natural product based acyclovir. In order to overcome viruses causing devastating and serious health damages to not only humans but insects, animals, plants, bacteria and fungi as well, world is turning towards natural products for antiviral leads due to diversity in structure and bioactivities. Although the search for naturally occurring products which can interfere with viral infections began with the successful isolation of antibiotics from microorganisms but it has not been as intensive as that of synthetic antiviral agents [86]. This is mainly due to the tendency of most virologists who adopt a rational design of antiviral agents rather than toward empiricism especially with the progress in knowledge of viral replication [87]. Additionally, there are few errors in the screening of crude extracts along with isolations, identifications and purifications of antiviral agents from plant sources. But the recent advancements in the chromatographic and spectroscopic techniques have led down these shortcomings. Some of the antiviral synthetics as well as of natural origin have showed promising antiviral effects *in vitro* but on *in vivo* investigations they were found substandard. This was probably thought of hurdles in transportation of these antiviral agents to the sites of infections especially in case where the infected tissue develops inflammation.

The virus-host interactions begin with the adsorption of virus to the host membrane from where a series of events take place which decide the fate of virus replication as well as drug targets. Viruses mostly replicate by following a temperate or lytic pathway. In a lytic pathway a fast process gets operated in which virus is quickly released as host cell witnesses rupture, lysis and death due to lost content. While in a temperate pathway, virus doesn't kill host cell in fact goes through a period of latency where genetic material of viruses remain inactive inside its host. In some cases of latency the viral genes become integrated into the host's DNA, replicated along with it and passed along to all daughter cells. In time, damage to the DNA or some other event may activate transcription of the viral genes therefore new viral particles can be produced and infected cells are destroyed [6]. Some of the events of virus-host interaction with possible targets are revealed in Fig. 4. The interaction of virus and host going through a series of events; (a) Attachment (adsorption) (b) Penetration into host (c) Uncoating, release and transport of viral nucleic acid and core proteins (d) Nucleic acid polymerase activation (e) Translation of m-RNA to polypeptides (f) Transcription of m-RNA (g) Replication of nucleic acids (h) Protein synthesis (i) Viral polypeptides cleavage into useful polypeptides (j) Morphogenesis and assemblage of viral capsids and precursors (k) Encapsidation of nucleic acid (l) Envelopment (M) Release.

Natural products show significant potency to act upon different target sites in viral-host association. The different attachment sites for antiviral action of natural products in virus-host association have been shown in Fig. 5.

8. Molecular scaffolds from Mother Nature with possible anti-SARS-CoV-2 potential

The development of natural products based drugs against a specific health disorder is more rapid than to develop a potential vaccine. Still, it remains a vertical task due to the enormous structural and chemical varieties of natural metabolites, their chemical extraction and complexity. To save the time involved in natural products research, virtual screening proves to be advantageous for phytochemical screening of natural products and their extracts. This virtual screening is termed as *in silico* analysis via molecular docking. Since the appearance of COVID-19 as a global pandemic, natural products were subjected to molecular docking to check their role against it. Independent of the class, natural products like steroids, terpenes, quinones, fatty acids, alkaloids, flavonols and flavones revealed similar docking score or binding energy, to that of repurposed drugs like chloroquine and remdesivir, with replicative proteins is SARS-CoV-2 (Fig. 6) including TMPRSS2, 3CLpro and ACE2 [88,89]. More emphasis was laid on ACE2 inhibitors as a probable consequence of primary binding concerning COVID-19

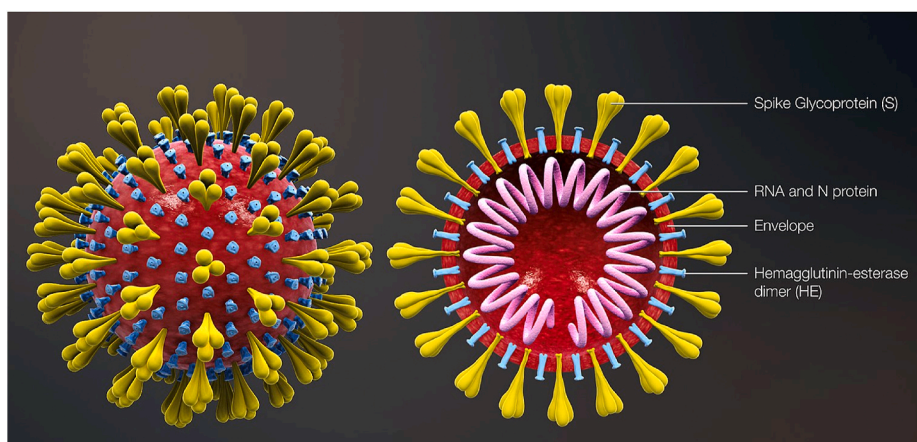


Fig. 6. Diagrammatic representation of the virion structure exhibiting typical spikes of the virus that are reminiscent of solar corona hence the name "corona". (Source: https://commons.wikimedia.org/wiki/File:3D_medical_animation_corona_virus.jpg).

Table 5

Phytochemicals screened against ACE2 as docking target and their binding energy. “x” represents the repurposed drugs used for reference.

S. no.	Phytochemical	Binding energy (Kcal. Mol ⁻¹)	Reference
1.	Zhebeinoside	-6.8	[90]
2.	Verdine	-6.6	[90]
3.	Pseudojervine	-6.8	[90]
4.	Hupehemoside	-7.1	[90]
5.	Nobiletin	-5.42	[91]
6.	Neohesperidin	-3.78	[91]
7.	Hesperetin	-6.09	[91]
8.	Hesperidin	-4.21	[91]
9.	Naringenin	-6.05	[91]
10.	Narigin	-6.85	[91]
11.	Chloroquine ^x	-8.01	[92]
12.	Phylligenin	-7.80	[92]
13.	Hinokinin	-7.11	[92]
14.	Withaferin A	-9.63	[92]
15.	Quercetin	-8.66	[92]
16.	Isoaloesin	-7.83	[92]
17.	Aloin	-8.38	[92]
18.	Taiwanhomoflavone A	-7.60	[93]
19.	Epicatechin-(4β,8)-epicatechin-(4β,6)-catechin	-8.20	[93]
20.	Epicatechin-4-epigallocatechin	-7.20	[93]
21.	Quercetin 3-glucosyl-(1,4)-rhamnoside	-6.50	[93]
22.	Lactucopicrin 15-oxalate	-8.30	[93]
23.	Lactucopicrin	-8.30	[93]
24.	Vitetrifolin D	-7.30	[93]
25.	Myricitrin	-7.10	[93]
26.	Apigenin	-7.10	[93]
27.	Kaempferol	-7.20	[93]
28.	(-)-Asperlicin C	-9.50	[93]
29.	Cassameridin	-8.10	[93]
30.	Oriciacridone F	-6.70	[93]
31.	Remdesivir ^x	-7.80	[93]
32.	Afzelin	-7.10	[93]
33.	Isoquercitrin	-7.80	[93]
34.	Silybin	-10.5	[92]
35.	Tetrahydrocurcumin	-8.00	[92]
36.	Corydine	-6.04	[92]
37.	Imperialine-3-β-D-glucoside	-7.1	[90]

replication. Some of the natural products subjected to virtual screening against ACE2 and 3CL Pro docking targets are listed in Tables 5 and 6.

Azadirachta indica (Neem), an indigenous Indian medicinal plant used in Traditional Indian Medicine, has been reported of remarkable antiviral potency against avian influenza virus, bursal disease virus, Newcastle disease virus, group B coxsackievirus, dengue virus type-2, duck plague virus, poliovirus type-1 and bovine herpes virus type-1 [98]. Neem has been extensively used to treat asthma, cough, fever and diarrhea in Ayurvedic system of medicine; these are the most prevalent symptoms in SARS-CoV-2 infection [99]. Under viral attack, Neem intake amplifies cell and humoral mediated immune responses. Thus, multidimensional antiviral therapeutic potency of Neem led to hypothesizing its possible implications on COVID-19 along with the modern system of medicine. It is believed that Neem may prove a leading natural agent against COVID-19 but requires translational experimentation and a series of experimental database that can support its activity.

India is putting all its efforts to design and discover natural products against SARS-CoV-2. As a result recently Dr. Shekhar Mande (Director General, Council of Scientific and Industrial Research; CSIR) reported that ACQH (secure drug) a plant based drug has been approved for clinical trials. The medicine has been developed by the Sun Pharmaceutical in association with CSIR Indian Institute of Integrative Medicine (IIIM) Jammu and The International Centre for Genetic Engineering and Biotechnology (ICGEB) New Delhi with the support of Direct Benefit Transfer (DBT) and CSIR. Director General said “We are going to attempt to combat COVID-19 and we hope that it is successful”.

Table 6

Phytochemicals screened against 3CL Pro as docking target and their binding energy. “x” represents the repurposed drugs used for reference.

S. no.	Phytochemical	Binding energy (Kcal. Mol ⁻¹)	References
1.	Epicatechin-(4β,8)-epicatechin-(4β,6)-catechin	-10.60	[93]
2.	Taiwanhomoflavone A	-9.60	[93]
3.	Quercetin 3-glucosyl-(1,4)-rhamnoside	-9.90	[93]
4.	Epicatechin-4-epigallocatechin	-10	[93]
5.	Lactucopicrin	-8.30	[93]
6.	Lactucopicrin 15-oxalate	-8.20	[93]
7.	Myricitrin	-8.90	[93]
8.	Vitetrifolin D	-7.30	[93]
9.	Kaempferol	-7.80	[93]
10.	Apigenin	-7.80	[93]
11.	(-)-Asperlicin C	-9.70	[93]
12.	Cassameridin	-9.30	[93]
13.	Oriciacridone F	-9.10	[93]
14.	Remdesivir ^x	-8.20	[93]
15.	Afzelin	-8.80	[93]
16.	Isoquercitrin	-8.20	[93]
17.	Amentoflavone	-9.28	[94]
18.	Glabrolide	-9.16	[94]
19.	Zeylanone	-9.12	[94]
20.	5,7,30,40-tetrahydroxy-2'--(3,3-dimethylallyl) isoflavone	-29.57	[95]
21.	Mirycitrin	-22.62	[95]
22.	Methyl rosmarinate	-20.62	[95]
23.	Amaranthin	-18.14	[95]
24.	Betulinic acid	-4.23	[63]
25.	Nelfinavir ^x	-10.72	[96]
26.	Apigenine-7-glucoside	-7.83	[96]
27.	(E)-β-Farnesene	-27.56	[97]
28.	Epicatechin-gallate	-6.67	[96]
29.	Gingerol	-5.38	[96]
30.	Zingerol	-5.40	[96]
31.	Sugiol	-6.04	[63]
32.	Cryptotanshinone	-6.23	[63]
33.	N-cis-feruloyltyramine	-6.25	[63]
34.	Quercetin	-8.47	[96]
35.	Kaempferol	-8.58	[96]
36.	Lupinavir	-9.41	[96]
37.	α-Copaene	-20.08	[97]

Glycyrrhiza glabra (licorice) may be involved to neutralize the activeness of SARS-CoV-2 due to the presence of active constituents like liquiritin, isoliquiritin, glycyrrhetic acid and glycyrrhizin [100]. An investigation regarding the involvement of natural products against COVID-19 has reported that plant extracted components target -OH (hydroxyl) groups of active components in virus thereby deactivating them through esterification.

Table 7

Molecules and their plant source showing efficacy against SARS-CoV-2.

	Plant source	Name of the plant metabolite
1.	Edible amaranth (<i>Amaranthus tricolor</i>)	Amaranthin
2.	Chinese liquorice (<i>Glycyrrhiza uralensis</i>)	Licoleafol
3.	Myricetin 3-O-beta-D-glucopyranoside	Tea tree (<i>Camellia sinensis</i>)
4.	Chinese flowering ash (<i>Fraxinus sieboldiana</i>)	Calceolarioside B
5.	Indian gooseberry (<i>Phyllanthus emblica</i>)	(2S)-Eriodictyol 7-O-(6''-O-galloyl)-beta-D-glucopyranoside
6.	Common bean (<i>Phaseolus vulgaris</i>)	3,5,7,3',4',5'-hexahydroxy flavanone-3-O-beta-D-glucopyranoside
7.	Marubio oscuro (<i>Hyptis atrorubens</i> Poit)	Methyl rosmarinate
8.	Wax myrtle (<i>Myrica cerifera</i>)	Myricitrin
9.	Mojave indigo bush (<i>Psoralea arborescens</i>)	5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone

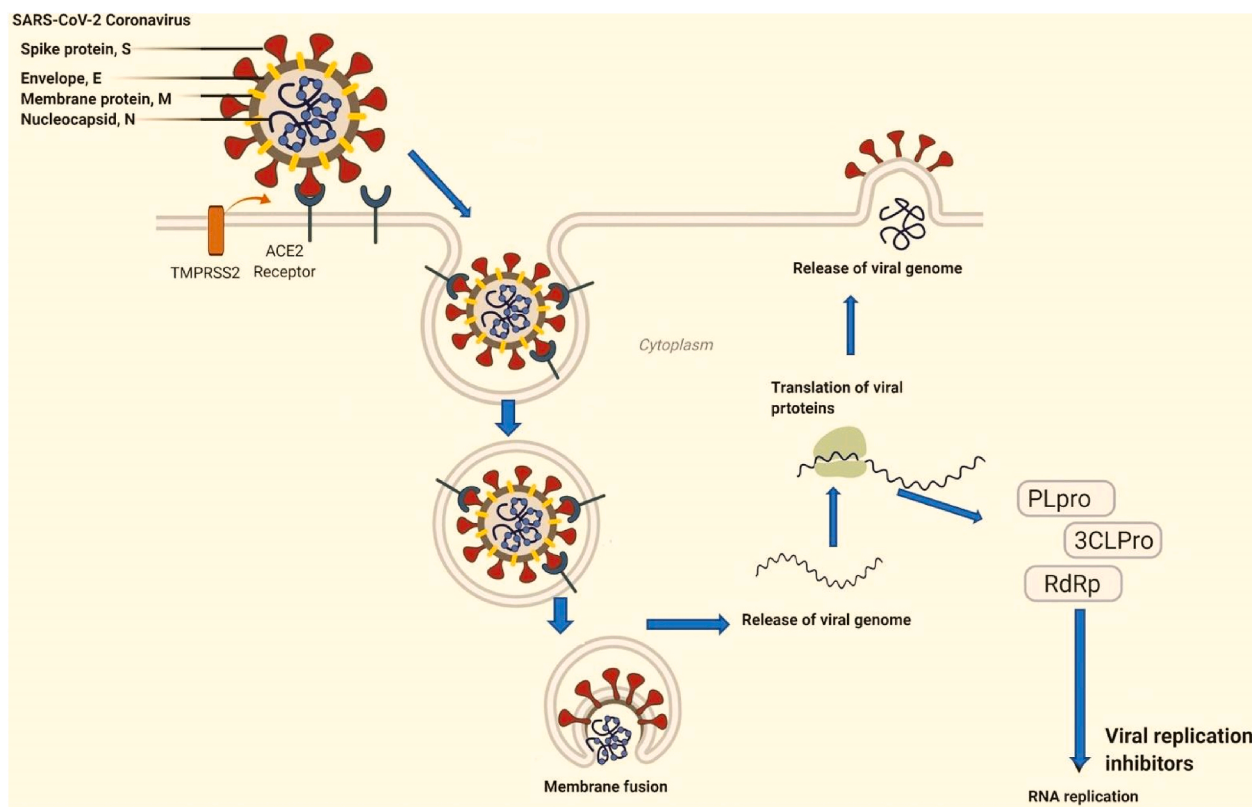


Fig. 7. Representation of virus and host membrane interaction and post association changes inside cytoplasm.

In a similar study, the Max Planck Institute and Interfaces (Potsdam, Germany) in collaboration with ArtemiLifer Inc. (US based company) medicinal researchers have shown in laboratory studies that aqueous and ethanolic extracts of specially bred sweet wormwood plants (*A. annua*) are active against the new coronavirus that has caused the COVID-19 pandemic [101].

The genomic studies of SARS-CoV-2 have reported that it is more similar to that of SARS-CoV-1, which caused an epidemic in at least 26 countries during 2002 and 2003. Therefore, Huazhong Agricultural University and Guangxi University researchers considered 3D homology model of sequence and screened medicinal plant library of 32,297 capable antiviral TCM compounds and phytochemicals. The outcomes of the investigation specified 9 plant based molecules which may be developed as potential drugs against COVID-19 (Table 7) [95].

Further, Indonesian researchers used main protease (Mpro) as target strategy and tested different inhibitors against Mpro in COVID-19 using molecular docking [101]. They went for bioactive molecules from plant source and came up with lopinavir and nelfinavir as potential treatment for SARS-CoV-2. In addition to this, epicatechin-gallate, catechin, curcumin, oleuropein, apigenin-7-glucoside, demethoxycurcumin and luteolin-7-glucoside, were reported of significant inhibitory potential against COVID-19 MPro [101]. Experimental data are needed to support these virtual molecular docking results.

9. Potential targets of antiviral drugs against coronaviruses

Coronaviruses (CoVs) are a large and diverse family of enveloped and single stranded RNA viruses. This exhibit broad host ranges and infect many mammalian and avian species causing gastrointestinal, upper respiratory, hepatic and central nervous system diseases [102]. Before 2019, only six CoVs were well-known to infect humans and cause health issues like HCoV-229E, HCoV-NL63, HCoV-OC43, HKU1, SARS-CoV and MERS-CoV. With birth of SARS-CoV-2, new member of human coronavirus has been added to this family. Probably the first

reported coronavirus-related disease was feline infectious peritonitis in 1912. Nevertheless, until the late 1960s coronaviruses did not receive much attention and were not recognized as lethal for humans. In 2003, human coronaviruses (HCoVs) received global attention with emergence of the severe and acute respiratory syndrome coronavirus (SARS-CoV) which became highly contagious and deadly and infected more than 8000 people in 32 countries, killing about 10%. With SARS-CoV in focus, increased research and studies on coronaviruses soon led to the breakthrough of one more human coronavirus (HCoV-NL63), prevalent in 7% of hospital patients and related with bronchiolitis and, probably, conjunctivitis. HCoVs account for 10%–20% of common colds, and cause respiratory tract infections, gastroenteritis, and rare cases of encephalitis.

Coronaviruses have the largest genomes among RNA viruses. It is enveloped and packed inside by a helical capsid formed of Nucleocapsid protein (N). Three structural proteins viz. membrane protein (M), envelope protein (E) and spike protein (S) are associated with viral envelop. Membrane protein (M) and envelope protein (E) are involved in viral assembly whereas spike protein (S) has critical role in virus entry into host cells. Besides, some coronaviruses encode hemagglutinin-esterase protein (HE) as well. Moreover, spike protein besides mediating virus entry, determines viral host range, tissue tropism and is a major inducer of immune response in host cells. Spike protein possesses three segments: short intracellular tail, single pass transmembrane anchor and a large ectodomain. Receptor binding subunit S1 and membrane-fusion subunit S2 are part of ectodomain. Studies from electron microscopy have revealed spike as clove-shaped trimer with three S1 heads and trimeric S2 stalk [6,7,103–105]. While entering into the cell, S1 of spike protein binds to cell surface receptor for viral attachment and S2 stalk fuses with host and viral membranes, allocating viral genomes to host cells (Fig. 7). These are the initial and critical steps in coronavirus infection cycle and also serve as main targets for human interventions.

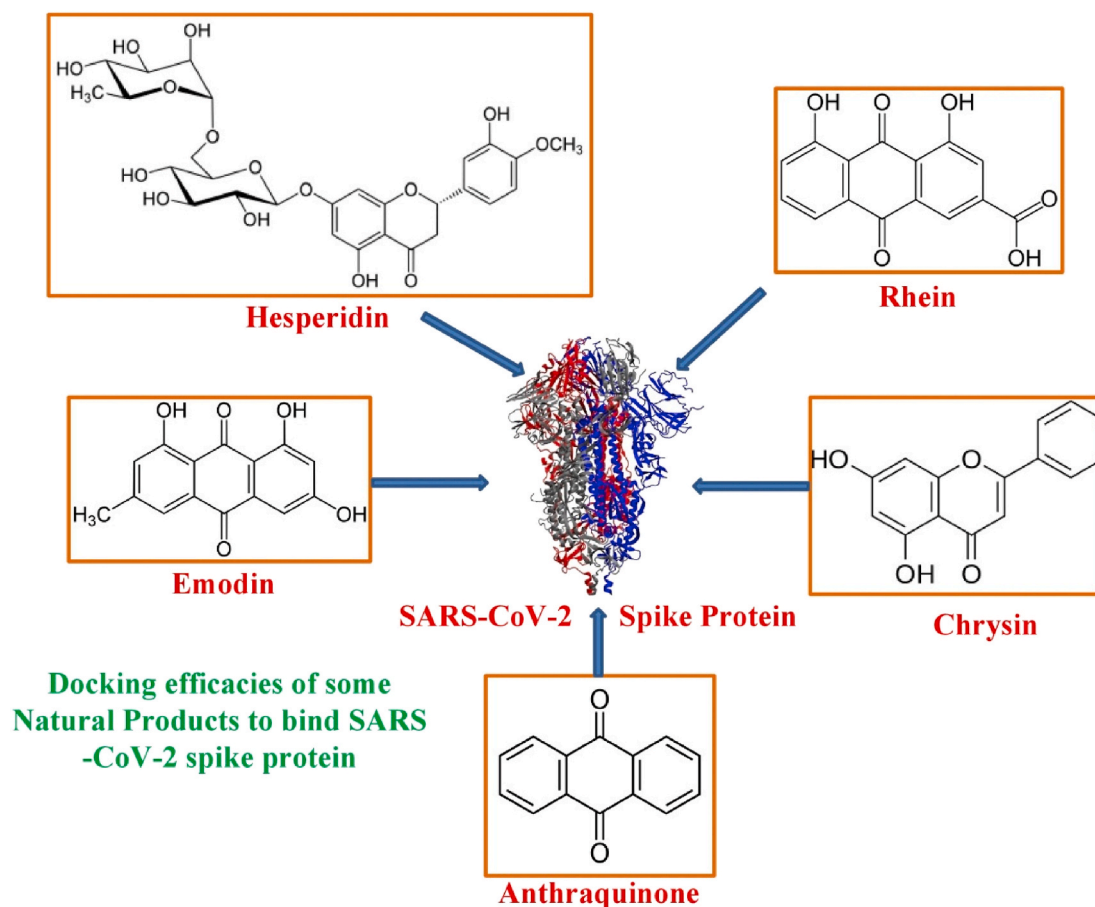


Fig. 8. Natural products that show significant binding score to spike protein of SARS-CoV-2.

10. Receptor recognition by coronavirus spike proteins

Coronaviruses exhibit a complex pattern for receptor recognition [106]. The alpha coronavirus HCoV-NL63 and beta coronavirus SARS-CoV both identify a zinc peptidase angiotensin converting enzyme 2 (ACE2) [107,108]. Other alphacoronavirus such as TGEV, PEDV and PRCV recognize aminopeptidase N (APNO) [109–112]. MERS-CoV and HKU4 recognize a serine peptidase, dipeptidase 4 (DPP4) [113,114]. Similarly, MHV recognizes a cell adhesion molecule, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) [115,116]. BCoV and OC43 recognize sugar [117]. In addition, alpha coronavirus TGEV and PDEV and gamma coronavirus IBV also use sugar as receptors or coreceptors [110,118–121]. Besides their role in viral attachment, these receptors have their own physiological functions [122–128]. Receptor diversity is an exceptional feature of coronaviruses. Subunit S1 of coronavirus consists of two domains, N-terminal domain (S1-NTD) and C-terminal domain (S1-CTD), have been identified with one or both of them potentially functioning as receptor binding domains (RBD). S1-NTDs binds sugar [110,111,129,130] with beta coronavirus MHV S1-NTD as only exception that recognizes protein receptor CEACAM1 [131]. S1-CTDs recognize protein receptors like ACE2, DPP4 and APN [110,132–137]. Crystal structures of S1 domains along with functional studies have revealed many interesting features about receptor recognition by coronaviruses [6].

SARS-CoV 2 and SARS-CoV both encode large (1253aa; 1273 aa) spike protein [138]. Sequence identity has revealed 76% identity of spike protein between these two origins with large variation at N terminus. For SARS-CoV there is receptor binding domain in the S1 region interacting with ACE2 with high affinity. For SARS-CoV2, it has also come to the fore that it uses S1 RBD to bind ACE2 for entering human

host cells. There is 73.5% sequence identity in RBD regions for these two viruses. Nevertheless, many non-conserved mutations have accumulated in two structural regions interacting directly with ACE2 [139]. Crystal and cryo-EM structures of SARS-CoV spike-ACE2 complex have revealed that regions 1 and 2 engage in hydrophobic interactions and hydrogen bonding with ACE2. Surprisingly, some residues in these regions have been replaced in SARS-CoV2, which eventually will lead loss of some of these interactions. Besides, SARS-CoV2 RBD has been predicted to be weakly interacting with ACE2 as compared to SARS-CoV [140]. In case of S2 region, there is no similarity in sequence between these two virus origins. After virus entry, genomic RNA attaches to the host ribosome and translates two large coterminal polypeptides, which are further processed by proteolysis for packaging into new virions [141]. Coronavirus main proteinase (3CLpro) and the papain-like protease (PLpro) are main proteases that participate in proteolysis process [142]. Furthermore, for replication of RNA, CoV encodes RNA dependent RNA polymerase RdRp, a replicase [143]. As these four proteins viz., Spike, CLpro, PLpro and RdRp, are key for pathogenesis of coronaviruses, therefore, therapeutics currently target them for treatment of SARS-CoV2.

Owing to its role in receptor binding and membrane fusion, spike protein of SARS-CoV is an ideal target for vaccine and antiviral development (Fig. 8). Several strategies and approaches like killed SARS-CoV, live-attenuated SARS-CoV, Viral vectored vaccines and DNA vaccines have been successfully experimented against animal SARS-CoVs [144–146]. For SARS-CoV 2, similar approaches could be applied for developing vaccines. Use of SARS-Cov 2 RBD in combination with immunity promoting adjuvants as vaccine to trigger antibodies in human body is an alternative approach to neutralize the virus [147]. Even though, therapeutic antibodies and peptides have been developed to

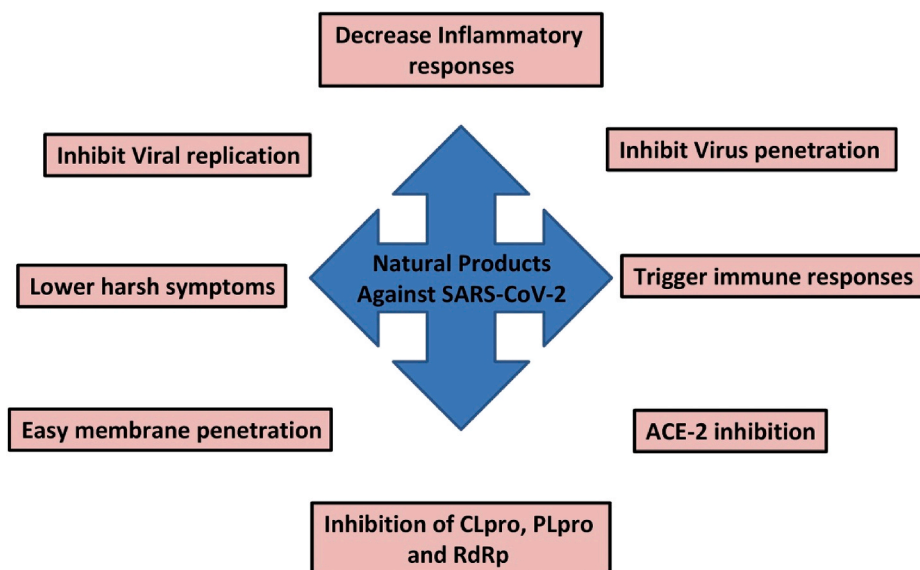


Fig. 9. Some potential targets of natural products against coronaviruses.

neutralize SARS-CoV spike protein, in case of SARS-CoV 2 these are expected to have little use as interactions between spike RBD for binding ACE2 are quite different in SARS-CoV2 and SARS-CoV. Novel antibodies and therapeutic peptides that potentially interact with RBD of SARS-CoV2 can be exploited to block its interaction with ACE2 [138]. In this regard, several research groups have developed methods for building macrocyclic peptide libraries for applying them to the speedy identification of macrocyclic peptide ligands for drug targets [148–153]. It will potentially lead to quick discovery of anti- SARS-CoV2 macrocyclic peptides. Learning from SARS-CoV studies, possible alternatives include direct use of peptides derived from SARS-CoV2 RBD and ACE2. SARS-CoV peptides derived from its RBD and ACE2 as new therapeutics against SARS-CoV infection by blocking binding of RBD and ACE2. For COVID-19, a possible quick solution to block RBD-ACE2 interaction is to use SARS-CoV 2 based peptides and cocktails thereof [138].

Viruses including human coronaviruses involve host cellular factors for successful replication process during infection [154]. Organized and systematic identification of Virus host protein – protein interactions (PPIs) present an effective way to elucidate mechanisms of viral infection [155]; 88 [138]. Afterwards, targeting cellular antiviral targets like virus host interactome offer novel strategy for the development of effective treatments against viral infections including, SARS-CoV and MERS-CoV [156].

SARS-CoV 2 and SARS-CoV share about 82% sequence identity at genomic RNA level whereas RdRp proteins have remarkable 96% sequence similarity. 3-chymotrypsin-like protease (3CLpro), RNA-dependent RNA polymerase, papain like protease (PLpro) and spike (S) proteins are major targets of drugs currently employed for SARS-CoV 2 treatment [157]. However, as of now no established antiviral therapies or preventive vaccines are available for its treatment [158]. RdRp with large and deep groove as an active site for RNA polymerization, shows variation at distal site of this active region for SARS-CoV2 as compared to SARS-CoV [159]. High sequence conservation between two enzymes makes it likely targeted with equal efficacy and potency by potent agents developed for SARS-CoV RdRp. Aurintricarboxylic acid (ATA) was one such compound with antiviral activity which targets RdRp. It is an anionic polymer which binds to protein targets and has been demonstrated to prevent replication [160–162]. But, despite computational models authorized against known ATA targets, predicting RdRp as bound target, no experimental evidence has demonstrated this relationship [163]. Several synthetic compounds including hydroxy-chloroquine and chloroquine [164,165], phosphate have been

occasionally used. Antiviral medications such as remdesiver [166,167], lopinavir [168] and arbidol [169] have shown promising results. Nucleoside analogs, peptide EK1 and neuraminidase inhibitors are some other treatments explored for controlling COVID-19 pandemic [170]. Purified natural products and traditional herbal medicines have also been surveyed and explored for developing novel antiviral drugs.

83 compounds were screened in Chinese traditional medicines against RdRp of SARS-CoV 2 [171]. Likewise, Zhang et al. [63] screened 115 compounds for further studies. Most of these were naturally occurring polyphenolic compounds such as kaempferol and quercetin, which have previously received considerable interest for treating other disease [172–174].

About 64 naturally occurring compounds were screened for activity against SARS-CoV helicase by Ref. [72]. The polyphenolics scutellarein and myricetin were identified as promising candidates. Both compounds did not directly inhibit helicase activity but inhibited SARS-CoV helicase (nsP13) [175]. reported that Chinese herbal medicine Lianhuaqingwen (mixture of plant species) showed antiviral activity against SARS-CoV 2, though EC50 was quite high (–411 µg/mL). Quercetin, a polyphenolic compound found in berries and herbs [176,177] also shows antiviral activity has IC50 value of 8.6 ± 3.2 µM against SARS-CoV PLpro [73]. Ethanolic extracts of *Psoralea corylifolia* seeds also possess polyphenolic compounds which were found to be responsible for activity against SARS-CoV PLpro [178].

Plant lectins are other naturally occurring compounds that may inhibit SARS –CoV. A total of 33 plant lectins were screened for the activity against SARS-CoV using cytopathicity effect (CPE) assay revealing a EC50 value of 0.45 ± 0.08 µg/mL for *Lycoris radiata* agglutinin [179]. In clinical trials, some lectins have demonstrated reasonable to good tolerability [180], hence with more testing, they may prove more promising classes of naturally derived compound(s) for the treatment of SARS-CoV- 2 and other coronavirus infections.

Silvestrol, which is a phytochemical from *Aglaia* sp., was found potent inhibitor of MERS-CoV replication [181]. It inhibits viral replication by binding RNA helicase eIF4A and preventing formation of replication/transcription complexes [181]. Likewise, Griffithsin, a lectin found in *Griffithsia* genus, is promising inhibitor of MERS-CoV. Its carbohydrate binding domains allows it to bind specifically to glycans of spike proteins and inhibit attachment of virus to the host cells in vitro trials against MERS-CoV [182] and several other human corona viruses [183]. Griffithsin also has low systematic toxicity with specificity index against HCoV cells estimated between 30 and 3100 [182], and hence has

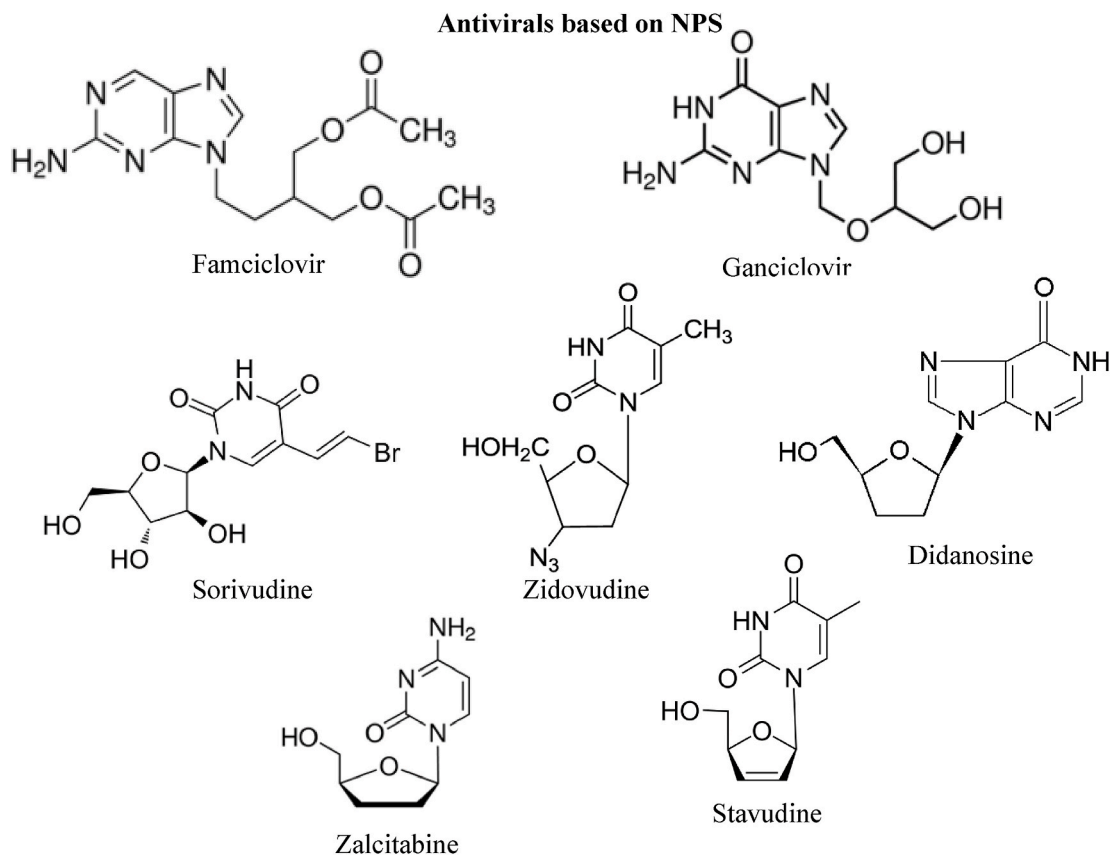


Fig. 10. Structure of some approved antiviral drugs based/modeled upon natural products.

the potential to be considered for clinical trials against SARS-CoV 2 [184]. Some of the possible targets of natural products are listed in Fig. 9.

11. Toxicity and adaptability of natural products in antiviral action

A big challenge is to find efficient drug candidates that can overcome infectious diseases with lower or no side-effects. Besides advancements that are being made towards the drug development for many diseases like HIV, AIDS, malaria and cancer, these drugs still cause unwanted side-effects to huge human population globally. Presently, it will be a viable methodology to turn back to "Nature" for answers because of their rich track record in the past. The natural products like taxol, vinblastine, quinine and artemisinin are well established drugs now used in the treatment of cancer and malaria. To address global health issues, the research and drug development concerning natural products plays a significant role in drug discovery. Faced with many stresses and challenges, coupled with being sedentary, plants have developed many molecules to ward off attacks from animals and environmental insults [185]. These phytochemicals show remarkable ability of colours, fragrances and undeniably toxicity. The use of plants by early humans against diseases must have been a trial and error exercise based on necessities. Several plants have been historically used for medicinal purposes including different pathological conditions [186–188]. Natural products are a pool of drugs especially for anticancer and antimicrobial agents. Despite significant potential, traditional medicine systems, which comprises mostly of natural products, is overshadowed by modern medicine. However, an increased interest towards natural products has been seen from previous few decades in both developing and developed countries due to promising health promontory and medicinal effects. Indeed, several plant extracts are now serving as prescribed

drugs in some big nations like Germany, UK, China and France [189]. Nearly a quarter of entire EMA and FDA approved drugs are based on phytochemicals, with renowned ones such as morphine and paclitaxel. There are certain drawbacks that make natural products based medicine some times less effective like scarcity of standard procedures, isolation of pure compounds, lesser known biological mechanisms and sub-standard clinical trials.

The therapeutic activity of plant extracts is usually because of the synergistic and simultaneous action of several chemicals. Given the complex nature of many diseases including cancer and degenerative diseases, it is not surprising that the reliance on single compound-based drug discovery has failed to provide effective cures. Plant-based drug discovery therefore must start with a combinatorial approach when evaluating candidate compounds. The advent of novel technologies including quantum computing, profiling techniques, computational biology techniques, big data, microfluidics and artificial intelligence will enable scientists to use a combinatorial approach to harness the therapeutic properties of plant-based natural products and simultaneously study their molecular effects in physiological conditions [190]. It is however possible that not all components of plant extracts have measurable effects.

Many antiviral active compounds are too toxic for therapeutic applications. However, natural products remain the best resource for chemically diverse new lead entities that could serve for future development as potent and safe antiviral agents. Recent analysis of the number and sources of antiviral agents reported mainly in the annual reports of medicinal chemistry from 1984 to 1995 indicated that seven out of ten synthetic agents approved by FDA between 1983 and 1994 are modeled on natural product parent. These drugs are: famciclovir, ganciclovir, sorivudine, zidovudine, didanosine, zalcitabine and stavudine (Fig. 10).

The recent COVID-19 outbreak has effected human race through

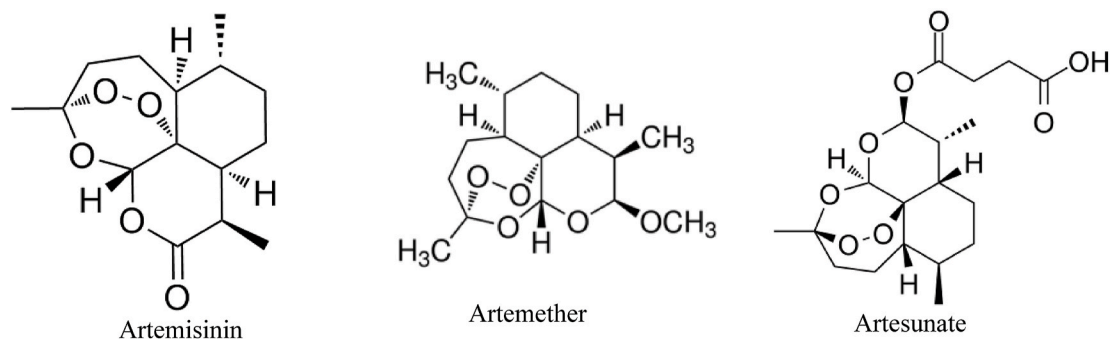


Fig. 11. Structure of Artemisinin, Artemether and Artesunate compounds tested effective *in vitro* against SARS-CoV-2.

a number of factors including health and economy. The serious availability of potential drugs and vaccines lacks in almost every corner of the world. Scientists and researchers are working day and night and are leaving no stone unturned in the race for finding efficient and long lasting solutions for COVID-19. Interestingly, more emphasis was laid over exploring natural products against COVID-19 with performing docking and *in-vitro* investigations. But following the previous track record natural products do not laid us down this time too, they come up with potential agents that can inhibit COVID-19 or prevent its lethal effects. In one such study, a library of about 686 plant based natural products were studied virtually against main protease (Mpro) of SARS-CoV-2 and results showed that 28 had efficient binding energy to Mpro. This study also investigated drug-likeness and toxicity of these natural products. Seven out of 28 drugs were found non-toxic rest showed significant toxicity. Those seven include Mpro-Dehydrctol, Epsilon-viniferin, Peimisine, Gmelanone, and Isocolumbin were non-toxic. These seven compounds showed significant binding efficacy to Mpro and result in stable complex formation and hence could be used as Mpro inhibitors [191].

Not only effective but cost effective and affordable treatments are wanted for COVID-19 due its pandemic form effects all sectors of the societies. A study reported by Gilmore et al. showed *in vitro* activity of *Artemisia annua* extracts along with some isolates of the plant like artemether, artesunate and artemisinin (Fig. 11). Some of these isolates of the plant have already been approved for anti-malarial activity. The results of their study revealed that subsequent dose-response based on immunostaining of SARS-CoV-2 spike glycoprotein, in treatment and pretreatment groups with extracts and these isolates showed preventive effects against SARS-CoV-2 infection in VeroE6 cells. In treatment assays, artesunate (50% effective concentration (EC50): 7 µg/mL) was more potent than the tested plant extracts (128–260 µg/mL) or artemisinin (151 µg/mL) and artemether (>179 µg/mL), while generally EC50 in pretreatment assays were slightly higher [101]. Therefore, *Artemisia annua* could be a breakthrough against COVID-19 due to easy availability, cost effective and natural presence.

12. Conclusion

Since the onset of COVID-19 pandemic natural product researchers have raised their efforts to explore potential drug candidates against this lethal disease. This has increased the number of studies performing on natural products. They have shown promising antiviral effects against several human infectious viruses in clinical studies. Natural products have been reported as lead molecules in different *in vitro*, *in vivo*, in silico and clinical studies. Due to immense molecular diversity in nature and structure of these molecules, they show strong antiviral efficacies. Natural products have shown to target virus binding and replication in SARS-CoV-2. Moreover, they suppress the disease symptoms caused by SARS-CoV-2 infection like cough, cold, fever, etc. A lot of effort is still needed in terms of drug design and development in the real sense as most of the current research efforts are based on theoretical calculations

and *in vitro* bioassays. Nonetheless, such research efforts become the foundation stone for any subsequent drug discovery and provide a guide for further in depth *in vivo* studies.

Declaration of competing interest

The authors declare that there is no conflict of interest to indicate.

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