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A review on potential of natural products in the management of COVID-19

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At the end of 2019, a life threatening viral infection (COVID-19) caused by a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reported. This virus has spread worldwide in a short duration and forced the world to face unprecedented life and economic loss. To date, there are no known specific drugs to combat this virus and the process for new drug development is lengthy. Most promising candidates, which emerged as potential leads, were abandoned in the later phases of clinical trials. Repurposing of already approved drugs for other therapeutic applications can be done only after extensive testing for safety and efficacy. With no definite therapeutics in the horizon, natural products are in extensive use arbitrarily as anti-viral agents and immune boosters. For ages it has been known that most natural products possess potent anti-viral activity and it is no different for SARS-CoV-2. It has been shown that natural products display inhibitory effects on MERS-CoV and SARS-CoV infections. *In silico* studies have shown that various natural products have strong binding affinity for and inhibitory action on the non-structural proteins of the virus, namely PL^{PRO}, M^{PRO}, and RdRp, and structural proteins such as spike (S) protein. Since the virus utilizes the transmembrane ACE2 receptor of the host cell, it also proves to be a valid target for drug development. In this review promising targets for drug development against SARS-CoV-2 and anti-viral activities of some of the known natural products are discussed.

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Introduction

Viruses are responsible for the pathogenesis of several human and animal diseases. Modern studies have revealed the link between viruses and diseases like type I diabetes mellitus,[1] hepatocellular carcinoma,[2] and Alzheimer's disease.[3] With the increase in urbanization, worldwide travel and immigration, the chances of epidemic outbreaks increase. Recurrences of such viral epidemics can cause a severe threat to public health since there are no proper vaccines and anti-viral therapies for most viral infections.[4] In recent years, several viral infection outbreaks have been reported such as the SARS-CoV outbreak in Foshan, China, in 2002,[5] avian influenza in humans (2005), H1N1 influenza (2009), MERS-CoV (2012 onwards) and Ebola outbreak in West Africa in 2014,[6] to name a few. A more recent explosion of the SARS-CoV-2 has wreaked havoc and has brought humanity to a standstill. According to the data furnished by https://www.worldometers.info/coronavirus/ (retrieved on 26th December, 2020), this virus has infected more than 80 million people worldwide. According to WHO, the most common symptoms of COVID-19 are fever, dry cough and fatigue. Apart from these, some affected people may experience loss of taste and smell, nasal congestion, conjunctivitis, sore throat, muscle and joint pain, diarrhoea, shortness of breath and hyperthermia. WHO also stated that people of all ages are susceptible to this viral infection. People with co-morbidity factors such as high blood pressure, pulmonary problems, obesity, cancer and diabetes are highly vulnerable.[7] Although most infected persons experience mild to moderate symptoms, some people may develop Acute Respiratory Distress Syndrome (ARDS). According to a study published in Lancet, the SARS-CoV-2 infection has long-term consequences such as severe fatigue, weight loss and memory loss.[8] As of December 2020, there were 60 vaccine candidates in the clinical development phase and 172 vaccine candidates in the pre-clinical development phase.[9] Implementing a successful vaccine requires extensive pre-clinical and clinical trials and only after ascertaining the safety and efficacy it can be administered to people. On 28th March, 2020, the US FDA approved hydroxychloroquine sulfate and chloroquine phosphate for use in hospitalized

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patients. These two repurposed drugs have been routinely used for decades for the therapy of malaria and autoimmune diseases.[10] Although these two drugs showed promising results in inhibiting SARS-CoV-2 *in vitro*,[11] there are no convincing shreds of evidence of their effect *in vivo*.[12] Other FDA approved anti-viral drugs like remdesivir, galidesivir, favipiravir, lopinavir, ribavirin, ritonavir, azithromycin (macrolide antibiotic) and ivermectin (antiparasitic) are being evaluated for the treatment of COVID-19.[13–15]

SARS-CoV-2, its genome organization, structural proteins and life cycle

SARS-CoV-2 is an enveloped, positive-sense RNA, non-segmented virus of *Sarbecovirus* subgenus and Orthocoronavirinae subfamily, which is broadly distributed in humans and other mammals.[16,17] The diameter of SARS-CoV-2 is about 65–125 nm and it has crown-like spikes on the outer surface. Like MERS-CoV and SARS-CoV, SARS-CoV-2 is also a β-coronavirus.[18]

Genome organization

Like other CoVs, SARS-CoV-2 also possesses a large genome of approximately 30 kb containing various genetic characteristics similar to other CoVs.[18] Its genome starts with a 5′ cap, followed by a leader sequence, 5′ UTR, ORF1ab encoding ORF1ab polyprotein, 3′ end possessing genes encoding structural proteins like spike (S), membrane (M), envelope (E), nucleocapsid (N) and other accessory proteins, 3′ UTR, ending with a poly-A tail[18] (Fig. 1).

Viral proteins

The SARS-CoV-2 genome encodes proteins possessing different functions, like structural proteins, non-structural proteins and accessory proteins. Out of a total of 29 proteins we will discuss only the critical structural and non-structural proteins.

Polyprotein 1ab synthesized from ORF1ab yields different proteins involved in the transcription, replication and post-translational modification. In SARS-CoV-2 spike protein there are two subunits, S1 and S2. S1 binds to the ACE2 receptor, whereas S2 facilitates the viral entry by viral and host cell membrane fusion.[19] A unique feature of SARS-CoV-2 spike (S) protein is that it has a functional polybasic cleavage site of 12 nucleotides cleaved by host furin protease.[20] SARS-CoV-2 S protein has 1273 amino acids and is 180–200 kDa in size.[21] SARS-CoV-2 envelope (E) protein has 76–109 amino acids, ranging from 8.4 to 12 kDa in size. E protein has a short, only 7–12 amino acids long, hydrophilic amino terminus, but a large hydrophobic transmembrane domain (TMD) consisting of 25 amino acids, and also possesses an extended hydrophilic carboxyl-terminus at the end. The envelope protein of SARS-CoV-2 plays multiple roles in virus pathogenesis,[22] assembly,[23] and viral release[17] and virulence.[24] The membrane protein (M) of SARS-CoV-2 comprises 222 amino acids and participates in viral assembly.[25] M protein, along with the nucleocapsid (N) protein, encapsulates the RNA genome.[26] The predicted molecular weight of SARS-CoV-2 N protein is 46 kDa and it possesses 419 amino acids. N proteins are involved in encasing the viral RNA into ribonucleocapsids (RNP) and enhancing viral genome replication efficiency.

Out of the 16 NSPs of SARS-CoV-2, four primary NSPs are NSP3 or papain like protease 3, NSP5 or 3C like proteinase,

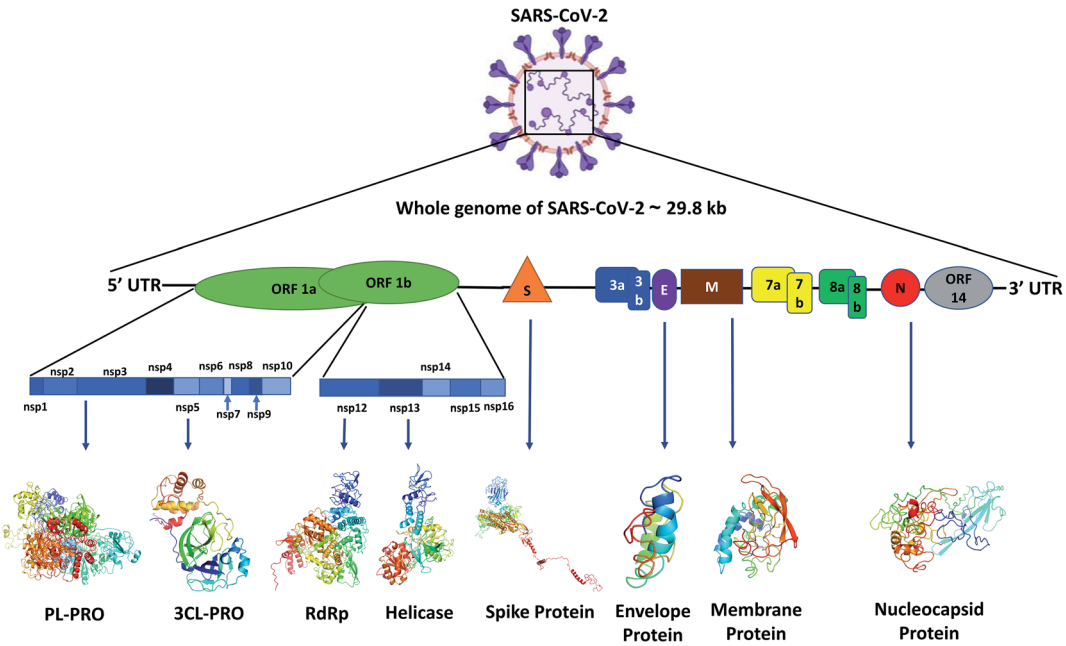


Fig. 1 Genome organization of SARS-CoV-2 and the different proteins encoded by various genes.

NSP12 or RdRp, and NSP13 or helicase. Papain-like proteinase or NSP3 is a 200 kDa protein which is responsible for the cleavage at the N-terminus of the replicase polyprotein.[27] This largest NSP having 1945 amino acid residues, *i.e.*, NSP3 along with NSP4, plays an essential role in viral replication by assembling the cytoplasmic double-membrane vesicles. It also suppresses the host's immune response by blocking NF-kappa-β signalling and IRF3. NSP5 or $3CL^{PRO}$ polypeptide is a 306 amino acids long protein of 33.8 kDa molecular weight.[28] The protease activity of $3CL^{PRO}$ cleaves polyprotein 1ab at 11 different sites to form all the non-structural proteins (NSPs).[29] NSP12 or RNA dependent RNA polymerase (RdRp) is the most versatile viral protein responsible for replication and transcription. For its activity, NSP12 needs NSP7 and NSP8, which act as co-factors and also prevent the dissociation of NSP12. NSP12 possesses around 600 base pairs and a molecular weight of probably of 106 kDa.[30] SARS-CoV-2 NSP13 or helicase is composed of 601 amino acids and is responsible for the viral RNA remodelling like introducing the 5′-terminal caps, which is essential for recognition sites for translation and splicing of mRNA.[31]

Other host proteins

Some host proteins play crucial roles like virus attachment to the host cell membrane and activation of the spike protein for viral entry in the host cell. ACE II comes first on the list as it is responsible for the viral entry.[32,33] SARS-CoV-2 spike protein attaches with ACE II to enter into the cell. This attachment of viral and host proteins depends on other host proteases like TMPRSS2 and cathepsin L, responsible for priming of the spike protein that ends up in activating the spike protein of SARS-CoV-2. TMPRSS2 also cleaves the ACE II, which augments the viral entry.[34–37] Like TMPRSS2, cathepsin L also cleaves the spike protein but in post-receptor-binding just before viral entry into the cell.[38] Finally, another host membrane-bound protease, *i.e.*, furin, cleaves the SARS-CoV-2 spike protein at the furin cleavage site, which is only present in SARS-CoV-2 and in no other coronaviruses.[39] The viral proteins as well as the host proteins (Table 1) can be potential targets for drug development against SARS-CoV-2.

The life cycle of SARS-CoV-2

SARS-CoV-2 can enter the host cell *via* endosome and plasma membrane fusion. The spike protein of SARS-CoV-2 attaches to a host cell membrane by binding with the Angiotensin-Converting Enzyme Receptor 2 (ACE2). To enter the host cell, SARS-CoV-2 needs host cells' serine protease, TMPRSS2, to activate the spike protein and cleave the ACE2 receptor that finally facilitates the attachment of SARS-CoV-2 to the cell membrane of the host cell and initiates viral and plasma membrane fusion.

After the entry, viral RNA gets released into the host cell and viral polyproteins are translated using the host cell ribosome. During translation, polyproteins (PP) PP1a and PP1ab are formed which are finally cleaved by the viral proteases, papain-

Table 1 List of important viral and host proteins which are targets for drug development

S. no.	Target protein	Presence in	Function	Size	Reference
1	Spike	SARS-CoV-2	Attaches to host cell membrane by interacting with ACE II	180–200 kDa	19–21
2	Envelope	SARS-CoV-2	Viral assembly, pathogenesis, release	8.4 to 12 kDa	22–24
3	Membrane	SARS-CoV-2	Encapsulates the RNA genome	Not found	25
4	Nucleocapsid	SARS-CoV-2	Encasing the viral RNA into ribonucleocapsid (RNP) and enhancing the efficiency of viral genomic replication	46 kDa (predicted)	26
5	Papain like protease	SARS-CoV-2	Cleaves at the N-terminus of the replicase polyprotein	200 kDa	27
6	3C like protease	SARS-CoV-2	Cleaves polyprotein 1ab at 11 different sites to produce all the non-structural proteins	33.8 kDa	28 and 29
7	RNA dependent RNA polymerase	SARS-CoV-2	Viral replication and transcription	106 kDa	30
8	Helicase	SARS-CoV-2	Formation of 5′-terminal caps for translation and mRNA splicing	66.85 kDa (predicted)	31
9	Angiotensin converting enzyme II	Vascular endothelia, gastrointestinal system, heart, and kidney	Provides attachment site for SARS-CoV-2 spike protein	92.5 kDa	32 and 33
10	Trans membrane protease serine 2	Respiratory tracts, gastrointestinal tract, prostate, colon, stomach, salivary gland, urogenital	Cleaves spike and ACE II protein that augment the virus entry	58 kDa	34–37
11	Cathepsin L	Host cells lysosome	Cleaves the spike protein in post-receptor-binding stage	19 kDa	38
12	Furin	Lungs colon, glands, liver, and kidney	Cleaves spike protein at furin cleavage site	86.7 kDa	39

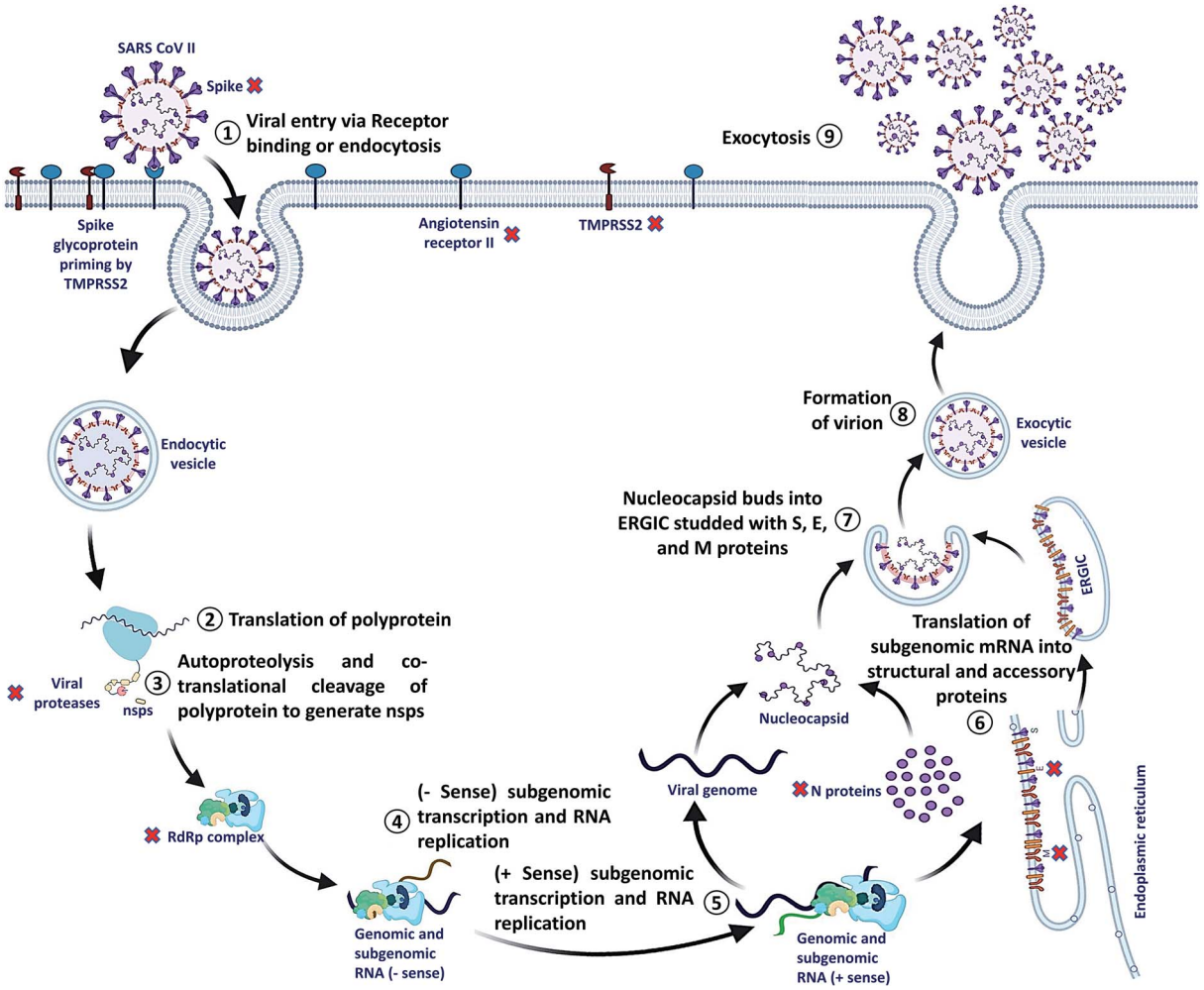


Fig. 2 SARS-CoV-2 life cycle. X Indicate potential drug targets.

like protease (PL^{PRO}) and 3C-like protease ($3CL^{PRO}$) to create functional Non-Structural Proteins (NSPs). The coronavirus genomic RNA encodes two types of proteins, NSPs crucial for viral RNA synthesis and structural proteins necessary for virion assembly.

After translation of structural proteins and NSPs, the Replicase–Transcriptase Complex (RTC) is formed by the assembly of RNA-dependent RNA polymerase (RdRp) (NSP12), helicase (NSP13) and other subunits like NSP7 and NSP8. Further, the complex transcribes a viral genome template of negative-sense genes, including progeny genome and subgenomic RNA as intermediate products, followed by the transcription of positive-sense mRNAs mediated by RdRp.[40–42]

After transcription, the subgenomic proteins get translated to form structural and accessory proteins such as M, S, and E proteins and encased into the endoplasmic reticulum and then transported to the Endoplasmic Reticulum–Golgi Intermediate Compartment (ERGIC). Next, the previously replicated viral genome can directly join the N protein to form the nucleocapsid that gets insulated into the ERGIC. Finally, nucleocapsids along with several other structural proteins form the virion particles in a vesiculated form, which is exported out of the cell through exocytosis to release virions[43,44] (Fig. 2).

Potential COVID-19 FDA approved therapeutics in clinical data

COVID-19 is a viral infection that originated from the novel SARS-CoV-2 and led to economic, health, social, and societal ramifications. The lack of an FDA approved line of therapy develops a lot of coercion on scientific and medical teams to generate treatment options.[45] The product development process is complicated when related to its mechanism, efficacy, and toxicity profiling at different stages. The Food and Drugs Act was established in 1906 to ensure the effectiveness and safety of drug candidates and medical devices.[46] The classical drug development process occurs in different stages: discovery and development, pre-clinical studies, clinical studies, and post-market surveillance[47] (Fig. 3). In the USA, drug development takes approximately 10–12 years, with 9.6 to 13.8% of the total drug candidates passing the FDA policies.[48,49] The drug discovery step involves selecting and validating the target,

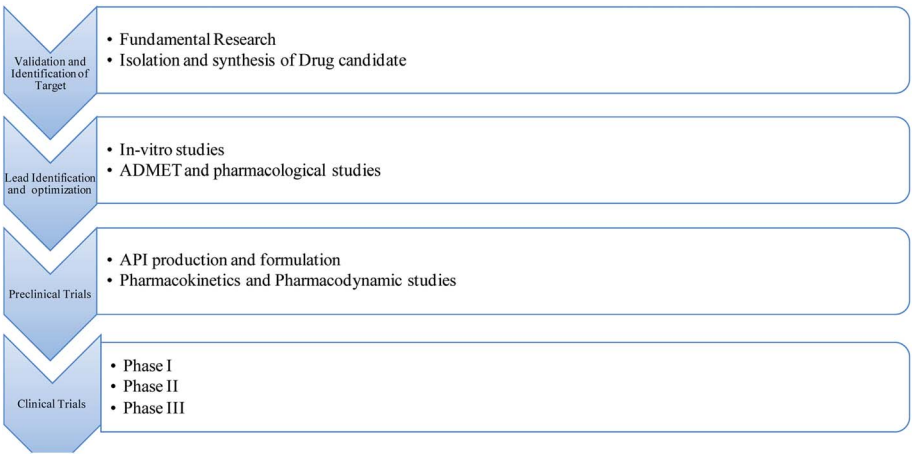


Fig. 3 The drug discovery/development process.

lead identification, and then followed by optimization.[50,51] The pre-clinical phase mainly focuses on manufacturing the active pharmaceutical ingredient, formulation, analytical methods for drug development, ADMET parameters, and Good Manufacturing Practices (GMP).[52] When API passes the above studies, phase I of the clinical trial stage can be initiated.[53] This phase contains 20 to 100 human candidates with the primary goal of the measurement of the dose and safety profile. In phase II clinical trials, the number of human candidates increase to analyse the drug's effectiveness and its adverse effects. Phase III, with human candidates being more than 3000, intends to compare the participant drug's efficacy with existing treatments. When the drug candidates pass the above phases, the scrutinizer files the New Drug Application *via* the FDA, which takes approximately ten months for approval for further studies.[54] Phase IV is considered the post-market surveillance to monitor the drug safety further.[53]

Researchers have analysed the existing information related to the replication and life cycle of SARS-CoV-2 to design the therapeutics of COVID-19.[55] Repurposing of FDA approved drugs for the therapeutics of COVID-19 is the fastest path to create a safe and potential treatment.[56] Hydroxychloroquine, a medicine for the cure and treatment of autoimmune disorders and malaria, was first investigated to treat SARS-CoV-2. Another traditional anti-viral drug remdesivir has shown effectiveness in earlier human CoV outbreaks. Remdesivir is an analogue of adenosine GS-441524, which acts *via* RNA-dependent RNA polymerase inhibition and active against most RNA-dependent viruses.[55] Remdesivir has primarily been investigated as a SARS-CoV and MERS-CoV regimen in pre-clinical and clinical trials.[57] In 2017, a study on remdesivir proved its efficacy against MERS-CoV, SARS-CoV, and bat CoV, which indicates its broad-spectrum anti-human CoV activity.[58] In cell culture studies, remdesivir showed an effective concentration, *i.e.*, EC_{50} of 0.069 μM against SARS-CoV and 0.074 μM for MERS-CoV.[59] In an animal model, remdesivir significantly reduced the viral load of the lung up to >2 order of magnitude in 4 days of post-infection.[60] Furthermore, remdesivir is used as a prophylactic in SARS-CoV to improve the respiratory function and clinical symptoms.[58] Remdesivir proved its potential against the SARS-CoV in *in vitro* and *in vivo* studies. Still, it was unclear whether the potential shown in SARS-CoV is generalizable to SARS-CoV-2 without further research. Before COVID-19, remdesivir was a potential drug with a fully documented safety and efficacy profile in human trials and pre-clinical trials in various RNA viruses.[58–60] The first study of remdesivir was conducted by Grein *et al.*, published in NEJM for the treatment of COVID-19. The primary goal of the study was to analyze the safety and efficacy of remdesivir in humans.[61] They selected 53 patients, and remdesivir was injected intravenously for ten days. The authors concluded that after 18 days, 25 patients successfully recovered, 17 patients were extubated from mechanical ventilation, and seven patients died. The FDA has approved chloroquine for the treatment of systemic lupus erythematosus and rheumatoid arthritis. In early studies, chloroquine inhibited antigen processing *via* endosomal/lysosomal and viral replication.[62] In animal models, chloroquine enhanced the survival rates in new born human coronavirus infected mice.[63] Chloroquine and hydroxychloroquine were the only credible options in China during December 2019 to manage SARS-CoV-2 due to existing *in vitro* studies.[64] A study conducted by Yao *et al.* showed that hydroxychloroquine is a better option in the safety profile for the treatment of COVID-19 than chloroquine. Hence this drug was an attractive candidate for the management of COVID-19 specifically, having FDA approval for the different indications with well-maintained documents.[65] An alternative regimen, a combination of azithromycin with antimalarial drugs, was thought to be efficacious for the treatment of SARS-CoV-2.[66] The combination of azithromycin with chloroquine and hydroxychloroquine was found to be beneficial for SARS-CoV-2 patients clinically, with no fatalities.[67] The cardiotoxicity caused by the antimalarial drugs alone or combined with azithromycin increases the adverse reactions, which raised the question whether the drugs can be used separately or in combination. In the reported cohort study, azithromycin with chloroquine/hydroxychloroquine prolonged the QT intervals.[68] Azithromycin did not prolong the QT intervals clinically, but the combination regimen significantly prolonged the QT interval. A

study was conducted to measure the risk of hydroxychloroquine alone and its combination with azithromycin in rheumatoid arthritis patients. The study concluded that combination therapy of hydroxychloroquine with azithromycin increases the danger of 30 day cardiovascular mortality, chest pain, angina, and cardiac failure.[69] These studies suggested that the combination of chloroquine/hydroxychloroquine with azithromycin may be avoidable for the management of SARS-CoV-2.

Current approaches for the management of COVID-19

Apart from the anti-viral drug therapy, clinicians are looking towards an immunotherapeutic approach through Convalescent Plasma Therapy (CPT).[76] While the anti-viral drugs are under clinical trials CPT emerges out as a possible line of treatment for COVID-19. This adaptive immunotherapy involves the administration of plasma collected from recovered subjects to the infected ones. The plasma contains a high titer of neutralizing antibody, which can provide an anti-viral effect.[76] Studies have shown that CPT is efficacious against COVID-19, and no severe adverse reactions were associated with this therapy.[70] Other studies also indicated the same aspect of this therapy. For example, in a Chinese pilot study (ChiCTR2000030046), 10 critically ill patients were all given a 200 ml CP dose with a neutralizing antibody titre >1 : 640. Out of ten, seven patients showed a remarkable improvement clinically and radiologically and reduced viral load.[71] Another study showed an improvement of the Sequential Organ Failure Assessment (SOFA) score from 2–10 before CPT to 1–4 after 12 days of therapy.[72] This study also revealed that in 5 critically ill patients, the titre value of the virus specific IgG and IgM was significantly higher and the viral infection's progression was lowered in all the patients. The potential drawback of this line of therapy was that upon implementation of CPT in MERS-CoV infected patients, a study showed a rapid decrease in the antibody titer within three months of the treatment. Another drawback of CPT is the anticipation of transfusion-transmitted infection since transfusion is involved in the therapy. Critically ill patients with impaired lung functions are particularly susceptible to Transfusion Related Acute Lung Injury (TRALI).[73] TRALI is caused by anti-human leukocyte antigen (HLA) antibody,[74] and such cases have been reported for CPT in Ebola virus outbreak.[75] It is recommended to carry out anti HLA antibody screening before implementing CPT for COVID-19.[76] Lastly, to render CPT effective, the procurement and utilization of the plasma must be in accordance with the scrupulous ethical guidelines since this is of human origin.[77]

The rationale for considering natural products as a potential line of treatment for COVID-19

The drugs mentioned above and the CPT confer some relief to the pandemic situation. Still, the exorbitant therapy, limited availability, unprecedented adverse effects of the drugs and ethical concerns regarding CPT make them difficult to implement worldwide. Moreover, the situation can be exacerbated by the mutation of the virus leading to drug-resistant mutants, which would render the anti-viral drugs useless since most of them target specific viral proteins.[78–81] Thus we can look for potential therapeutics from the point of view of natural products. A large number of studies have been conducted on anti-viral effects of natural products and herbal medicines. Extensive studies have shed some light on these natural products' mechanism of action and the possible targets like viral entry, replication, assembly, release, and virus–host specific interactions.[4,82] In the following sections of this review, we have discussed some of the potential anti-viral compounds used for the management and prophylaxis of COVID-19.

Role of polyphenols in combating the SARS COVID-19 pandemic

Potential therapies for SARS-CoV-2 can be categorized into two groups based on targets; drugs that target the virus and drugs that target the host and its immune system.[83] The target proteins in SARS-CoV-2 are categorized as non-structural proteins (M^{PRO}, PL^{PRO} and RdRp) and spike protein (S protein) (Table 1). Resveratrol, a well-known phytoalexin, showed potent inhibitory action against MERS-CoV in an *in vitro* study. The same study also indicated that resveratrol could prolong the cellular survival after viral infection.[84] Emodin, an anthraquinone polyphenol found in the roots of rhubarb, was found to inhibit the interaction of ACE2 and S protein (Table 1).[85] Molecular docking studies have shown that polyphenols from *Curcuma* sp. (curcumin and its derivatives) and *Citrus* sp. (hesperetin, hesperidin, and tangeretin) have a stronger binding affinity for the S protein than the reference compound nafamostat.[86] Naringenin was found to have more substantial binding energy to viral spike glycoprotein (PDB: 6VSB) than remdesivir,[87] an anti-viral which was approved by the FDA for the therapy of COVID-19.[88] Tetra-*O*-galloyl-β-D-glucose (TGG) and luteolin were found to bind with SARS-CoV surface protein and thus hinder the virus's entry into the host cell.[89]

The target for the binding of the SARS-CoV-2 is the ACE2, which is a transmembrane metallocarboxypeptidase.[90] This receptor thus serves as a potential target for anti-viral drug discovery. Eriodictyol, a flavanone found in *Eriodictyon californicum*, showed the highest affinity for ACE2 among 77 candidates.[91] Although *in silico* studies can identify promising candidates, more *in vitro* and *in vivo* studies are required to assess their actual impact on the pandemic. A study found that mice having inactivated or knocked-out ACE2 developed severe SARS-CoV infection, and they sustained lung injury worse than the wild type control group. The symptoms were alleviated upon administration of recombinant ACE2.[92] A cell-based assay revealed that the entry of both SARS-CoV and SARS-CoV-2 was blocked when soluble ACE2 was introduced, thus confirming that recombinant ACE2 can be used as a decoy target against

viral S protein.[93,94] Since ACE2 plays a vital role in human physiology, targeting it for anti-viral drug discovery should be done after careful assessment of its risks. Protease inhibitors are a class of compounds that have been extensively used in the management of viruses like HIV, MERS-CoV and SARS-CoV.[95,96] The structural and non-structural proteins essential for the life cycle of the coronavirus are proteolytically processed from the polyprotein by $3CL^{PRO}$ (M^{PRO}) and the PL^{PRO}.[97] Natural products like diarylheptanoids,[98] terpenoids,[99] flavonoids[100] and coumarins[100] are potent inhibitors of the SARS-CoV proteases. *In silico* and *in vitro* analyses have found that epigallocatechin gallate (IC_{50} = 73 μM), gallocatechin gallate (IC_{50} = 47 μM) and quercetin (IC_{50} = 73 μM) are potent inhibitors of the SARS-CoV-2 M^{PRO}.[101,102] Flavonoids such as kaempferol and isoliquiritigenin synergistically inhibited the SARS-CoV-2 M^{PRO} and PL^{PRO} *in vitro*.[103] Gentile *et al.* screened a library of Marine Natural Products (MNP Library) and identified potent inhibitors of the SARS-CoV-2 M^{PRO} *via* molecular docking analysis. The potent inhibitors of the viral M^{PRO} were heptafuhalol A, phlorethopentafuhalol B, pseudopentafuhalol C, phlorethopentafuhalol A, hydroxypentafuhalol A and pentaphlorethol B, 1,3,5-trihydroxybenzene from *Sargassum spinuligerum* and 8,8′-bieckol, 6,6′-bieckol and dieckol from *Ecklonia cava*.[104] Flavonoids from traditional Chinese medicines, like herbacetin, rhoifolin, and pectolinarin, were found to inhibit the M^{PRO} of SARS-CoV.[105] Jo *et al.* found that flavonoids like herbacetin, isobavachalcone and helichrysetin have an inhibitory effect on MERS-CoV M^{PRO}.[106] Wen *et al.* investigated over 200 plant extracts to find their inhibitory effect on SARS-CoV. SARS-CoV induced cytopathogenic effects were studied in Vero E6 cell lines and they have shown that herbal extracts from *Gentianae radix*, *Dioscoreae rhizoma*, *Cassiae semen* and *Loranthi ramus* and *Rhizoma cibotii* in the concentrations from 25 to 200 μg ml^{-1} proved to have a potential inhibitory effect on SARS-CoV.[107] A recent *in silico* study on naturally derived compounds came up with 3 potential leads which can block the entry of the SARS-CoV-2 in the host cells by inhibiting the host target protein TMPRSS2. The same study also showed that the three compounds (glucogallin, mangiferin, and phlorizin) could also be used to restrict the virus's life cycle inside the host due to their inhibitory action on the viral M^{PRO}.[108] The possible anti COVID-19 mechanism of action of the above-mentioned compounds in this section are compiled in a column in Table 2.

Role of alkaloids in combating the COVID-19 pandemic

Alkaloids are a class of Plant Secondary Metabolites (PSM) that are basic in nature and contain at least one nitrogen atom in their structure. Alkaloids are produced by higher terrestrial plants,[109] from fungi such as psilocybin from *Psilocybe* and animals like bufotenin from toad skin.[110] Apart from these, the marine organisms also produce alkaloids.[111] The genetic material of a virus may be DNA or RNA. There are many PSMs that attack DNA or RNA.[112] DNA intercalating agents are generally lipophilic, planar aromatic compounds which get stacked between DNA base pairs or paired regions of RNAs.[113] Isoquinoline, quinolone and β-carboline alkaloids possess intercalating characteristics and they have shown potent anti-viral activity.[114–118] SARS-CoV replication was inhibited by isoquinoline alkaloids such as berberine, berbamine, berberrubine, coptisine, dicentrine, jatrorrhizine, palmatine, tetrandrine, fangchinoline, and cepharanthine.[115–118] The rationale for considering the intercalators as potent anti-viral compounds for SARS-CoV-2 is that chloroquine, the FDA approved drug of choice for the current SARS-CoV-2 pandemic, is a derivative of the alkaloid quinine, which has intercalating properties.[115,116] More extensive *in vitro* and *in vivo* analysis should be performed prior to assigning the intercalating alkaloids as adjunctive therapeutic candidates. A molecular docking study showed that the tropane alkaloid schizanthine Z, obtained from *Schizanthus porrigens*, has strong binding to the viral PL^{PRO} which can inhibit the protease.[119] Another *in silico* study showed that 10-hydroxyusambarensine, an alkaloid found in the roots of *Strychnos usambarensis*,[120] and cryptoquindoline and cryptospirolepine, two alkaloids found in *Cryptolepis sanguinolenta*,[121] had high binding affinity for SARS-CoV-2 M^{PRO}. The same study indicated that 10-hydroxyusambarensine exhibited the strongest interactions with $3CL^{PRO}$ of SARS-CoV-2, and cryptospirolepine showed the highest binding affinity and selectivity for $3CL^{PRO}$ of SARS-CoV and MERS-CoV.[122] Another *in silico* study found that the alkaloids from *Cryptolepis sanguinolenta*, namely cryptomisrine, cryptospirolepine, cryptoquindoline, and biscryptolepine, showed strong binding to the RdRp, suggesting that they can be potential RdRp inhibitors.[123] Anisotine, adhatodine, vasicoline and vasicine, alkaloids from *J. adhatoda* leaves, also showed potent inhibition to the SARS-CoV-2 M^{PRO} *via* a molecular dynamics study, making them suitable candidates for the protease inhibitor class of drugs.[124] The possible anti-COVID-19 mechanism of action of the compounds mentioned above in this section are compiled in a column in Table 2.

Role of terpenoids and glycosides in combating the COVID-19 pandemic

Terpenoids or isoprenoids are a diverse class of natural compounds derived from isoprene (5 carbon compound) units. The isoprene monomers polymerize to form terpenes. Terpenoids have numerous medicinal properties like anti-viral activity,[125] antibacterial activity,[126] anti-oxidant activity,[127] *etc.* Wen *et al.* studied the effect of more than 200 naturally occurring terpenoids and lignoids against SARS-CoV. The virus induced cytopathogenic activity of the compounds was studied on VERO E6 cell lines and they found that the most potent inhibitory compounds were ferruginol, [8-β-hydroxyabieta-9(11),13-dien-12-one], 7-β-hydroxydeoxycryptojaponol, 3-β,12-diacetoxyabieta-6,8,11,13-tetraene and betulonic acid. The same study showed that betulinic acid and savinin were competitive inhibitors of the SARS-CoV MPRO.[128] A recent *in silico* study

Table 2 List of natural products, their classification, potential targets and possible mechanism of action (from *in silico* and *in vitro* studies)

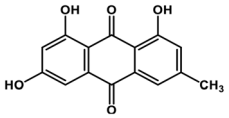
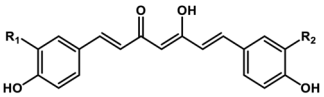
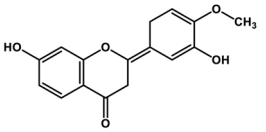
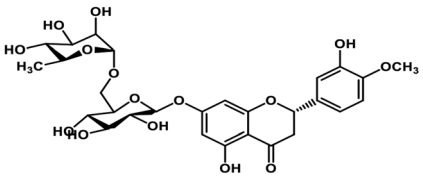
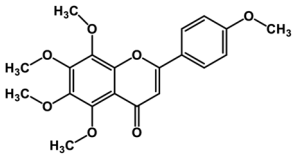
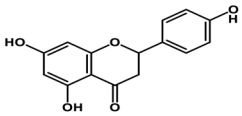
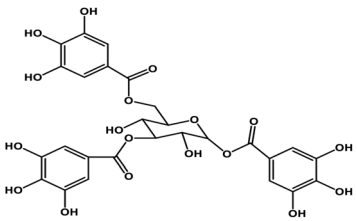
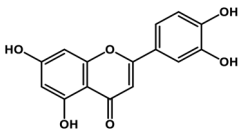
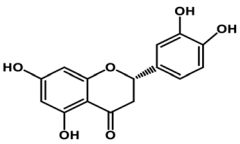
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
1	Emodin		Anthraquinone polyphenol	Host ACE2 receptor and viral S protein	Inhibition of viral entry in host cell	85
2	Curcumin and its derivatives	 Curcumin (R1 = OCH3, R2 = OCH3) Demethoxycurcumin (R1 =OCH3, R2 = H) bis-Demthoxycurcumin (R1 = H, R2 = H)	Flavonoid polyphenol	MERS-CoV S protein	Inhibition of viral entry in host cell	86
3	Hesperetin		Flavonoid polyphenol	MERS-CoV S protein	Inhibition of viral entry in host cell	86
4	Hesperidin		Flavonoid polyphenol	MERS-CoV S protein	Inhibition of viral entry in host cell	86
5	Tangeretin		Flavonoid polyphenol	MERS-CoV S protein	Inhibition of viral entry in host cell	86
6	Naringenin		Flavanone	SARS-CoV-2 S protein	Inhibition of viral entry in host cell	87
7	TGG		Polyphenol	SARS-CoV S protein	Inhibition of viral entry in host cell	89
8	Luteolin		Tetrahydroxy flavone	SARS-CoV S protein	Inhibition of viral entry in host cell	89
9	Eriodictyol		Flavanone	Host ACE2 transmembrane receptor	Inhibition of viral entry in host cell	91

Table 2 (*Contd.*)

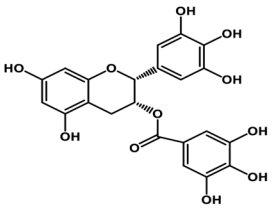
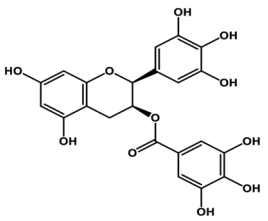
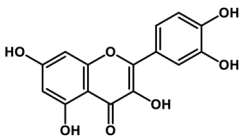
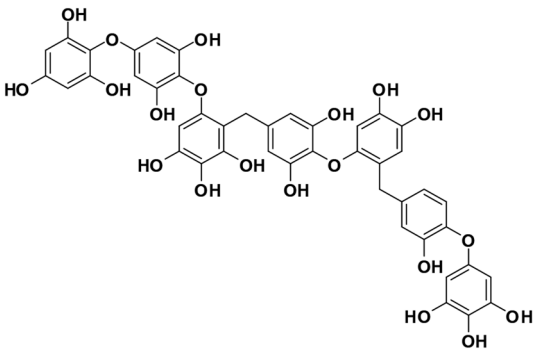
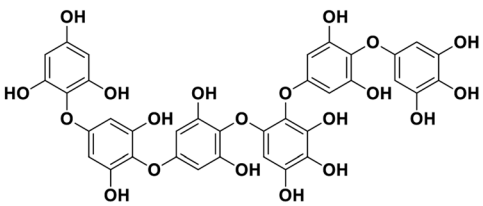
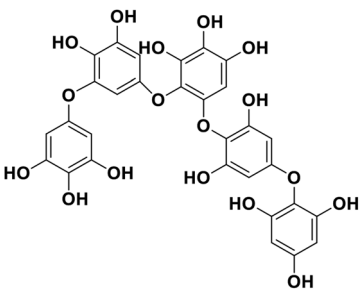
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
10	Epigallocatechin gallate		Catechin polyphenol	SARS-CoV M^{PRO}, SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	101 and 102
11	Gallocatechin gallate		Catechin polyphenol	SARS-CoV M^{PRO}, SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	101 and 102
12	Quercetin		Flavonoid	SARS-CoV S protein, SARS-CoV M^{PRO}	Inhibition of viral entry in host cell, inhibits viral life cycle in the host	101 and 102
13	Heptafuhalol A		Marine phorethol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	104
14	Phlorethopenta fuhalol B		Marine phorethol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	104
15	Pseudopenta fuhalol C		Marine phorethol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	104

Table 2 (*Contd.*)

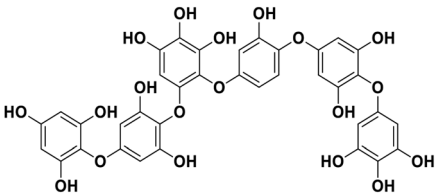
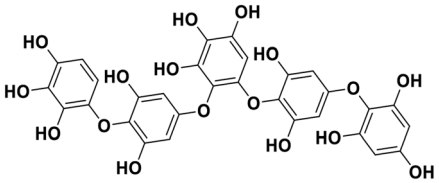
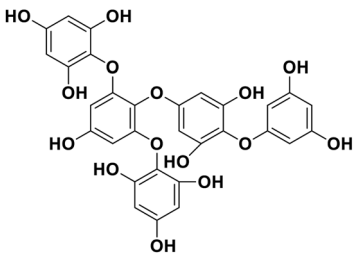
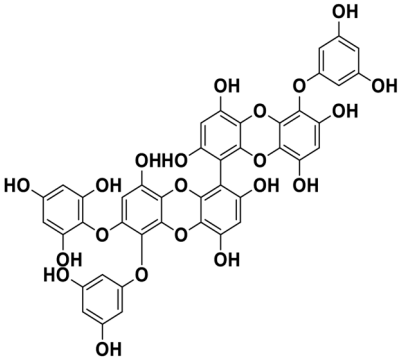
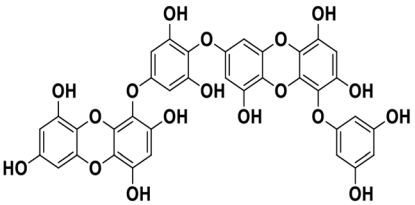
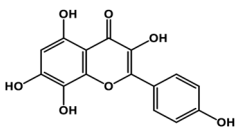
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
16	Phlorethopentafuhalol A		Marine phorethol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	104
17	Hydroxypentafuhalol A		Marine phorethol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	104
18	Pentaphlorethol B		Marine phorethol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	104
19	6,6′-Bieckol		Polyphenol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	83
20	Dieckol		Polyphenol	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	83
21	Herbacetin		Flavonol	SARS-CoV-2 M^{PRO}, MERS CoV M^{PRO}	Inhibition of viral life cycle inside host	105 and 106

Table 2 (*Contd.*)

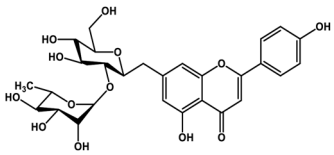
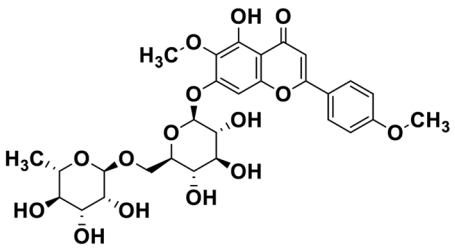
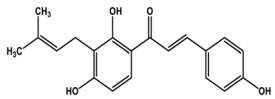
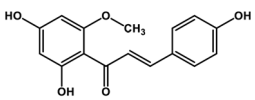
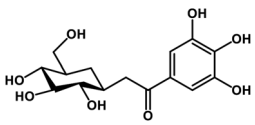
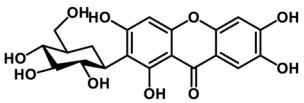
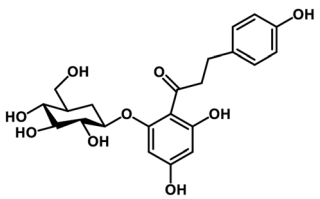
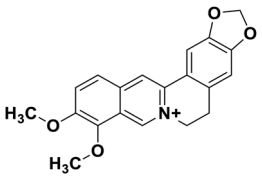
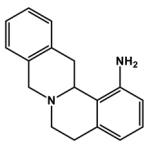
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
22	Rhoifolin		Flavonoid glycoside	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	105
23	Pectolinarin		Flavonoid glycoside	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	105
24	Isobavachalcone		Chalcone polyphenol	MERS-CoV M^{PRO}	Inhibition of viral life cycle inside host	106
25	Helichrysetin		Polyphenol	MERS-CoV M^{PRO}	Inhibition of viral life cycle inside host	106
26	Glucogallin		Tannin	SARS-CoV-2 M^{PRO}, host TMPRSS2	Inhibition of viral entry into host, inhibition of viral life cycle inside host	108
27	Mangiferin		Xanthone	SARS-CoV-2 M^{PRO}, host TMPRSS2	Inhibition of viral entry into host, inhibition of viral life cycle inside host	108
28	Phlorizin		Flavonoid glycoside	SARS-CoV-2 M^{PRO}, host TMPRSS2	Inhibition of viral entry into host, inhibition of viral life cycle inside host	108
29	Berberine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
30	Berbamine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118

Table 2 (*Contd.*)

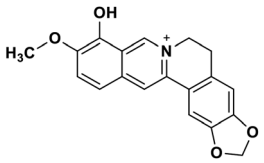
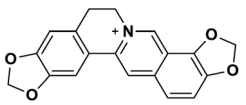
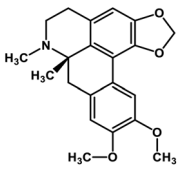
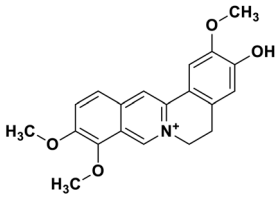
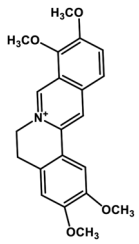
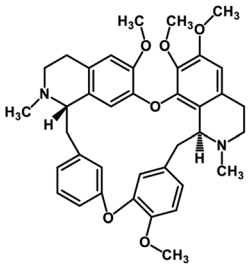
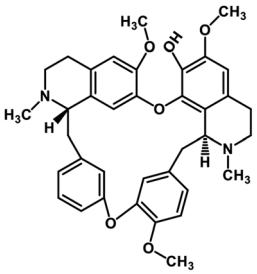
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
31	Berberrubine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
32	Coptisine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
33	Dicentrine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
34	Jatrorrhizine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
35	Palmatine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
36	Tetrandrine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
37	Fangchinoline		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118

Table 2 (*Contd.*)

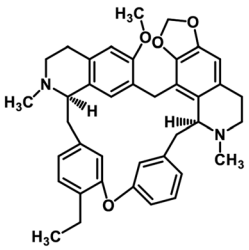
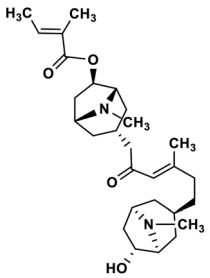
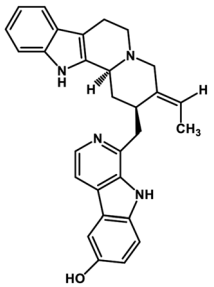
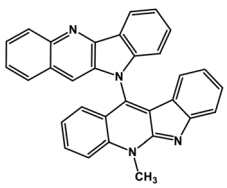
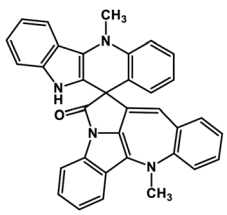
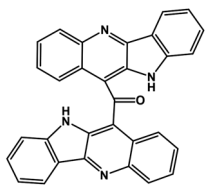
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
38	Cepharanthine		Isoquinoline alkaloid	SARS-CoV nucleic acid intercalation	Inhibition of viral replication	115–118
39	Schizanthine Z		Tropane alkaloid	SARS-CoV-2 PL^{PRO}	Inhibition of viral life cycle inside host	119
40	10-Hydroxyusambarensine		Indole alkaloid	SARS-CoV-2 M^{PRO}, SARS CoV M^{PRO}, MERS CoV M^{PRO}	Inhibition of viral life cycle inside host	122
41	Cryptoquindoline		Indole alkaloid	SARS-CoV-2 M^{PRO}, SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	122
42	Cryptospirolepine		Indole alkaloid	SARS-CoV-2 M^{PRO}, SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	122 and 123
43	Cryptomisrine		Indole alkaloid	SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	123

Table 2 (*Contd.*)

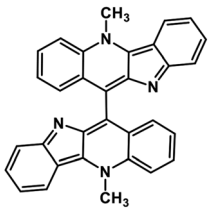
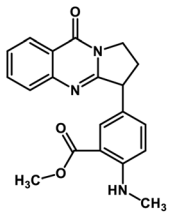
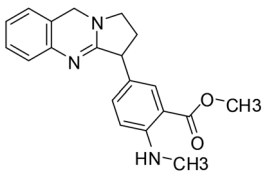
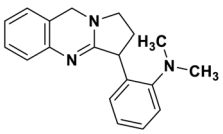
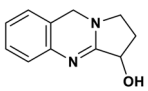
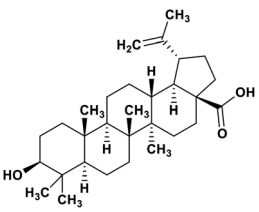
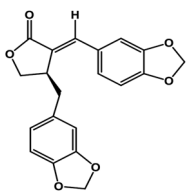
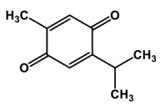
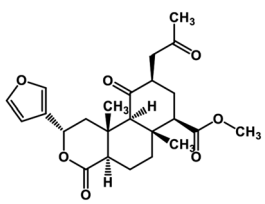
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
44	Biscryptolepine		Indole alkaloid	SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	123
45	Anisotine		Quinolone alkaloid	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	124
46	Adhatodine		Quinoline alkaloid	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	124
47	Vasicoline		Quinoline alkaloid	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	124
48	Vasicine		Quinoline alkaloid	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	124
49	Betulinic acid		Pentacyclic triterpenoid	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	128
50	Savinin		Benzodioxole lignan	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	128
51	Thymoquinone		Monoterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
52	Salvinorin A		Terpenoid	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129

Table 2 (*Contd.*)

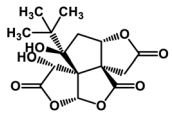
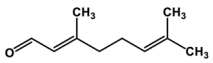
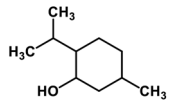
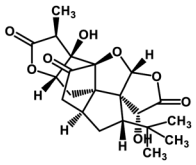
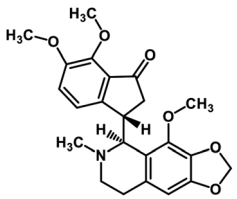
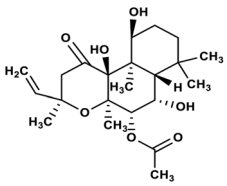
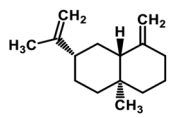
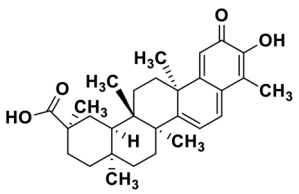
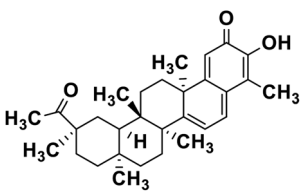
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
53	Bilobalide		Terpenictri lactone	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
54	Citral		Monoterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
55	Menthol		Monoterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
56	Ginkgolide A		Diterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
57	Noscapine		Isoquinoline alkaloid	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
58	Forskolin		Labdane terpenoid	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
59	β-Selinene		Sesquiterpenes	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	129
60	Celastrol		Quinone methide triterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	130
61	Pristimerin		Quinone methide triterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	130

Table 2 (*Contd.*)

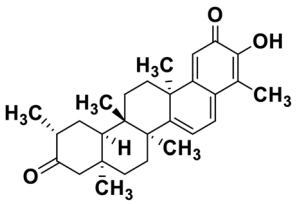
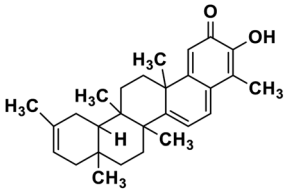
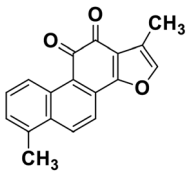
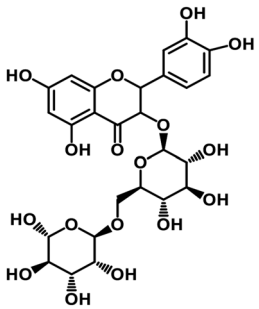
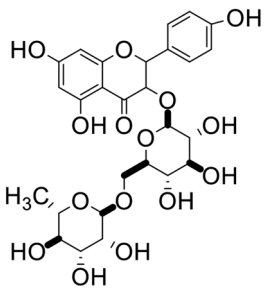
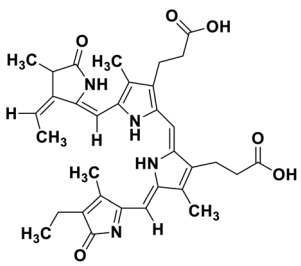
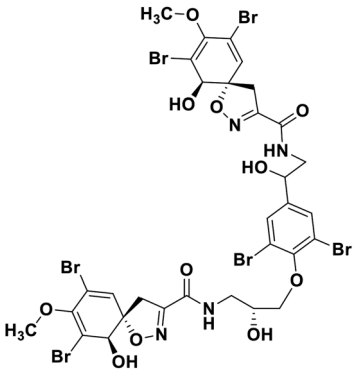
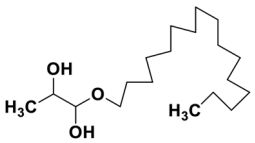
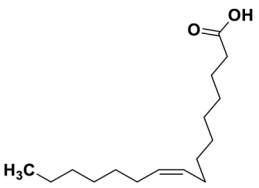
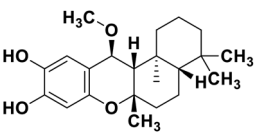
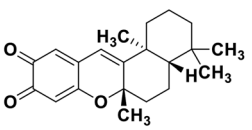
S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
62	Tingenone		Quinone methide triterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	130
63	Iguesterin		Quinone methide triterpene	SARS-CoV M^{PRO}	Inhibition of viral life cycle inside host	130
64	Tanishone		Abietane diterpene	SARS-CoV M^{PRO}, SARS-CoV PL^{PRO}	Inhibition of viral life cycle inside host	131
65	Rutin		Flavonoid glycoside	SARS-CoV-2 M^{PRO}, SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	136
66	Nicotiflorin		Flavonoid glycoside	SARS-CoV-2 M^{PRO}, SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	136
67	Phycocyanobilin		Marine tetrapyrrole chromophore	SARS-CoV-2 M^{PRO}, SARS-CoV-2 RdRp	Inhibition of viral life cycle inside host	139

Table 2 (*Contd.*)

S. no.	Name of natural product	Structure	Class of the compound	Potential target(s) (Table 1)	Possible mechanism of action of the compounds	Ref.
68	Fostularin 3		Marine natural product	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	146
69	1-Hexadecoxy propane-1,2-diol		Marine natural product	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	146
70	Palmitoleic acid		Marine natural product	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	146
71	15alpha-methoxy puupehenol		Marine natural product	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside host	146
72	Puupehedione		Marine natural product	SARS-CoV-2 M^{PRO}	Inhibition of viral life cycle inside the host	146

showed that terpenoids such as thymoquinone from *Nigella sativa*, salvinorin A from *Salvia divinorum*, bilobalide from *Ginkgo biloba*, citral from *Backhousia citriodora*, menthol from *Mentha*, ginkgolide A from *Ginkgo biloba*, noscapine from the Papaveraceae family, forskolin from *Plectranthus barbatus* and beta selinene from *Apium graveolens* have SARS-CoV M^{PRO} inhibitory action.[129] Quinone methide triterpenes such as celastrol, pristimerin, tingenone, and iguesterin isolated from *Tripterygium regelii* showed potent inhibitory action against SARS-CoV M^{PRO}.[130] Tanshinone, which contains the abietane diterpene moiety, isolated from *S. miltiorrhiza* showed selected inhibition against SARS-CoV M^{PRO} and PL^{PRO}.[131] The possible anti-COVID-19 mechanism of action of the compounds mentioned above in this section are compiled in a column in Table 2.

Cardiac glycosides like digitoxin and digoxin were studied during previous pandemics including MERS-CoV and SARS-CoV.[132,133] The studies found that these cardiac glycosides could inhibit the transmembrane internalization of the virus due to their capacity to deplete the host intracellular potassium which resulted in abrogation of signal transduction of the Na, K-ATPase pump. This in turn resulted in interruption of the viral life cycle in the host. A study by Yang *et al.* in 2005 showed that cardiac glycosides downregulated various cytokines such as NF-κB, TNFα, TNFβ, *etc.*[134] Furthermore, previous studies established that SARS-CoV-2 infection was associated with catastrophic cytokine storm in the target organs.[135]

So, repurposing of cardiac glycosides for treatment of SARS-CoV-2 can be considered after proper clinical investigation. Flavonoid glycosides like rutin and nicotiflorin from *Dysphania ambrosioides* and their glucuronide and sulfate derivatives were

found to be potent inhibitors of the SARS-CoV-2 M^{PRO} and RdRp *via* a molecular docking approach.[136]

Natural products from marine sources: a new-fangled avenue to obtain natural compounds for combating the SARS COVID-19 pandemic

Natural products from marine sources are being used as potential therapeutic agents recently. Marine micro-algae belonging to phyla Rhodophyta and Phaeophyta were studied and the various bioactive compounds like phycocyanin, lutein, polysaccharides, vitamins and other phenolics showed anti-microbial, anticancer, anti-inflammatory, and other crucial pharmacological activities.[137] Hirata *et al.* in 2010 studied the anti-viral and antioxidative effects of phycocyanobilins, a class of tetrapyrrole chromophores present in certain types of marine cyanobacteria.[138] Pendyala and Patras in 2020 showed that phycocyanobilins demonstrated high binding affinity for the SARS-CoV-2 M^{PRO} and RdRp *via in silico* molecular docking studies.[139] Lectins are a class of compounds that have affinity for carbohydrates. Griffithsin, a lectin derived from red algae, was studied for its potential application, and studies have shown its anti-viral activity against HIV-1 (ref. 4) and hepatitis-C.[140,141] A recent *in vitro* study by Millet *et al.* showed that griffithsin had inhibitory action against MERS-CoV.[142] *In vitro* studies of sulfated polysaccharides or fucoidans sourced from brown microalgae *Sargassum henslowianum* on HSV showed potent inhibitory action.[143] Kwon *et al.* in 2020 reported that the fucoidans obtained from macroalgae *Saccharina japonica* had significant anti-viral activity against SARS-CoV-2. Out of the two fucoidans involved in their study, the fucoidan labelled as RPI-27 showed more potent anti-viral activity than remdesivir. They concluded that fucoidans can be co-administered with other anti-viral compounds to elicit potent anti SARS-CoV-2 activity.[150] Esculetin ethyl ester from marine sponge *Axinella* cf. *corrugate* showed strong interaction with SARS-CoV-2 protease to be used as an anti COVID-19 drug.[144] Carrageenans, a class of marine sulphated polysaccharides, are considered to be inhibitors of several viruses. They act *via* inhibiting the binding of the virus and its subsequent internalization. Nagle *et al.* thus speculated the use of these compounds as coating materials on sanitary items to prevent COVID-19 infection.[145] In recent times, *in silico* studies contributed towards identifying potential lead compounds for drug development against the COVID-19 pandemic. Khan *et al.* in their molecular dynamic study came up with 5 potent SARS-CoV-2 M^{PRO} inhibitors (fostularin 3, 1-hexadecoxypropane-1,2-diol, palmitoleic acid, 15alpha-methoxypuupehenol and puupehedione) from marine sources which can be utilized for hampering the viral life cycle in the host.[146] Finding potent natural compounds from marine sources remains a challenge due to the scarce availability, difficult collection, and rarity of marine organisms. In the past few decades, the search for potent natural compounds from marine sources which can exhibit a plethora of activities is going on and is bringing positive results. So we can extrapolate these findings to find a possible cure from the naturally occurring marine organisms.

Possible relationship between the viral protein structure and the functional groups present in the molecular structures of natural metabolites

Naturally derived plant secondary metabolites can be of various classes like polyphenolics, alkaloids, terpenoids, *etc.* They possess diversity in their structure and the different chemical moieties present in them contributes towards their specific function in biological systems. Polyphenols are a class of natural products having a plethora of activities including anti-viral activity.[147] Polyphenols like kaempferol (structure in Table 2), herbacetin (structure in Table 2) and rhoifolin (structure in Table 2) share structural similarity. The phenyl moiety of kaempferol and the chromen-4-one moiety are responsible for its binding with the SARS-CoV M^{PRO}. Herbacetin has an additional 8-hydroxyl group which results in strong binding to the SARS-CoV M^{PRO}. Rhoifolin (structure in Table 2) has a bulky α-L-rhamnopyranosyl β-D-glucopyranoside moiety along with the chromen-4-one moiety which explains its strong binding to the SARS-CoV M^{PRO} since the bulky group fits in the pockets of the protein with hydrogen bonds.[100] Alkaloids are a diverse group of plant secondary metabolites having different chemical moieties. The different moieties are responsible for their activities. For example, indole alkaloids like 10-hydroxyusambarensine contain the pyrido-indole moiety (structure in Table 2). This pi-bond enriched system is responsible for binding with the amino acid residues present in the SARS-CoV-2 M^{PRO} *via* pi–alkyl interaction. Terpenoids are another important class of natural compounds formed by polymerization of the isoprenoid moiety. Terpenoids having the quinone-methide moiety like iguesterin, pristimerin and tingenone (structures in Table 2) show binding affinity for the SARS-CoV M^{PRO} active site. This binding is due to the presence of the OH group in the quinone-methide moiety which forms a hydrogen bond with the CO group of the cysteine and OH group of threonine residues present in the active site of the viral protein. Modification of the hydroxyl group in the quinone-methide moiety resulted in the abrogation of the binding affinity of these terpenoids.[125] Both the glycone and aglycone moieties of glycosides are responsible for their binding affinity with viral proteins like MPRO and RdRp. For example in rutin (structure in Table 2) the OH groups present in the rutinose moiety forms a hydrogen bond with the amino-acid residues and the aromatic rings undergo pi–pi interaction with the aromatic amino acid residues in the target proteins.[131] Marine natural products have complex chemical structures and their bulky nature accounts for fitting in the target protein pocket. For example the carbonylamino group and the OH group in the oxa-azispiro moiety of fostularin 3 (structure in Table 2) is responsible for its binding with the serine and methionine residues of the SARS-CoV M^{PRO} active site. In another instance the 2 OH groups present in 1-hexadecoxypropane-1,2-diol (structure in Table 2) are

responsible for its binding to the active site pocket of the SARS-CoV M^{PRO}.[141] In a nut-shell it can be concluded that the diverse functional groups present in the different classes of natural compounds are responsible for their binding to the specific target proteins. *In silico* studies predict the possible ligand–target interaction and pave the way towards finding new drug molecules.

Conclusion and future prospects

The novel coronavirus (SARS COVID-19) has claimed over a million lives and is still continuing to affect thousands at a daily rate and has proved to be an important target for immediate drug development. More concerning news that shocked the world was the identification of a new variant of the SARS-CoV-2 in the UK, named VUI-202012/01. This new variant had 17 mutations and one of the most significant was the N501Y mutation in the spike protein which could render it more infectious.[148] Laboratories all around the globe are frantically searching for an effective vaccine but it takes time to develop a successful one. According to the WHO there are 3 vaccine candidates which are in the pipeline, but only one (developed by Pfizer) received WHO EUL/PQ authorization. The vaccines developed by Pfizer, Moderna and AstraZeneca are being used on a small to medium scale worldwide and their safety and efficacy results are reported in press conferences and that of AstraZeneca has been published in a peer reviewed journal.[149] Till then we must look for small molecules that can effectively reduce the mortality of the virus. Synthetic small molecules like chloroquine and hydroxychloroquine are being used to treat the patients affected by this virus but the limited availability and adverse reactions make this line of treatment somewhat inefficacious. It has been known that natural products and plant extracts have potent anti-viral activities and they have shown inhibitory effects on the viral enzymes which are essential for the viral life cycle. From the *in silico* data received we have compiled a large number of potent anti-viral compounds which need extensive *in vitro* and *in vivo* analysis prior to being used as drugs.

Abbreviations

μM	Micromolar
5′ UTR	5′ untranslated region
ACE2	Angiotensin-converting enzyme 2
ADMET	Absorption, distribution, metabolism, excretion, and toxicity
ARDS	Acute respiratory distress syndrome
CoV	Coronavirus
CPT	Convalescent plasma therapy
DNA	Deoxyribonucleic acid
EC_{50}	Half maximal effective concentration
ERGIC	Endoplasmic reticulum–Golgi intermediate compartment
EUL/PQ	Emergency use listing procedure
GMP	Good manufacturing practices
IC_{50}	Half maximal inhibitory concentration
kb	Kilobase
kDa	Kilodaton
M^{PRO}($3CL^{PRO}$)	Main protease (3C-like protease)
mRNA	Messenger ribonucleic acid
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
nm	Nanometre
NSP	Non-structural proteins
ORF	Open reading frame
PL^{PRO}	The papain-like protease
PP	Polyproteins
PSM	Plant secondary metabolite
RdRp	RNA dependent RNA polymerase
RNA	Ribonucleic acid
RNP	Ribonucleocapsid
SOFA	Sequential organ failure assessment
TGG	Tetra-*O*-galloyl-β-D-glucose
TMD	Transmembrane domain
TMPRSS2	Trans membrane protease serine 2
TNFα	Tumor necrosis factor alpha
TNFβ	Tumor necrosis factor beta
TRALI	Transfusion related acute lung injury
US FDA	United States Food and Drug Administration
WHO	World Health Organization
μg/ml	Micrograms/milliliter

Conflicts of interest

The authors declare no conflict of interest.

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