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Review

Current approaches for target-specific drug discovery using natural compounds against SARS-CoV-2 infection

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ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) recently caused a pandemic outbreak called coronavirus disease 2019 (COVID-19). This disease has initially been reported in China and also now it is expeditiously spreading around the globe directly among individuals through coughing and sneezing. Since it is a newly emerging viral disease and obviously there is a lack of anti-SARS-CoV-2 therapeutic agents, it is urgently required to develop an effective anti-SARS-CoV-2-agent.Through recent advancements in computational biology and biological assays, several natural compounds and their derivatives have been reported to confirm their target specific antiviral potential against Middle East respiratory syndrome coronavirus (MERS-CoV) or Severe Acute Respiratory Syndrome(SARS-CoV).These targets including an important host cell receptor, i.e., angiotensin-converting enzyme ACE2 and several viral proteins e.g. spike glycoprotein (S) containing S1 and S2 domains, SARS CoV Chymotrypsin-like cysteine protease ($3CL^{pro}$), papain-like cysteine protease (PL^{pro}), helicases and RNA-dependent RNA polymerase (RdRp). Due to physical, chemical, and some genetic similarities of SARS CoV-2 with SARS−COV and MERS−COV, repurposing various anti-SARS−COV or anti-MERS−COV natural therapeutic agents could be helpful for the development of anti−COVID-19 herbal medicine. Here we have summarized various drug targets in SARS−COV and MERS−COV using several natural products and their derivatives, which could guide researchers to design and develop a safe and cost-effective anti-SARS−COV-2 drugs.

1. Introduction

The outbreaks of coronavirus (CoV) infection that have already threatened the world by SARS and MERS in the first decade of 21st century have recently come up with a novel strain of lethal coronavirus named as 2019 novel coronavirus (SARS-CoV-2). In December 2019, the disease was originally started in the local seafood market of Wuhan of China (Hui et al., 2020; Perlman, 2020; Zhu et al., 2020). Since then this new coronavirus strain has spread across the globe very rapidly with the catastrophic effects. Coronaviruses are the non-segmented, enveloped viruses with positive-sense RNA as their genetic material belonging to the family Coronaviridae. They are pleomorphic and club-shaped spikes are present on their cell surface. The disease is characterized as respiratory disorders with flu-like symptoms such as a sore throat, fever, cold, cough and severe pneumonia is also reported in more critical cases. SARS-CoV-2 can be transmitted through coughing and sneezing droplets of infected individuals; these virions containing droplets retained on the hard surfaces for a longer time and can spread to a fresh individual by direct inhalation or by touching the infected surfaces. As of 31st August 2020, the complete number of affirmed COVID-19 cases reported globally is more than 25 million and the mortality has crossed more than 850,600.

Recently many efforts have been made to develop the therapeutic agents to control COVID-19, but so far no medicine is significantly effective against SARS-CoV-2 (Tu et al., 2020), and further supportive care is also needed to the individual for proper breathing. While the development of a vaccine may also take 12–18 months (Pandey et al., 2020), repurposing of the drugs (from Ebola to malaria to arthritis) is the only feasible option for treating the patients in this current situation (Simsek Yavuz and Unal, 2020). Progress in drug discovery and development largely depends on the identification of potential drug targets. For the management of COVID-19 infection, various molecular targets playing important role in the SARS-CoV-2 life cycle including host cell receptor-Angiotensin-converting enzyme ACE2 (PDB ID 3D0G) and viral proteins such as S protein (containing S1 and S2 domains) (PDB ID 6XM0); various cysteine proteases such as papain-like cysteine protease

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(PL^{pro}) (PDB ID 6WX4) or Chymotrypsin like nprotease (3CL^{pro}) (PDB ID 1P9U), helicases and RNA-dependent RNA polymerase (RdRp) (PDB ID 6M71) could be evaluated.

Nature has provided us with an immense supply of natural products. Interestingly, the nutraceuticals market hugely depends on the success of natural drugs for the treatment of infectious diseases (Williamson et al., 2020). So these natural products and their derivatives could offer new scope for the control and prevention of various ailments including

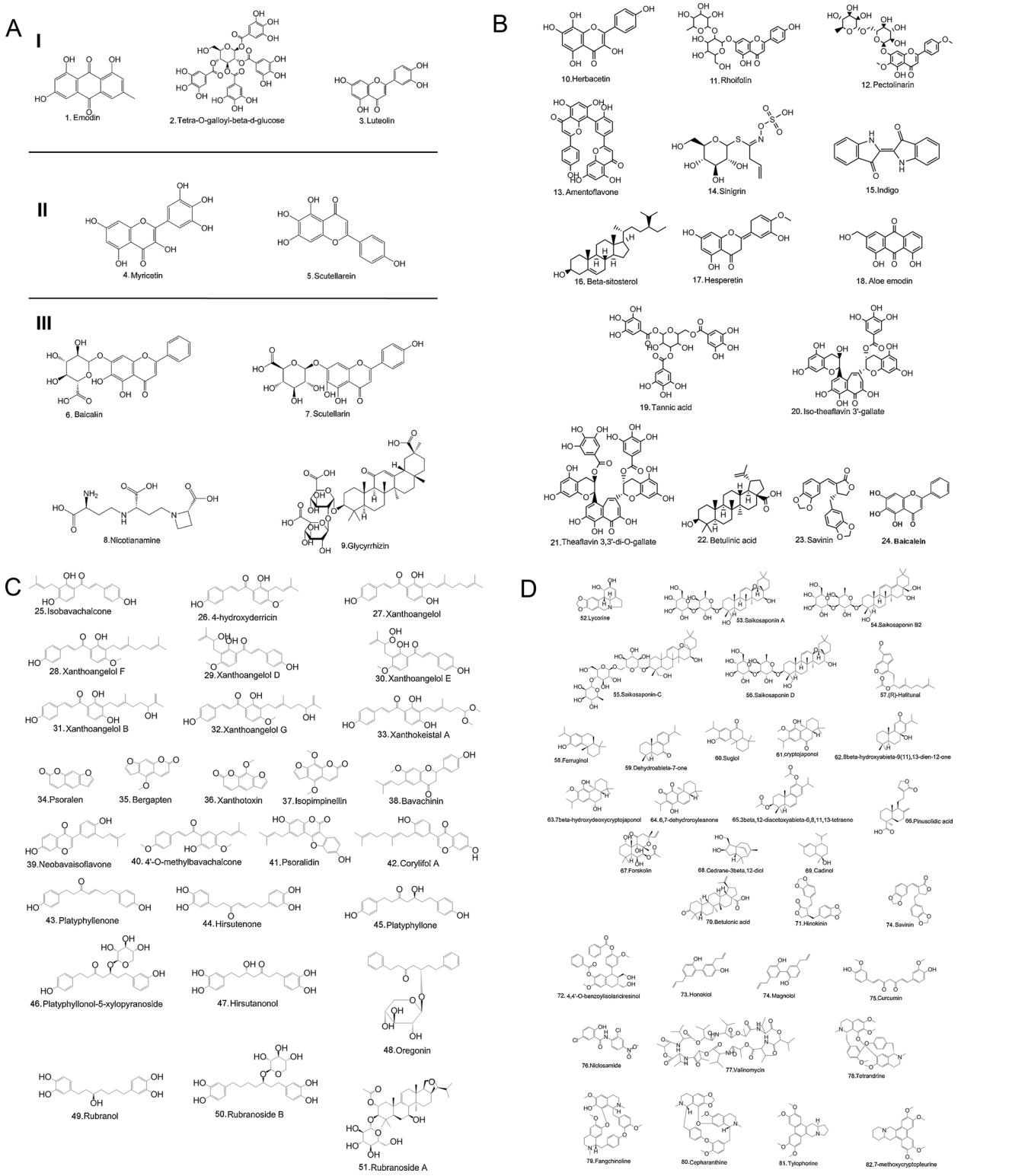

Fig. 1. A-Chemical structure of different natural compounds targeting Group I- Spike Protein; Group II- Helicase; Group III- Angiotensin-converting enzyme ACE2 receptor.
B-Chemical structure of natural compounds targeting SARS-CoV 3CL protease.
C- Chemical structure of natural compounds targeting papain- like cysteine protease.
D - Chemical structure of natural compounds having unknown targets in SARS-CoV and MERS-CoV.

Table 1A
Various natural compounds targeting specific proteins in SARS-CoV.

Compound	IC_{50}/EC_{50}	Target	Reference
Emodin	200μM	Spike Protein (S)	(Ho, 2007)
Tetra-O-galloyl-β-D-glucose (TGG)	50−4.5 μM	Spike Protein (S)	(Yi, 2004)
Luteolin	10.6μM	Spike Protein (S)	(Yi, 2004)
Myricetin	2.5−3.0 μM	Helicase	(Yu, 2012)
Scutellarein	0.4−1.24 μM	Helicase	(Yu, 2012)
Baicalin	2.24 mM	Angiotensin-converting enzyme 2 (ACE2) receptor	(Deng et al., 2012)
Scutellarin	44−52 μM	ACE2 receptor	(Wang et al., 2016)
Nicotianamine	84nM	ACE2 receptor	(Chen, 2020)
Glycyrrhizin	NA	ACE2 receptor	(Chen, 2020)
Flavinoids:	33.17μM	Chymotrypsin like protease ($3CL^{pro}$)	(Jo, 2020)
Herbacetin			
Rhoifolin	27.45 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Jo, 2020)
Pectolinarin	37.78 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Jo, 2020)
Amentoflavone		Chymotrypsin like protease ($3CL^{pro}$)	(Ryu, 2010)
Sinigrin	217 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Lin, 2005)
Indigo	752 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Lin, 2005)
Beta-sitosterol	1210 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Lin, 2005)
Hesperetin	365 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Lin, 2005)
Aloe emodin	8.3μM	Chymotrypsin like protease ($3CL^{pro}$)	(Lin, 2005)
Tannic acid	3 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Chen, 2005)
Isotheaflavin-3-gallate (TF2B)	7μM	Chymotrypsin like protease ($3CL^{pro}$)	(Chen, 2005)
Theaflavin-3,3′-digallate (TF3)	9.5 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Chen, 2005)
Betulinic acid	10 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Wen, 2007)
Savinin	25 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Wen, 2007)
6. Baicalin	6.41 ± 0.95 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Su et al., 2020)
Baicalein	0.94 ± 0.20 μM	Chymotrypsin like protease ($3CL^{pro}$)	(Su et al., 2020)
Isobavachalcone	Cell-free cleavage- 39.4 ± 5.2 μM Cell-based cleavage-11.9 ± 2.8 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
4-hydroxyderricin	Cell free cleavage 81.4 ± 8.5 μM Cell based cleavage 50.8 ± 3.0 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthoangelol	Cell free cleavage38.4 ± 3.9 μM Cell based cleavage5.8 ± 0.63.0 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthoangelol F	Cell free cleavage34.1 ± 4.8 μM Cell based cleavage32.6 ± 2.2 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
xanthoangelol D	Cell free cleavage26.6 ± 5.2 μM Cell based cleavage9.3 ± 1.2 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthoangelol E	Cell free cleavage11.4 ± 1.4 μM Cell based cleavage7.1 ± 0.8 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthoangelol B	Cell free cleavage22.2 ± 6.5 μM Cell based cleavage8.6 ± 2.6 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthoangelol G	Cell free cleavage129.8 ± 10.3 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthokeistal A	Cell free cleavage44.1 ± 1.3 μM Cell based cleavage 9.8 ± 2.3 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Psoralen	Cell free cleavage45 % at 200 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Bergapten	Cell free cleavage40 % at 200 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Xanthotoxin	Cell free cleavage 40 % at 200 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Isopimpinellin	Cell free cleavage 40 % at 200 μM	Papain- like cysteine protease (PL^{pro})	(Park et al., 2016)
Bavachinin	12.99 μg/mL	Papain- like cysteine protease (PL^{pro})	(Kim, 2014)
Neobavaisoflavone	5.9 μg/mL	Papain- like cysteine protease (PL^{pro})	(Kim, 2014)
25.Isobavachalcone	7.3 ± 0.8 μM	Papain- like cysteine protease (PL^{pro})	(Kim, 2014)
4′-O-methylbavachalcone	3.6 μg/mL	Papain- like cysteine protease (PL^{pro})	(Kim, 2014)
Psoralidin	1.412 μg/mL	Papain- like cysteine protease (PL^{pro})	(Kim, 2014)
Corylifol A	12.62 μg/mL	Papain- like cysteine protease (PL^{pro})	(Kim, 2014)
Platyphyllenone	>200μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Hirsutenone	4.1 ± 0.3 μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Platyphyllone	>200μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Platyphyllonol-5xylopyranoside	>200μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Hirsutanonol	7.8 ± 1.7 μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Oregonin	20.1 ± 2.2 μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Rubranol	12.3 ± 0.9 μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Rubranoside B	8.0 ± 0.2 μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Rubranoside A	9.1 ± 1.0 μM	Papain- like cysteine protease (PL^{pro})	(Park, 2012)
Houttuynia cordata extract	251.1 μg/mL	RNA dependent RNA polymerase	(Fung, 2011)
Ganoderma lucidum extract	41.9 μg/mL	RNA dependent RNA polymerase	(Fung, 2011)

Table 1B
Various natural compounds having unknown targets in SARS-CoV.

Compound	IC_{50}/EC_{50}	Reference
9. Glycyrrhizin	600−2400 mg/L	(Cinatl, 2003)
52. Lycorine	4.5 ng/mL	(Li et al., 2005)
Saikosaponins: Saikosaponin A	8.6 ± 0.3 μmol/L	(Cheng et al., 2006)
Saikosaponin B2	1.7 ± 0.1 μmol/L	(Cheng et al., 2006)
Saikosaponin C	19.9 ± 0.1 μmol/L	(Cheng et al., 2006)
Saikosaponin D	0.02 ± 0.001 μmol/L	(Cheng et al., 2006)
R-Halitunal	NA	(Koehn et al., 1991b)
Diterpenes ferruginol	0.40 μg/mL	(Wen et al., 2007)
dehydroabieta-7-one	4.00 μM	(Wen et al., 2007)
Sugiol	NA	(Wen et al., 2007)
cryptojaponol	>3.3 μg/mL	(Wen et al., 2007)
8β-hydroxyabieta-9(11), 13-dien-12-one	0.44 μg/mL	(Wen et al., 2007)
7β-hydroxydeoxycryptojaponol	1.15 μM	(Wen et al., 2007)
6,7-dehydroroyleanone	5.55 μM	(Wen et al., 2007)
3β, 12-diacetoxyabieta-6, 81,113-tetraene	0.48 μg/mL	(Wen et al., 2007)
pinusolidic acid	4.71 μM	(Wen et al., 2007)
forskolin	3.1 μg/mL	(Wen et al., 2007)
Sesquiterpenes cedrane-3β,12-diol	>2.3 μg/mL	(Wen et al., 2007)
Cadinol	1.04 μg/mL	(Wen et al., 2007)
Triterpenes 22. betulinic acid	>4.5 μg/mL	(Wen et al., 2007)
betulonic acid	0.29 μg/mL	(Wen et al., 2007)
Lignins: 71. hinokinin	>10 μM	(Wen et al., 2007)
savinin	0.40 μg/mL	(Wen et al., 2007)
4,4′-O-benzoylisolariciresinol	NA	(Wen et al., 2007)
Honokiol	6.5 μM	(Wen et al., 2007)
Magnolol	3.80 μM	(Wen et al., 2007)
75. Curcumin	>10 μM	(Wen et al., 2007)
76. Niclosamide	<0.1 μM	(Wen et al., 2007)
77. Valinomycin	1.82 μg/mL	(Wen et al., 2007)
78.Tetrandrine	0.21 μg/mL	(Kim et al., 2019)
79.Fangchinoline	1.01 μM	(Kim et al., 2019)
80. Cepharanthine	0.53 μg/mL	(Kim et al., 2019)
81. Tylophorine	58 nM	(Yang et al., 2010)
82. 7-methoxy - cryptopleurine	20 nM	(Yang et al., 2010)

viral infections (Fig. 1A-D and Tables 1A, 1B, 1C) (Chen and Du, 2020; Ganjhu et al., 2015; Islam et al., 2020; Jo et al., 2020; Lin et al., 2014; Wang et al., 2014). This article gathers information on the use of herbal-based drugs and/or their derivatives for target-specific drug discovery against SARS CoV2 infection (Fig. 2).

2. Various drug targets

Initially, CoV was known to cause mild disease, but the recent outbreaks (SARS-CoV outbreak of China and MERS-CoV outbreak of Saudi Arabia and now COVID-19 originated from Wuhan, Hubei, China) signifies the importance of understanding the structure, metabolism, and pathophysiology of CoV-associated diseases to identify major drug targets (J Alsaadi and Jones, 2019).

The viral RNA codes for some conserved genes: ORF1a, ORF1b, OEF3S, E, M, and N gene. The ORF1a/b genes code for viral replicase polyproteins (PPs) PP1A and PP1ab. These PPs are further processed to form sixteen mature non-structural proteins (NSPs), which play a crucial role in the formation of the replicase transcriptase complex. Other structural proteins viz. membrane (M), envelope (E), spike (S), nucleocapsid as well as other accessory proteins are encoded by rest of the genome (McBride et al., 2014) and the beta-CoVs also have hemagglutinin esterase (HE) glycoprotein (Hilgenfeld, 2014). All these proteins play a significant role in virulence and for viral multiplication. Hence these viral proteins could be the potential targets for the treatment of SARS CoV2 infection.

2.1. Spike (S) glycoprotein

Spike proteins are glycoprotein which facilitates the attachment of coronavirus to the target cells via a specific receptor present on the cell surface of host i.e. Angiotensin-converting enzyme ACE2 receptor in SARS-CoV(Li et al., 2003; Zhou et al., 2020) and dipeptidyl peptidase-4 [DPP-4] in MERS-CoV(Mubarak et al., 2019). The coronavirus relies on the association of viral envelope protein with host cell membrane for delivering their nucleocapsid. The spike proteins (S) are responsible for viral entry inside the host cell and are accountable for disease progression in a specific types of host cells. During the fusion of S protein with a specific receptor on the host cell membrane, a crucial conformational change occurs in S glycoprotein (Belouzard et al., 2012). So the S-glycoprotein could be evaluated as a potential drug target. So far various natural compounds and their derivatives have been tested for anti-SARS-CoV activity against this protein (Ho et al., 2007). Several extracts/derivatives from the herbs belonging to family polygonaceae have been reported to inhibit the SARS-CoV S protein interaction with Angiotensin-converting enzyme ACE2 receptor. Anthraquinone compound namely emodin (1), a plant extract isolated from genus *Polygonum,* and *Rheum* has efficiently impeded the interaction of S protein and Angiotensin-converting enzyme ACE2 receptor. Moreover, it also hampered S protein-pseudo typed retrovirus infectivity to Vero E6 cells. These observations indicated the potential role of emodin as a drug candidate against S protein (Ho et al., 2007; Yi et al., 2004). Two naturally occurring compounds tetra-O-galloyl-β-D-glucose (TGG) (2) and luteolin (3) derived from *Galla chinensis* were reported to possess anti-SARS-CoV activities. TGG and luteolin have a high affinity for S2 domain of spike protein. This indicates the anti-SARS activity of TGG and luteolin is due to inhibition of virus and host cell fusion however the exact mechanism remains unknown (Yi et al., 2004). These observations indicate that TGG and luteolin could be used for drug development against COVID-19 targeting S2 domain

2.2. Helicase

Helicase also known as NTPase is involved in the replication of viral genomic RNA as well as in transcription and translation (Frick and Lam, 2006). SARS-CoV helicase is an enzyme of the SF1 family, which hydrolyzes all NTPs and utilizes ATP, dATP, and dCTP as substrates (Karpe and Lole, 2010). CoV helicase nsP13 has been reported to retain dsRNA unwinding activity with translocation along the nucleic acid by ATP hydrolysis (Adedeji et al., 2012). Various natural compounds have also

Table 1C
Various natural compounds having unknown targets in HCoV and other coronaviruses.

Compound	Test System	IC_{50}/EC_{50}	Reference
Saikosaponins: Saikosaponin A	HCoV-229E	8.6 ± 0.3 μmol/L	(Cheng et al., 2006)
Saikosaponin B2	HCoV-229E 1	1.7 ± 0.1 μmol/L	(Cheng et al., 2006)
Saikosaponin C	HCoV-229E	19.9 ± 0.1 μmol/L	(Cheng et al., 2006)
Saikosaponin D	HCoV-229E	EC50−0.02 ± 0.001 μmol/L	(Cheng et al., 2006)
R. Halitunal	Coronavirus A59	NA	(Koehn et al., 1991b)
78. Tetrandrine	HCoV-OC43	0.33 μM	(Kim et al., 2019)
79. Fangchinoline	HCoV-OC43	1.01 μM	(Kim et al., 2019)
80. Cepharanthine	HCoV-OC43	0.83 μM	(Kim et al., 2019)

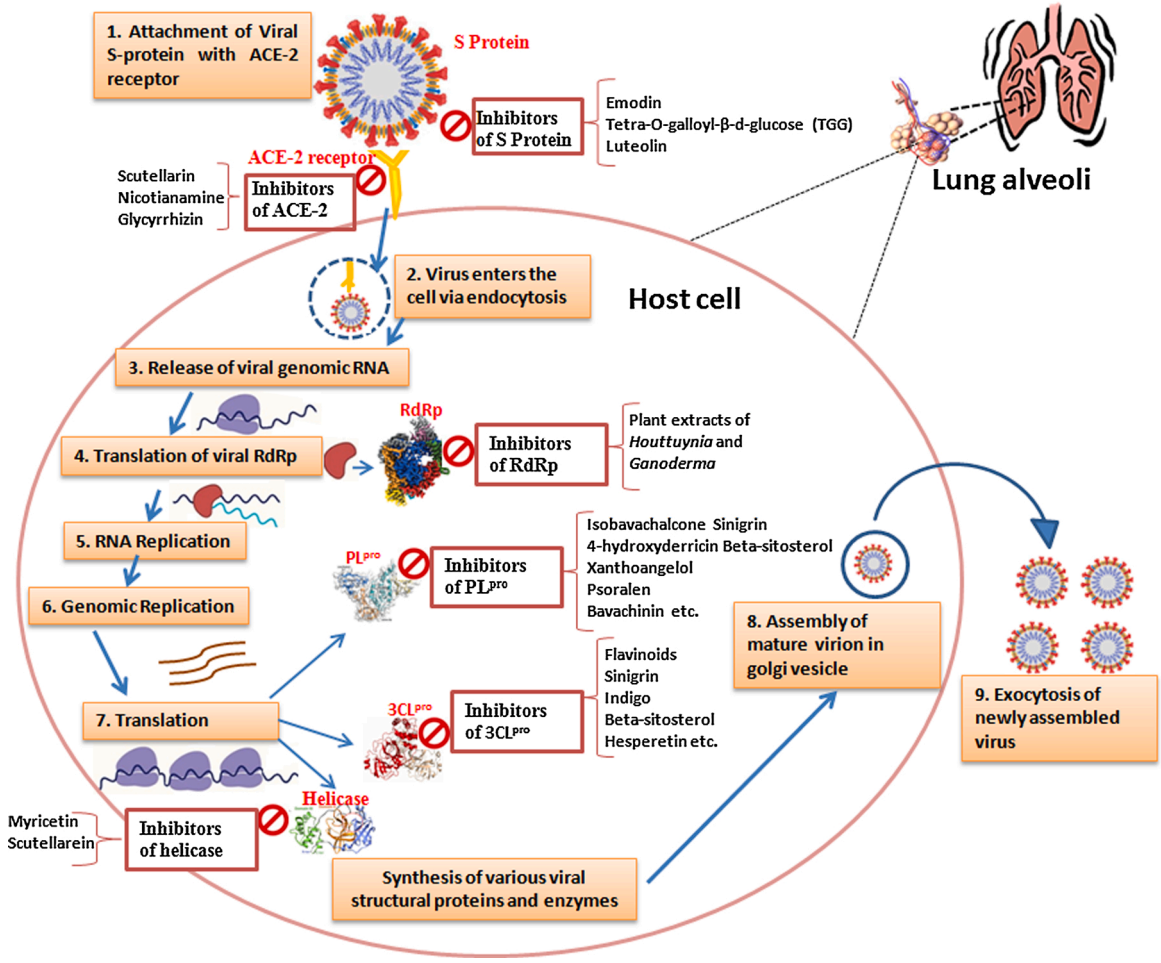

Fig. 2. Schematic representation of SARS-CoV-2 life cycle highlighting the various drug targets along with their potential inhibitors.

been reported to inhibit helicases of SARS-CoV-2. The activity of two naturally occurring flavonoids namely myricetin (4) and scutellarein (5) have been shown to inhibit potential against SARS CoV helicase nsP13. These compounds have been reported to inhibit helicase protein by affecting the ATPase activity (Yu et al., 2012).Therefore, helicases could be a potential drug target for anti−COVID-19 therapy.

2.3. Human-based targets

2.3.1. ACE2 receptor

Angiotensin-converting enzyme ACE2 receptor is a human receptor to the SARS and SARS-CoV-2 (Zhang et al., 2020). Angiotensin-converting enzyme ACE2 receptor is mostly present as cell surface receptors and rarely circulates in soluble form. These receptors facilitate entry of three CoV strains (e.g. NL63, SARS-CoV, and SARS-CoV-2), which are present most abundantly in the lungs (predominantly in type 2 pneumocytes and macrophages), testis, brain, heart, blood vessels, and kidney (Verdecchia et al., 2020). The overexpression of ACE2 receptor from human, pig, civet in HeLa cells permitted replication of SARS-CoV-2, thus proving it to be the principal receptor for CoV entry (Zhou et al., 2020). Drugs targeting the ACE2 receptor could be efficient for anti CoV drugs. Various natural compounds such as baicalin, (6) scutellarin (7), nicotianamine (8) (docking score -5.1) and glycyrrhizin (9) (docking score -9) (supplementary Table 1) have been reported to have potential anti-2019-CoV effects by preventing the attachment and entry of virus (Chen and Du, 2020), Particularly baicalin, extracted from plant *Scutellaria baicalensis* Georgi demonstrated an excellent antiviral and anti-SARS activity (Chen et al., 2004). Another such compound scutellarin, is reported to reduce ACE2 activity in brain tissues (Wang et al., 2016) and therefore this compound can also be evaluated as an ACE2 receptor inhibitor to block the entry of SARSCoV2. Stilbenoids belonging to other phenolic natural compounds were reported to possess inhibitory activity against ACE2 receptor (Wahedi et al., 2020). Furthermore, natural extracts isolated from garlic were also observed to have inhibitory effects against ACE2 receptor (Thuy et al., 2020).

2.4. SARS-CoV chymotrypsin like protease ($3CL^{pro}$)

SARS-CoV Chymotrypsin protease ($3CL^{pro}$) is mainly associated with the maturation process of the virus by cleavage of viral polyproteins (Koulgi et al., 2020). It releases the two important enzymes for replication, viz. RdRp and helicase from the precursors of polyprotein (Thiel et al., 2003). Because of its involvement in the SARS-CoV life cycle, the 3CL protease could be a prominent drug target. Several natural compounds derived from plants have been known to manifest anti-SARS-CoV activity against SARS-CoV 3CL protease. *Rhizomacibotii*; the dried rhizome of *Cibotiumbarometz* (CBM) and *Dioscoreaerhizoma*; the tuber of *Dioscoreabatatas* (DBM) displayed a significant reduction in protease activity of SARS-CoV 3CL (Wen et al., 2011). Flavonoids are polyphenolic plant secondary metabolites present in different fruits and vegetables. Recently flavonoids such as herbacetin (10) (Docking Score –9.263), rhoifolin (11) (Docking Score —9.565), and pectolinarin (12) demonstrated anti-SARS-CoV $3CL^{pro}$ activity (Jo et al., 2020). $3CL^{pro}$ has 3 domains at substrate binding site -S1, S2, and S3. S1 represents the polar site of $3CL^{pro}$, S2 represents the hydrophobic site, while S3 has no

strong tendency. Molecular docking showed the binding affinity of three flavonoids with 3 domains of $3CL^{pro}$ (Jo et al., 2020). Another flavonoid amentoflavone (13) (Docking Score −11.42) is the most effective flavonoid inhibiting SARS-CoV $3CL^{pro}$ (Ryu et al., 2010) (supplementary Table 1). Thus, flavonoids could serve as a promising anti-CoV compound and could be explored in the development of antiviral drugs. The root extracts of *Isatis indigotica* are also reported to have anti CoV activity by inhibiting the SARS-CoV $3CL^{pro}$ enzyme (Lin et al., 2005). Various root extracts viz. sinigrin (14), Indigo (15) β-sitosterol (16), hesperetin (17) and, aloe emodin are (18) reported to be efficient in inhibiting the $3CL^{pro}$ activity in concentration-dependent manner (Lin et al., 2005). Further *Houttuynia cordata* extract (Lau et al., 2008) as well as tannic acid (19), isotheaflavin-3-gallate [(TF2B) (20)] and theaflavin-3, 3′-digallate [(TF3) (21)] belonging to polyphenols of tea were reported to exhibit antiviral properties by their inhibitory potential against $3CL^{Pro}$ (Chen et al., 2005). Triterpenes [betulinic acid (22) and savinin (23)] were reported to possess anti 3CLpro activity (Wen et al., 2007). Recently, a sum of 28 natural compounds was identified from the Shuanghuanglian preparations. Out of which two major bioactive compounds baicalin (6) and baicalein, (24) were found to possess significant inhibitory activity against SARS-CoV $3CL^{pro}$ by inhibiting the proliferation in Vero E6 cells (Su et al., 2020)

2.5. Papain- like cysteine protease (PL^{pro})

The papain-like cysteine protease (PL^{pro}) plays an important role in SARS-CoV viral genomic RNA replication. It cleaves the N terminal site of polyproteins (PPs) to generate three nonstructural proteins (NSPs-1, 2, and 3) (Hilgenfeld, 2014; Lindner et al., 2005). PL^{pro} also contains a catalytic core domain and a consensus sequence LXGG which is required for cleaving replicase substrate (Barretto et al., 2005). Thus PL^{pro} could be used as a crucial drug target for anti-SARS drug development (Park et al., 2017). Recently 13 chalcones that includes isobavachalcone (25) (Dockind Score −8.82), 4-hydroxyderricin (26) (Docking Score −8.26), xanthoangelol (27) (Docking Score −8.6), xanthoangelol F (28) (Docking Score −7.84), xanthoangelol D (29) (Docking Score −6.69), xanthoangelol E (30) (Docking Score −7.45), xanthoangelol B (31) (Docking Score −7.16), xanthoangelol G (32) (Docking Score −9.43), xanthokeistal A (33) (Docking Score −6.31), psoralen (34) (Docking Score −7.42), bergapten (35) (Docking Score −6.94), xanthotoxin (36) (Docking Score −7.37) and isopimpinellin (37) (Docking Score- −8.09) isolated from *Angelica keiskei* have exhibited anti-SARS CoV activity targeting PL^{pro}. Moreover, chalcones 3 and 6 were most efficient in inhibiting the activity of PL^{pro}-cleavage (Park et al., 2016). Further anti PL^{pro} activity of phenolic compounds was evaluated isolated from seeds of *Psoraleacorylifolia* (Kim et al., 2014). Total 6 compounds bavachinin (38), neobavaisoflavone (39), isobavachalcone (25), 4′-O-methylbavachalcone (40), psoralidin (41), and corylifol-A (42) were identified. Among them, isobavachalcone and psoralidin demonstrated promising PL^{pro} inhibitory activity. Hence, future studies targeting papain-like cysteine protease with these natural extracts may lead to the better management against COVID-19 infection. In another study, 9 diarylheptanoids namely platyphyllenone (43), hirsutenone (44), platyphyllone (45), platyphyllonol-5-xylopyranoside (46), hirsutanonol (47), oregonin (48) rubranol (49), rubranoside B (50) and rubranoside A (51), isolated from *Alnus japonica* have demonstrated anti SARS-CoV potential by blocking PL^{pro} activity. Among them, the hirsutenone was found to manifest the highest anti PL^{pro} activity (Park et al., 2012).

2.6. RNA-dependent RNA polymerase (RdRp)

The RNA-dependent RNA polymerase of SARS-CoV (SARS-CoV RdRp) is an important enzyme, which can be utilized for the synthesis of both sense and antisense RNA. This enzyme is needed for replication and is expected to possess accessory cellular and viral proteins (Thiel et al., 2003). Only a few reports are available regarding the evaluation of RNA-dependent RNA polymerase as a drug target using natural compounds. The anti-SARS-CoV RdRp activity was reported using natural *Houttuynia cordata* that effectively inhibited the polymerase (Lau et al., 2008). Further, extracts from *Ganoderma lucidum* were also reported to be potent antiviral agents against SARS-CoV by targeting viral RdRp (Fung et al., 2011).

2.7. Plant extracts with unknown targets

Besides the target-specific herbal therapeutic agents, a large number of plant extracts have been reported to demonstrate anti-SARS and anti-MERS activity. Glycyrrhizin (9) that is isolated from liquorice roots and considered to be the active component is reported to have the antiviral activity. It inhibits replication, adsorption, and penetration of virus. The efficacy of glycyrrhizin was higher after the viral adsorption (Cinatl et al., 2003). The exact mechanism of viral inhibition is unknown but glycyrrhizin affects signaling pathways such as casein kinase II; protein kinase C; and transcription factors like nuclear factor κB and activator protein 1. The aglycone metabolite of glycyrrhizin (18β glycyrrhetinic acid) upregulates the nitrous oxide synthase and also increases the production of NO in macrophages (Jeong and Kim, 2002). Another compound lycorine (52) from the extracts of *Lycoris radiate* identified as an efficient and safe antiviral agent against SARS-CoV(Li et al., 2005).

Saikosaponins A (53), B2 (54), C (55), and D (56) are natural triterpene glycosides that are isolated from *Bupleurum*spp, *Heteromorpha* spp., and *Scrophulariascorodonia*also demonstrated anti−HCoV-22E9 activity by inhibiting viral penetration into the host cells. So these compounds could be important for inhibiting the early stages of CoV infection (Cheng et al., 2006). Moreover, extracts from *Nigella sativa*, *Anthemishyalina*, and *Citrus sinensis*demonstrated potent in vitro anti CoV activity (Ulasli et al., 2014). R. Halitunal (57) from *Halimeda tuna* was reported to inhibit Murine coronavirus A59. However, the precise target and mechanism are still unknown (Koehn et al., 1991). Evaluation of anti- SARS activity was also carried out using various phytochemicals such as diterpenes [ferruginol (58), dehydroabieta-7-one (59), sugiol (60), cryptojaponol (61), 8β-hydroxyabieta-9(11)13-dien-12-one (62), 7β-hydroxydeoxycryptojaponol (63), 6,7-dehydroroyleanone (64), 3β, 12-diacetoxyabieta-6, 81,113-tetraene (65), pinusolidic acid (66), forskolin (67)] ; sesquiterpenes [cedrane-3β 12-diol (68), Cadinol (69),] ; Triterpenes [betulinic acid (22) and betulonic acid (70)]; lignins [hinokinin (71), savinin (23), 4,4′-O-benzoylisolariciresinol (72), honokiol (73), magnolol (74)] and curcumin (75), niclosamide (76), valinomycin (77) which significantly inhibited the viral multiplication (Wen et al., 2007). Similarly, *Toonasinensis*aquas leaf extract was also reported to stop the replication of SARS CoV (Chen et al., 2008). Further tetrandrine (78), fangchinoline (79), cepharanthine (80), alkaloids were also reported to inhibit HCoV−OC43-viral infection in MRC-5 human lung cell lines (Kim et al., 2019). Further two natural compounds, tylophorine (81) and 7-methoxycryptopleurine (82) derived from *Tylophoraindica* reported to prevent the viral genomic RNA replication. Further, these compounds could also inhibit TGEV, SARS-CoV, MERS-CoV (Yang et al., 2010). Moreover, the natural plant extract compounds with unknown targets that possess antiviral activities and are previously reported against SARS or MERS could serve to be a potential agent in the treatment of COVID-19.

3. Discussion

It is a big challenge to develop an effective antiviral therapeutic agent. Various inverse agonists are currently being explored against COVID-19. The nucleoside inhibitor (Gilead's Nuc inhibitor) which has shown disappointment in the treatment of Ebola is effective in the treatment of a 2019-CoV patient in the USA, but the higher rate of mutation in this virus have restricted the use of this drug for treating the n-Cov patients (Nguyen et al., 2020). Moreover, remdesivir another drug recommended for the treatment of Ebola and other RNA viruses have

also been found useful in some of the patients (Gordon et al., 2020; Hillaker et al., 2020; Shannon et al., 2020). Recently anti-influenza drug favipiravir or avigan was considered as an efficient treatment regimen for COVID-19 patients as compared to other antiviral agents (Chibber et al., 2020; Rosa and Santos, 2020; Zhu et al., 2020). Likewise, chloroquine and hydroxychloroquine which is effective against malaria, lupus, and rheumatoid arthritis (Garcia-Cremades et al., 2020; Rosa and Santos, 2020; Zhu et al., 2020) have also been found effective in coronavirus infection (Wang et al., 2020). Only limited therapeutic options are available against SARS-CoV2. Due to the high failure rate of antiviral agents, there is an urgent need for innovative drug development strategies by acquiring knowledge from the natural products to combat viral diseases. So far the antiviral potential has been reported by various herbal-based drugs and their derivatives (Lin et al., 2014) viz. antiviral activity against hepatitis C virus was reported by *Nigella sativa* (Oyero et al., 2016), similarly some marine fungi also showed antiviral potential (Moghadamtousi et al., 2015) and further some other natural compounds have demonstrated antiviral action against dengue and chikungunya virus (Moghadamtousi et al., 2015; Oliveira et al., 2017). Moreover, some natural compounds and their synthetic derivatives (Neumann and Neumann-Staubitz, 2010) as well as marine based natural products (Wang et al., 2014) have also exerted significant antiviral potential. However, the potential of these natural drugs has not been much explored against SARS-CoV-2 but employing the computational approaches and advanced biotechnological assays, various herbal-based drugs and their derivatives have been evaluated and confirmed their anti-SARS-CoV and anti-MERS-CoV activity. Further due to physical, chemical and some genome sequence similarity between SARS CoV-2 and SARS-CoV or MERS-CoV (Andersen et al., 2020), repurposing these anti SARA−COV and anti MERS−COV natural agents could lead to develop a cost-effective and safe anti−COVID-19 drug. Development of anti−COVID-19 agents not only fights against CoV but also provides efficient protection from the future viral attack. Due to the involvement of *in silico* approaches in pharmaceutical research, now it is quite possible to identify the specific drug targets and understanding the mechanism of action of various natural products and their derivatives (Supplementary information). In this review, we have summarized various drug targets for natural drugs and their synthetic compounds, which were used to treat SARS CoV and MERS CoV. We have discussed the importance of various herbal-based compounds that can inhibit viral infectivity by blocking the ACE2 receptor of host or interrupt the activity of various viral proteins/enzymes such as spike glycoproteins (S protein), 3CL protease, PL^{pro}, helicase, and RNA dependent RNA polymerase. We have documented the mechanism of action of various herbal-based drugs so; these natural compounds could be important substitutes of synthetic drugs for the treatment of viral infections due to their low cost and safety efficacy.

4. Conclusion

In summary, we have identified and discussed the target-specific antiviral potential of several natural compounds against various strains of CoV, which might directly impede the COVID-19 pandemics. Further pharmaceutical companies should also give more emphasis on natural product research for the development of novel therapeutic agents against various viral infections to achieve sustainable development goals on health.

Author statement

Prashant Khare and Mukesh Samant collected the information and wrote the manuscript; Utkarsha Sahu and Satish Chandra Pandey assisted in the modification and adaptation of the text. Prashant Khare, Utkarsha Sahu and Mukesh Samant made the final revision of the manuscript. All authors approved the final submitted version of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.virusres.2020.198169.

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