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Review

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

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A B S T R A C T

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 (3CLpro), papain-like cysteine protease (PLpro), 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 threatened the world by SARS and MERS in the first decade of 21st century. 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 (Simske 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...
(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

| Compound | IC<sub>50</sub>/EC<sub>50 | Target | Reference |
|----------|------------------------|--------|-----------|
| Emodin   | 200 μM                | Spike Protein (S) | (Ho, 2007) |
| Tetra-O-galloyl-β-D-glucose (TGG) | 50 - 45 μM | Spike Protein (S) | (Yi, 2004) |
| Luteolin | 10 μM                 | Spike Protein (S) | (Yi, 2004) |
| Myricetin | 2.5 - 3.0 μM         | Helicase | (Yu, 2012) |
| Scutellarin | 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 | 84 nM          | ACE2 receptor | (Chen, 2020) |
| Glycyrhrizin | NA                 | ACE2 receptor | (Chen, 2020) |
| Flavonoids | 33.17 μM             | Chymotrypsin like protease (3CL<pro>) | (Jo, 2020) |
| Rubraetin | 27.45 μM             | Chymotrypsin like protease (3CL<pro>) | (Jo, 2020) |
| Peptolinarin | 37.78 μM         | Chymotrypsin like protease (3CL<pro>) | (Jo, 2020) |
| Amentoflavone | 7 μM              | Chymotrypsin like protease (3CL<pro>) | (Yi, 2004) |
| Scutellarin | 44 - 52 μM           | ACE2 receptor | (Wang et al., 2016) |
| Nicotianamine | 84 nM          | ACE2 receptor | (Chen, 2020) |
| Glycyrhrizin | NA                 | ACE2 receptor | (Chen, 2020) |
| Flavonoids | 33.17 μM             | Chymotrypsin like protease (3CL<pro>) | (Jo, 2020) |
| Rubraetin | 27.45 μM             | Chymotrypsin like protease (3CL<pro>) | (Jo, 2020) |
| 4-hydroxyderricin | Cell free cleavage 39.4 ± 5.2 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Xanthoangelol | Cell free cleavage 38.4 ± 3.9 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Xanthoangelol F | Cell free cleavage 34.1 ± 4.8 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Xanthoangelol D | Cell free cleavage 32.6 ± 2.2 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Xanthoangelol E | Cell free cleavage 11.4 ± 1.4 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Xanthoangelol B | Cell free cleavage 22.2 ± 6.5 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Xanthoangelol G | Cell free cleavage 29.8 ± 10.3 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Isopinellin | Cell free cleavage 40 % at 200 μM | Papain-like cysteine protease | (Park et al., 2016) |
| Bavachinin | 12.99 μg/mL           | Papain-like cysteine protease | (Kim, 2014) |
| Neohavainol flavone | 5.9 μg/mL            | Papain-like cysteine protease | (Kim, 2014) |
| 25-Isopinellin | 7.3 ± 0.8 μM          | Papain-like cysteine protease | (Kim, 2014) |
| 4-O-methylbavachalcone | 3.6 μg/mL         | Papain-like cysteine protease | (Kim, 2014) |
| Psoralen | 1.412 μg/mL           | Papain-like cysteine protease | (Kim, 2014) |
| Corylifol A | 12.62 μg/mL           | Papain-like cysteine protease | (Kim, 2014) |
| Platyplyphylone | >200 μM            | Papain-like cysteine protease | (Park, 2012) |
| Hirsutene | 4.1 ± 0.3 μM          | Papain-like cysteine protease | (Park, 2012) |
| Platyplyphylone | >200 μM            | Papain-like cysteine protease | (Park, 2012) |
| Platyplyphenol-Sxylpyranoside | >200 μM | Papain-like cysteine protease | (Park, 2012) |
| Hirsutinanol | 7.8 ± 1.7 μM         | Papain-like cysteine protease | (Park, 2012) |
| Oregonin | 20.1 ± 2.2 μM         | Papain-like cysteine protease | (Park, 2012) |
| Rubral | 12.3 ± 0.9 μM         | Papain-like cysteine protease | (Park, 2012) |
| Rubranoside B | 8.5 ± 0.2 μM         | Papain-like cysteine protease | (Park, 2012) |
| Rubranoside A | 9.1 ± 1.0 μM         | Papain-like cysteine protease | (Park, 2012) |
| Houttuynia cordata extract | 251.1 μg/mL | RNA dependent RNA polymerase | (Fung, 2011) |
| Gunoderma lucidum extract | 41.9 μg/mL | RNA dependent RNA polymerase | (Fung, 2011) |
viral infections (Fig. 1A-D and Tables 1A, 1B, 1C) (Chen and Du, 2020; Ganju 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-2 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 (Alsaadi and Jones, 2019).

The viral RNA codes for some conserved genes: ORF1a, ORF1b, ORF2, ORF3a, ORF3b, ORF4, ORF5, ORF6, ORF7, ORF8, ORF9c, ORF10, ORF11, and ORF12. ORF1a/b encodes for RNA helicase, RNA polymerase, and replications, while ORF3a encodes for protease (Pap). The polyproteins are cleaved by the papain-like protease and 3C-like protease. The viral proteins are then translocated along the genome to produce mature proteins.

Various drug targets include the S protein, which is the main target for drug development. The S protein interacts with the host cell receptor, ACE2, which is a viral entry receptor. The interaction can be inhibited by various compounds, such as emodin and luteolin, which have been reported to inhibit SARS-CoV S protein interaction (Yi et al., 2004). These observations indicate the potential role of emodin as a drug candidate against S protein.

2.1. Spike (S) glycoprotein

Spike proteins are glycoprotein which facilitates the attachment of virus to the host cell surface. They 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.

2.2. Helicase

Helicase also known as NTPase is involved in the replication of viral genomic RNA as well as in transcription and translation (Prick 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 (Adedjji et al., 2012). Various natural compounds have also been tested as inhibitors of CoV helicase.

| Table 1B | Various natural compounds having unknown targets in SARS-CoV. |
|-----------|---------------------------------------------------------------|
| Compound  | IC50/EC50 | Reference |
| 9. Glycyrrhizin | 600–2400 mg/L | (Cianci, 2003) |
| 52. Lycorine | 4.5 mg/mL | (Li et al., 2005) |
| Saikosaponins | 8.6 ± 0.3 µmol/L | (Cheng et al., 2006) |
| Saikosaponin A | 1.7 ± 0.1 µmol/L | (Cheng et al., 2006) |
| Saikosaponin B2 | 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 | 0.40 µg/mL | (Wen et al., 2007) |
| ferruginol | 4.00 µg/mL | (Wen et al., 2007) |
| dehydroabietic acid | 0.91 µg/mL | (Wen et al., 2007) |
| Saikosaponin A | 1.15 µg/mL | (Wen et al., 2007) |
| Saikosaponin B2 | 5.55 µg/mL | (Wen et al., 2007) |
| 3β, 12-diacetoxyabietic acid | 0.48 µg/mL | (Wen et al., 2007) |
| cryptoptaaponol | >3.3 µg/mL | (Wen et al., 2007) |
| 8β-hydroxyabietic acid | 0.44 µg/mL | (Wen et al., 2007) |
| 7β-hydroxyabietic acid | 1.15 µg/mL | (Wen et al., 2007) |
| 6,7-dehydroabietic acid | 5.55 µg/mL | (Wen et al., 2007) |
| forskolin | 3.1 µg/mL | (Wen et al., 2007) |
| Resiquiterpenes | >2.3 µg/mL | (Wen et al., 2007) |
| cedrene-3β,12-diol | 1.04 µg/mL | (Wen et al., 2007) |
| Cadinol | >4.5 µg/mL | (Wen et al., 2007) |
| 22β-betulinic acid | 0.29 µg/mL | (Wen et al., 2007) |
| betulinic acid | >10 µg/mL | (Wen et al., 2007) |
| 71. hinokinin | 0.40 µg/mL | (Wen et al., 2007) |
| 4′, 6-O-benzylisoraricinesol | NA | (Wen et al., 2007) |
| Honokiol | 6.5 µg/mL | (Wen et al., 2007) |
| Magnolol | 3.80 µg/mL | (Wen et al., 2007) |
| Curcumin | >10 µg/mL | (Wen et al., 2007) |
| Nirosamide | <0.1 µg/mL | (Wen et al., 2007) |
| Valinomycin | 1.82 µg/mL | (Wen et al., 2007) |
| Tetrandrine | 0.21 µg/mL | (Kim et al., 2019) |
| Fangchinoline | 1.01 µg/mL | (Kim et al., 2019) |
| Cepharanthine | 0.53 µg/mL | (Kim et al., 2019) |
| Tylophorine | 0.53 µg/mL | (Kim et al., 2019) |
| Cephargine | 0.53 µg/mL | (Kim et al., 2019) |

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

| Table 1C | Various natural compounds having unknown targets in HCoV and other coronaviruses. |
|-----------|--------------------------------------------------------------------------------|
| Compound  | Test System | IC50/EC50 | Reference |
| Saikosaponins | HCoV-229E | 8.6 ± 0.3 µmol/L | (Cheng et al., 2006) |
| Saikosaponin A | HCoV-229E | 1.7 ± 0.1 µmol/L | (Cheng et al., 2006) |
| Saikosaponin B2 | HCoV-229E | 19.9 ± 0.1 µmol/L | (Cheng et al., 2006) |
| Saikosaponin D | HCoV-229E | 0.70–0.02 ± 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) |
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 over-expression 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 SARS-CoV2. 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 (Kougi 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 *Cibotium barometz* (CBM) and *Dioscoreaerhizoma;* the tuber of *Dioscorea batatas* (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 3CLPro (Jo et al., 2020). Another flavonoid amentoflavone (13) (Docking Score −11.42) is the most effective flavonoid inhibiting SARS-CoV 3CLPro (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 3CLPro enzyme (Lin et al., 2005). Various root extracts viz. sinigirin (14), Indigo (15) β-sitosterol (16), hesperetin (17) and, aloe emodin are (18) reported to be effective in inhibiting the 3CLPro activity in concentration-dependent manner (Lin et al., 2005). Further *Houttuynia cordata* extract (Lau et al., 2006) 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 3CLPro (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 baicain (24) were found to possess significant inhibitory activity against SARS-CoV 3CLPro by inhibiting the proliferation in Vero E6 cells (Su et al., 2020).

2.5. Papain-like cysteine protease (PLPro)

The papain-like cysteine protease (PLPro) 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). PLPro also contains a catalytic core domain and a consensus sequence LXGG which is required for cleaving replicase substrate (Barretto et al., 2005). Thus PLPro could be used as a crucial drug target for anti-SARS drug development (Park et al., 2017). Recent 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 PLPro. Moreover, chalcones 3 and 6 were most effective in inhibiting the activity of PLPro-cleanage (Park et al., 2016). Further anti PLPro activity of phenolic compounds was evaluated isolated from seeds of *Psoralacorylifolia* (Kim et al., 2014). Total 6 compounds bavachinin (38), neobavaisoflavone (39), isobavachalcone (25), 4′-O-methylbavachalcone (40), psoralidin (41), and corylifoliol A (42) were identified. Among them, isobavachalcone and psoralidin demonstrated promising PLPro 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 platyphyllene (43), hirsutene (44), platyphylline (45), platyporphyrin-5-xylopyranoside (46), hirsutanol (47), oregonin (48) rubralin (49), rubranoside B (50) and rubranoside A (51), isolated from *Alnus japonica* have demonstrated anti SARS-CoV potential by blocking PLPro activity. Among them, the hirsutene was found to manifest the highest anti PLPro 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 caspase kinase II; protein kinase C; and transcription factors like nuclear factor xB 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, berberine (52) from the extract of *Lycoris radiata* 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, Heteromorpha* spp., and *Scrophulariascorodonia* also demonstrated anti–HCoV-229E 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, Anthemis hypalynia*, and *Citrus sinensis* demonstrated potent in vitro anti CoV activity (Ulasli et al., 2014). B. 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–nine (59), sugiol (60), cryptojaponol (61), 8β-hydroxyabieta-9(11)-dien-12-one (62), 7β-hydroxydeoxyxycryptajaponol (63), 6,7-dehydroxyoleanane (64), 3β, 12-diacetoxyabieta-6, 8,11,13-tetraene (65), pinusolidic acid (66), forskolin (67)]; sesquiterpenes [cende-rap-3β-12-diol (68), Cadolin (69)]; Triterpenes [betulinic acid (22) and betulinic acid (70)]; lignins [hinokinin (71), savinin (23), 4′,4′-benzoylsofocurciresinol (72), honokiol (73), magnolol (74)] and curcumin (75), nicosamide (76), valinomycin (77) which significantly inhibited the viral multiplication (Wen et al., 2007). Similarly, *Toonasinensi*s was also reported to stop the replication of SARS CoV (Chen et al., 2008). Further tetrandrine (78), fangchinoline (79), cepharanthin (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-methoxycthryptopureline (82) derived from *Tylophoraindiva* reported to prevent the viral genomic RNA replication. Further, these compounds could also inhibit TGEV, SARS-CoV, MER-S-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 ‘cure 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 (García-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-CoV-2. 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 (Moghadmatousi et al., 2015) and further some other natural compounds have demonstrated antiviral action against dengue and chikungunya virus (Moghadmatousi 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 sufficient 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, PLpro, 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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