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Natural products as a therapy to combat against SARS-CoV-2 virus infection

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7.1 Introduction

The coronavirus disease 19 (COVID-19) is a highly transmissible and life-threatening disease which could be caused by the SARS-CoV-2 virus first appeared in Wuhan, China in December 2019 and has since spread around the world. The World Health Organization Labeled this viral disease as a pandemic in March 2020 and considered as the world's most serious public health catastrophe, which poses a challenge to scientific civilization in terms of developing effective pharmaceuticals for its prevention and treatment. COVID-19, new coronavirus-related pneumonia, has been spreading since its discovery in December 2019. [Service \(2020\)](#) According to an epidemiological research survey, the incubation period for this disease is between 1 and 14 days, and the serial interval is between 4 and 8 days. It takes roughly 3–7 days for the number of illnesses in an epidemic to double. At present, 90 million people have been infected with the virus, and more than 1.9 million people have died due to COVID-19. Furthermore, the pandemic has wreaked havoc on the worldwide economy. SARS-CoV-2 belongs to the family of Betacoronaviridae family and shares a place along with SARS-CoV and Middle East respiratory disease coronavirus. It is an enclosed virus with a positive nonsegmented single-stranded RNA genome ([Kaul, 2020](#)). SARS-CoV-2 is more contagious than SARS-CoV or MERS-CoV, as reported by epidemiological studies ([Cui et al., 2019](#); [Marra et al., 2003](#); [Ruan et al., 2003](#)). Improved tactics for treating and preventing COVID-19 are urgently needed to curb down greater infection incidence of SARS-CoV-2 ([Parihar et al., 2020](#)). The scarcity in a few countries and the absence of viable treatment approaches for COVID-19 has created havoc.

The COVID-19 has been labeled a Public Health Emergency of International Concern (PHEIC) by WHO, indicating that this pandemic requires a coordinated worldwide response in all medical aspects due to the lack of early detection and specialized drugs or vaccines to detect and cure the virus (De Wit et al., 2016; Wu et al., 2020).

There are various proteins of coronavirus through which a drug or an antiviral compound could bind which includes structural protein and nonstructural protein. Structural protein includes spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins while nonstructural proteins include 3C-like protease (3CLpro), papain-like protease (PLpro), and other NSPs that play significant roles in virus propagation are also recognized as important therapeutic targets (Nittari et al., 2020; Vankadari, 2020). The S protein binds to the host cell receptor angiotensin-converting enzyme 2 (ACE2) which is referred to as the critical step for SARS-CoV-2 entrance into host cells (Matías-Guiu et al., 2020). Furthermore, the S protein's interaction with the cellular transmembrane serine protease (TMPRSS2) may facilitate virus entrance into host cells. As a result, ACE2 and TMPRSS2 could be used as pharmaceutical targets to prevent SARS-CoV-2 from infecting cells (Elhusseiny et al., 2020; Matías-Guiu et al., 2020). Recent research has clearly demonstrated that blocking either the ACE-2 host receptor or the S-protein will eventually limit coronavirus entrance at the early stages, preventing the host from becoming infected further (Paraskevis et al., 2020). Therefore, finding phytochemicals with a higher affinity for the ACE-2 receptor is critical for lowering SARS-host CoV-2 receptor availability. Here, in this chapter, we discussed the natural molecules (phytochemicals) based therapeutic strategies against potential multiple targets to combat COVID-19 as the recent crisis urges for quick as well as cost-effective treatment at a greater concern in all medical aspects due to the lack of early detection and specialized drugs or vaccines to detect and cure the virus.

7.1.1 Natural product-based therapeutic strategies to combat COVID-19

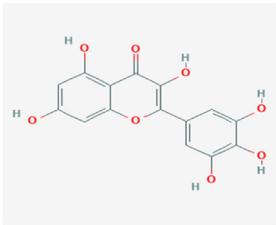
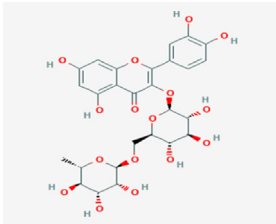
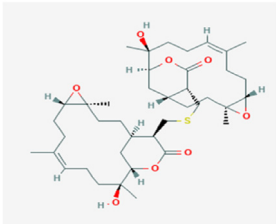
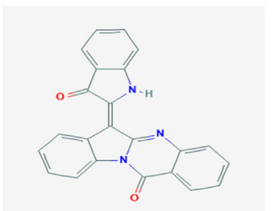
Recently natural molecules derived from the plant have gained considerable attention due to their lesser side effect and comparable therapeutic efficacy when compared to available treatment modalities for the treatment of COVID-19. In this section, we will discuss about various targets of SARS-CoV-2, which can be effectively used for screening plant-based phytochemicals. SARS-CoV-2 binds to the nasal cavity and then enters the host cell after connecting to the specific host receptor, angiotensin-converting enzyme 2 (ACE-2). The host ACE-2 recognizes the active receptor-binding domain (RBD) located in the viral spike protein (S-protein) which initiates the early event of coronavirus infection. When the 394-glutamine residue of RBD in SARS-CoV-2 is identified by the critical lysine 31 residue of host receptor ACE-2, significant van der Waals forces are established, resulting in strong contact (Li et al., 2003; Tikellis & Thomas, 2012; Zhou et al., 2020). The ACE-2 receptor is an integral membrane glycoprotein that is found mostly in the endothelium, kidney, heart, and lungs (Roberts et al., 2007; Tikellis & Thomas, 2012). Recent studies have clearly shown that blocking either the ACE-2 host receptor or the S-protein will eventually limit coronavirus entry at the very starting stage, preventing the host from further infection (Paraskevis et al., 2020). As a result, discovering phytochemicals with increased affinity for the ACE-2 receptor is vital for reducing the availability of host receptors for SARS-CoV-2.

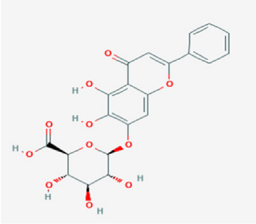
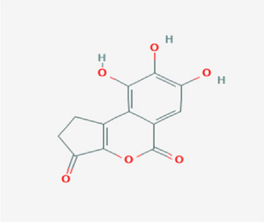
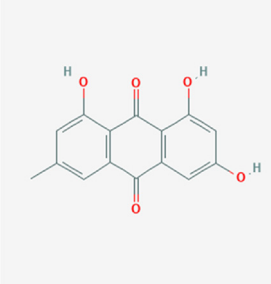
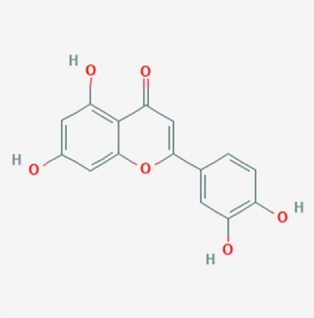
SARS-CoV-2 requires main protease (Mpro), also known as 3-chymotrypsin like protease, (3CLpro) for proteolytic maturation shortly after being recognized by the ACE-2 receptor. Targeting 3CLpro could limit viral polyprotein cleavage and, as a result, viral replication in host cells. The 3CLpro amino acids Thr24, Thr26, and Asn119 have previously been hypothesized to have an important role in drug interaction (Ton et al., 2020; Zhang et al., 2020). As a result, 3CLpro is gaining popularity as a promising target for the development of antiviral medicines (Alagu Lakshmi et al., 2020; Lung et al., 2020). Similarly, RdRp plays an important role in viral transcription and maturation within the host (Lung et al., 2020). As a result, traditional herbs that inhibit protease (3CLpro) and polymerase (RdRp) could potentially reduce viral replication and infection in the respiratory tract.

One of the possible therapeutic techniques for COVID-19 virus infection is the search for enzyme inhibitors in natural chemicals utilizing molecular docking to obtain medicines with lesser adverse effects (Mouffouk et al., 2021). Phytochemicals are secondary metabolites generated by plants that play important roles in plant physiology and have a wide range of potential biologically effective aspects which includes anti-inflammatory, antibacterial, antioxidant, antifungal, anticancer, and antiviral properties (Islam et al., 2021; Kumar & Pandey, 2013; Panche et al., 2016; Wang et al., 2018). Table 7.1 presents a list of phytochemicals with proven antiviral activity against SARS-CoV-2 targets. Various phytochemicals including flavones and flavonols have been carefully researched for their antiviral activities which when investigated Fig. 7.1 in vitro and in vivo tests, most among them were found to exhibit substantial antiviral responses (Gupta et al., 2021; Nijveldt et al., 2001). Curcumin, luteolin, kaempferol, resveratrol, quercetin, fisetin, apigenin are some kinds of phytochemicals that are known to have therapeutic actions against many known fatal viruses. Hence, they have been screened and found efficacious to play a crucial role in testing their specificity for targets of SARS-CoV-2. Another phytochemical namely, curcumin which is a component of turmeric, has been shown to have improved antiviral action against a variety of viruses, including viruses like dengue virus (serotype 2), herpes simplex virus, human immunodeficiency virus, Zika, chikungunya, etc. (Mounce et al., 2017; Praditya et al., 2019). Luteolin, another well-known flavone, has been demonstrated to have considerable antiviral effects on both reactivations of HIV-1 as well as Epstein-Barr virus (EBV) in cells. Apart from these antiviral aspects, luteolin has also been investigated to inhibit viruses like the Chikungunya virus, the Japanese encephalitis virus, the severe acute respiratory syndrome coronavirus (SARS-CoV), and the rhesus rotavirus (Fan et al., 2016; Wu et al., 2020). Owing to these advantages phytochemicals can be considered for their therapeutic actions against SARS-CoV-2 as well imputable to their antiviral activities.

Not only this but another flavonol isolated from *Ficus Benjamina* leaves, kaempferol, has been proven to suppress HCMV, HSV-1, HSV-2, influenza A virus, etc (Lyu et al., 2005; Zakaryan et al., 2017) which could also be considered as a cure for the treatment of coronavirus disease. Phytochemicals such as resveratrol and pterostilbene have also been shown to exhibit antiviral properties against numerous viruses (Lyu et al., 2005; Zakaryan et al., 2017). It has also been demonstrated to inhibit the replication of the pseudorabies virus (PVR) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV), as well as the production of the MERS-CoV nucleocapsid (N) protein, (Campagna & Rivas, 2010; Docherty et al., 2005; Lin et al., 2017; Zhao et al., 2017) which indicates its therapeutic properties against viruses.

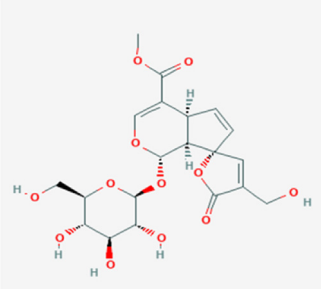
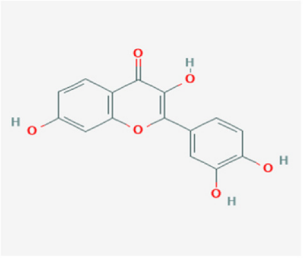
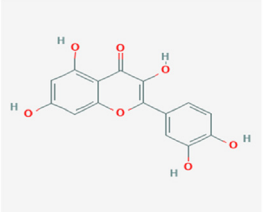
TABLE 7.1 List of potential phytochemicals with proven antiviral activity against SARS-CoV-2 targets.

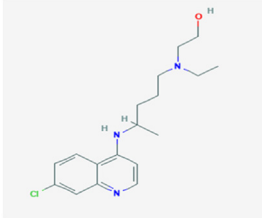
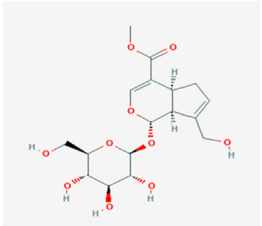
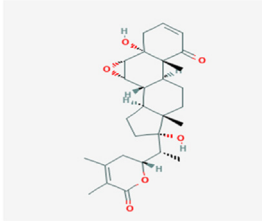
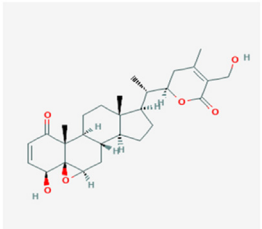
S. no.	SARS-CoV 2 targeting site	Name of phytochemical	Sources	Structure	Mechanism of action	References
1	Targetting ACE 2 receptor	Myricetin	<i>Myrica rubra</i>		Interact with the ACE2 receptor causing conformational changes and viral entry inhibition	Ngwa et al. (2020)
2		Rutin	Buckwheat; tobacco; forsythia; hydrangea; viola, etc.		Proteolytic cleavage of the S1/S2 junction of the ACE2 receptor leading to viral endocytosis	Balmeh et al. (2020)
3		Thioflexibilolide A	<i>Simularia flexibilis</i>		Interact with the prefusional RBD of spike protein or the connective interface of spike-ACE2 complex protein	Chen, Yao, et al. (2020) , Chen, Yang, et al. (2020) , Goyal and Goyal (2020)
4		Candidine	<i>Phaius mishmensis</i>			

5	Baicalin	<i>Scutellaria baicalensis</i>		Bind the human ACE2 receptor, thereby possibly blocking SARS-CoV-2 cell entry	Chen, Yao, et al. (2020)	
6	Geranium	Geranium essential oil		Downregulate ACE2 expression in epithelial cells, thereby blocking virus entry into host cells	Kumar and Pandey (2013)	
7	Targeting spike protein	Emodin	<i>Rheum palmatum</i>		Inhibit interaction of SARS-CoV spike protein	Ho et al. (2007)
8	Luteolin	<i>Galla chinensis</i>		Avidly binds with surface spike protein of SARS-CoV	Yi et al. (2004)	

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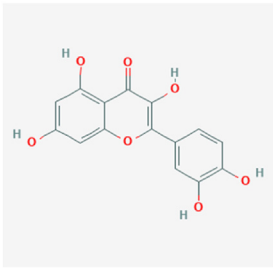
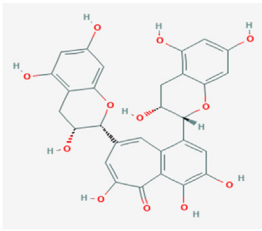
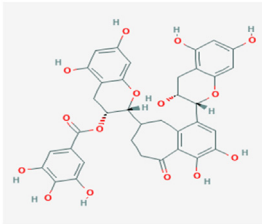
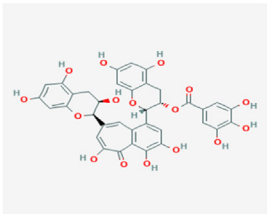
TABLE 7.1 (Continued)

S. no.	SARS-CoV 2 targeting site	Name of phytochemical	Sources	Structure	Mechanism of action	References
9		Iridoid	<i>Veronica linariifolia</i>		Binds with surface spike protein of corona virus	Xiong et al. (2013)
10		Fisetin	Strawberries, apples, mangoes, persimmons, kiwis, and grapes		Interacts with SER 730, THR 778 and HIS 1058 residues through H-bonding and exhibits hydrophobic interaction with ILE 870, PRO 880 and THR 732 residues of S2 domain of the spike protein	Pandey et al. (2020)
11		Quercetin	Apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea, and tomatoes		Forms hydrogen bonds with LYS 733, LEU 861, MET 731, SER 730, PRO 1057, GLY 1059, HIS 1058 and ALA 1056 residues and displayed hydrophobic interaction with ILE 870, ASP 867, MET 730, VAL 860 and PRO 863	

12	Hydroxychloroquine	Derivative of chloroquine		Interacts with ALA 520, GLN564, PHE 565, ARG 567, and HIS 519 residues through hydrogen bond formation, forms the hydrophobic interaction with LEU 518, LEU 517, CYS 391, LEU 546, and ALA 522	
13	Targeting TMPRSS2	Geniposide	<i>Gardenia jasminoides</i>		Interaction with TMPRSS2, forms 10 hydrogen bonds with the active site residues of the receptor protein Pandey et al. (2020)
14	Withanone	Ashwagandha		Downregulation of TMPRSS2 suggesting dual potential of Wi-N to block TMPRSS2, and hence the entry of SARS-CoV-2 to host cells Boukhatem and Setzer (2020)	
15	Withaferin-A	<i>Physalis longifolia</i>		Bind and stably interact at the catalytic site of TMPRSS2	

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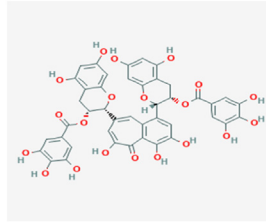
TABLE 7.1 (Continued)

S. no.	SARS-CoV 2 targeting site	Name of phytochemical	Sources	Structure	Mechanism of action	References
16	Targeting RdRp	Quercetin	<i>Houttuynia cordata</i>		Block viral RNA-dependent RNA polymerase activity	Lau et al. (2008)
17		Theaflavin	Black tea		Strongly bind to the catalytic site of the SARS-CoV-2 RdRp and are expected to inhibit the RdRp activity, and thus blocking the replication and preventing viral transcription	Singh et al. (2020)
18		Theaflavin-3'-O-gallate	Tea, german camomile, and peppermint			
19		Theaflavin-3'-gallate	Derivative of theaflavin			

20

Theaflavin 3,3'-digallate

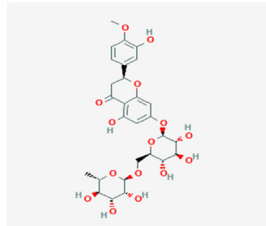
Derivative of theaflavin



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Hesperidin

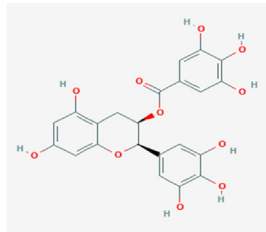
Herperitin



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Epigallocatechin gallate

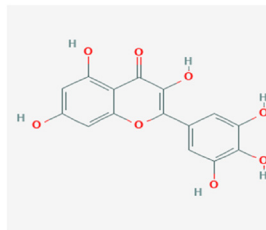
Green tea extract, caffeine and various herbal, fruit and vegetable extracts



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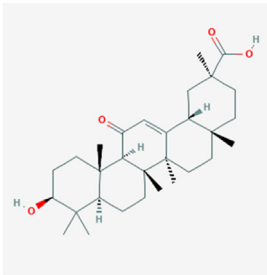
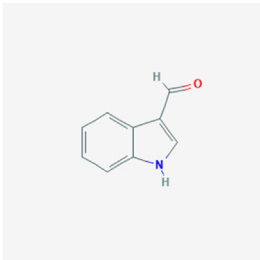
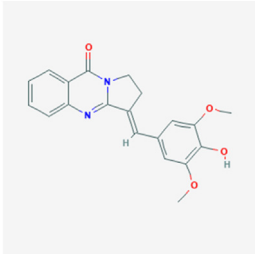
Myricetin

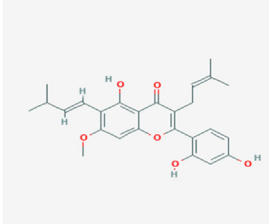
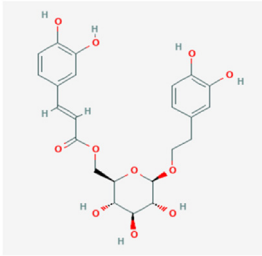
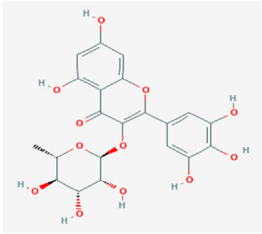
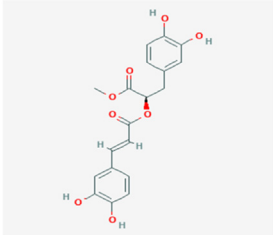
Myrica rubra



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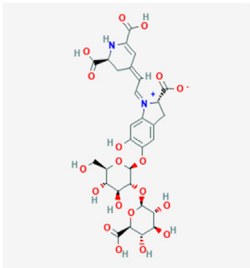
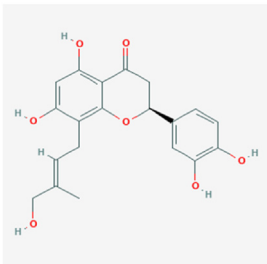
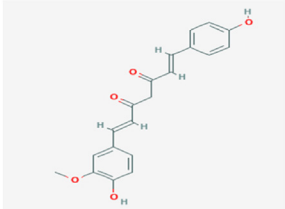
TABLE 7.1 (Continued)

S. no.	SARS-CoV 2 targeting site	Name of phytochemical	Sources	Structure	Mechanism of action	References
24	Targeting main protease	Glycyrrhetic acid (GA)	<i>Glycyrrhiza uralensis</i>		Inhibit SARS-3CLpro activity	Chen, Yang, et al. (2020)
25		Indole-3-carboxaldehyde	<i>Isatis indigotica</i>		Inhibit the cleavage activity of SARS-3CLpro enzyme	S.C. Lin et al. (2017)
26		Isaindigotone	<i>Isatis indigotica</i>		Inhibit the cleavage activity of SARS-3CLpro enzyme	

27	Lectin	<i>Astragalus membranaceus</i>		Inhibit SARS-3CLpro activity	Yang et al. (2020)
28	Calceolarioside B	<i>Fraxinus sieboldiana</i>		Inhibit 3CLpro interacting through His41, Gly143, Cys145, Glu166, Thr24, Thr25 H-bonding	Tahir ul Qamar et al. (2020)
29	Myricitrin	<i>Myrica cerifera</i>		Inhibit 3CLpro interacting through Gly143, Cys145, His41, Thr24, Thr25, Thr26 H-bonding	
30	Methyl rosmarinate	<i>Hyptis atrorubens</i> Poit		Inhibit 3CLpro interacting through Cys145, His41, Thr24, Thr25, Thr26, H-bonding	

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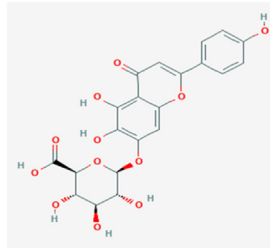
TABLE 7.1 (Continued)

S. no.	SARS-CoV 2 targeting site	Name of phytochemical	Sources	Structure	Mechanism of action	References
31		Amaranthin	<i>Amaranthus tricolor</i>		Inhibit 3CLpro interacting through Thr26, Glu166, Cys145, His41, Thr24 H-bonding	
32		Licoleafol	<i>Glycyrrhiza uralensis</i>		Inhibit 3CLpro interacting through Cys145, His41, Thr24, Thr25, Thr26 H-bonding	
33	Targeting endoribonuclease	Demethoxycurcumin	<i>Curcuma zedoaria</i> and <i>Etlingera elatior</i>		Binding affinity of -7.51 Kcal/mol and formed five hydrogen bonds with Lys-290, Gly-248, His-235, Thr-341, and Glu-340 amino acid residue	Sharma et al. (2020)

34

Scutellarin

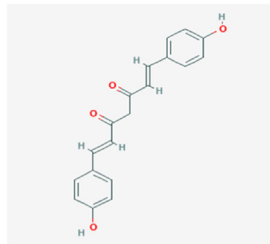
*Scutellaria
lateriflora,
Scutellaria
lateriflora*



Binding affinity of -6.97 Kcal/mol with Lys-290, His-250, Gly-248, and Glu-340 amino acids formed four hydrogen bonds

35

Bisdemethoxycurcumin *Curcuma longa*



Binding affinity of -6.56 Kcal/mol and one hydrogen bond formation with Lys-290

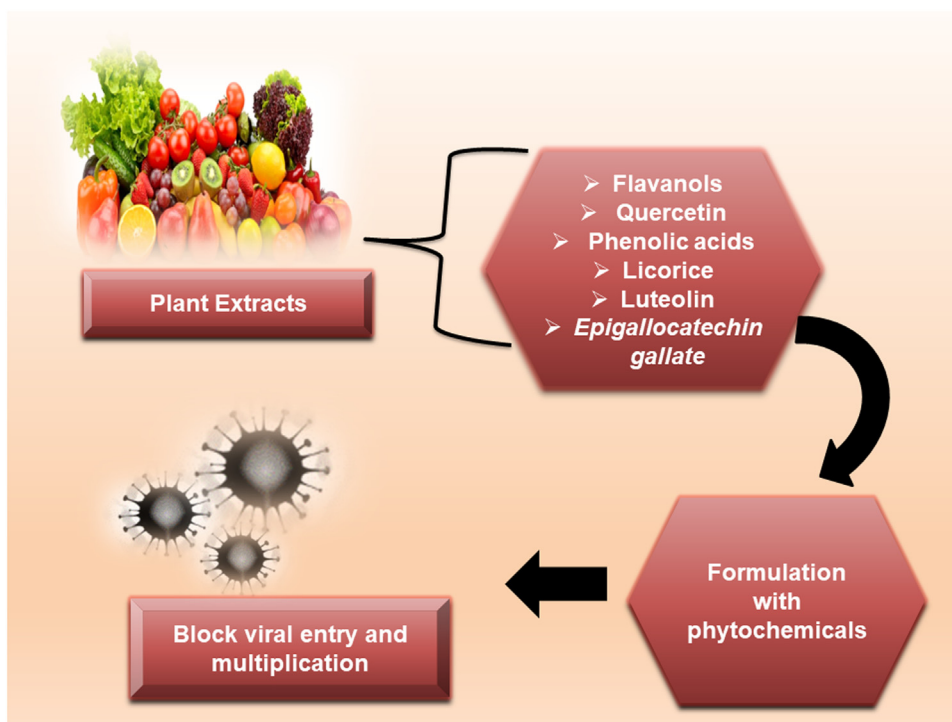


FIGURE 7.1 Natural molecules extracted from plant sources causes blocking of the multiplication of the SARS-CoV 2.

By limiting viral entrance and virus-cell fusion, another natural molecule, fisetin which is a modified flavonol, has been demonstrated to limit both CHIKV and HIV-1 infection (Zakaryan et al., 2017). The antiviral effect of quercetin has been studied most thoroughly among all the phytochemicals. In vitro studies have shown that quercetin has antiviral action against enormous viruses including viruses such as HSV-1, respiratory syncytial virus, HSV-2, poliovirus type 1, etc. As per recent investigations it has been suggested that quercetin could also be used as a prophylactic against Ebola virus infection (Hasan et al., 2021; Kaul, 2020). A few studies have been done to ensure Apigenin's significance towards antiviral activity against hepatitis B virus, adenoviruses, African swine fever virus, and certain RNA viruses, which indicates its efficacious role against combatting viruses (Adedeji et al., 2013; Chiang et al., 2005; Wu et al., 2017). Given the contagiousness of COVID-19 and its implications, it is critical to discover an effective medication to stop the virus from spreading and to safely treat those who have been infected. Repurposing existing medications like chloroquine and hydroxychloroquine which are FDA-approved are nowadays being attempted in this regard solely either alone or in combination with other known medications (Al-Bari, 2017; Yao et al., 2020).

Although some of these early studies yielded encouraging outcomes, much more research is needed to determine their compatibility, cost, accessibility, side effects, doses, and other factors. Currently, scientists are focusing their efforts on finding appropriate

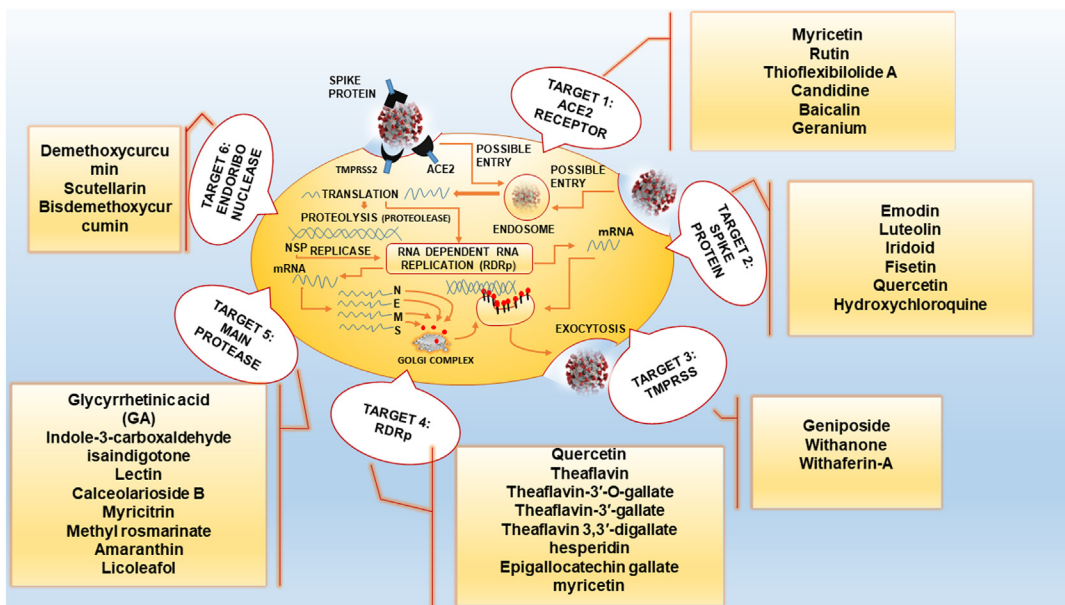


FIGURE 7.2 Mechanism of action of various natural molecules which can bind with various targets of SARS-CoV-2 and inhibit the viral replication.

natural drug like molecules that can target and alter unique or novel locations on the surface of SARS-CoV-2, such as the spike glycoprotein (S) (Adedeji et al., 2013; Elfiky & Azzam, 2021; Sarma et al., 2021; Walls et al., 2020). About ten of these chemicals attach to the C-terminal area of either the S1 or S2 domains of SARS-CoV-2S, and their binding relationship is more persistent than that of HCQ. These natural chemicals can bind to the SARS-CoV-2 S protein's S1 or S2 domains, preventing it from connecting to the hACE2 receptor or internalization during fusion (Zhou et al., 2020). Furthermore, investigations show that the phytochemicals fisetin, quercetin, and kaempferol have a lower affinity for binding to the hACE2-S protein complex's junction. Additionally, further research in vitro and in vivo with these lead compounds may aid in the development of novel anti-COVID-19 therapies (Pandey et al., 2020). The schematic in Fig. 7.2 shows the mechanism of action of potential phytochemicals which bind to the SARS-CoV-2 targets cause their inhibition.

7.1.1.1 Natural molecules targeting ACE-II receptor

SARS-CoV-2 are thought to reach the CNS mostly through the ACE2 or TMPRSS2 receptors. These receptors are present in brain/spinal cord glial cells, facilitating coronavirus invasion into the spinal cord, which is required for SARS-CoV-2 host cell entrance and plasma membrane fusion (Mohammed El Tabaa & Mohammed El Tabaa, 2020; Nemoto et al., 2020). ACE2 phosphorylation at Ser680 prevents ubiquitination and increases related membrane expression, according to studies (Amraei & Rahimi, n.d.). The renin-angiotensin system (RAS), which includes angiotensin II (Ang II), ACE, ACE2, angiotensin type-1 receptor (AT1R), angiotensin type-2 receptor (AT2R), and Mas receptor (MAS), has

been shown to perform important physiological roles. According to research, Ang II inhibits COVID-19 infection by binding to AT1R and triggering ACE2 internalization, followed by a decrease in ERK1/2 and p38 MAPK Pathway (Divani et al., 2020; Fernandes et al., 2011; Koka et al., 2008). ACE2 activity should be reduced to prevent SARS-CoV-2 entrance and accompanying adverse effects. ACE2 has been discovered to be a crucial enzyme in the RAS, which plays an important role in the human body (Khan, Islam, et al., 2021; Khan, Jha, et al., 2021) Renin produced in the kidneys cleaves angiotensinogen from the liver to produce Ang I, which is then cleaved by ACE into Ang-II which is the substrate of ACE2. Ang I binds to the AT1R and AT2R, and the RAS system plays a crucial role in SARS-CoV-2 infection (Battagello et al., 2020). ACE2 is an enzyme located in the human cell's outer membrane that serves as a binding site for the S protein. Several investigations have demonstrated that ACE2 and S protein have a strong relationship. Blocking ACE2 is thus another important approach for combating SARS-CoV-2 (Li et al., 2003). Flavonoids inhibit ACE2 expression by activating Nrf2, thereby inhibiting SARS-CoV-2 interactions (Mendonca & Soliman, 2020; Mughtaridi et al., 2020). Some examples of potential phytochemicals which target the ACE 2 receptor are listed below.

Myricetin: Myricetin is a hexahydroxyflavone, which is a flavone with hydroxy groups replaced at positions 3, 3', 4', 5, 5', and 7. It has been isolated from *Myrica rubra* and other plants' leaves. It is a cyclooxygenase 1 inhibitor, antineoplastic drug, antioxidant, plant metabolite, a dietary component, and hypoglycemic agent. It contains both hexahydroxyflavone and 7-hydroxyflavonol. Myricetin is a phytochemical which could be extracted from *M. rubra* and is known to interact with the ACE2 receptor and as result cause conformational changes which leads to the inhibition of SARS-CoV-2 virus entry into the host body cells (Ngwa et al., 2020).

Rutin: Rutin is a rutinoside that is quercetin with the hydroxy group replaced with glucose and rhamnose sugar groups at position C-3. It functions as both a metabolite and an antioxidant. It's a disaccharide derivative, quercetin O-glucoside, tetrahydroxyflavone, and rutinoside all rolled into one. Rutin which could be extracted from natural plant extracts has good sources as buckwheat; tobacco; forsythia; hydrangea; viola, etc. It plays a crucial role in inhibiting the viral entry through the ACE 2 receptor into the body of the host cell. It creates a proteolytic cleavage at the S1/S2 junction of the ACE 2 receptor leading to the endocytosis of the SARS-CoV 2 virus (Balmeh et al., 2020).

Thioflexibilolide A and candidine: These two phytochemicals could be extracted majorly from *Sinularia flexibilis* and *Phaius mishmensis* respectively. They have been investigated to interact with the perfusional RBD of spike protein or the connective interface of spike-ACE2 complex protein leading to the inhibition of viral entry into the host cell (Chen, Yao, et al., 2020; Chen, Yang, et al., 2020; Goyal & Goyal, 2020).

Baicalin: Baicalin is a glycosyloxyflavone that is found in the 7-O-glucuronide form. It functions as a nonsteroidal anti-inflammatory medication, a prodrug, and a plant metabolite, as well as an EC 3.4.21.26 (prolyl oligopeptidase) inhibitor. It's a glucosiduronic acid derivative that's also a glycosyloxyflavone, a dihydroxyflavone, and a monosaccharide. It comes from the baicalein plant. It binds with the human ACE2 receptor, thereby possibly blocking SARS-CoV-2 entry into the host cell. Hence,

reduces the chances of coronavirus complications (Chen, Yao, et al., 2020; Goyal & Goyal, 2020).

Geranium: Recent studies investigated that geranium essential oils are found to downregulate the expression of ACE2 receptors into the epithelial cells in the host body. This downregulation leads to the blockage of the viral entry of SARS-CoV-2 into the body of the host (Islam et al., 2021; Kumar & Pandey, 2013; Wang et al., 2018).

Natural molecules targeting Spike protein The S protein also known as spike protein is a homotrimeric glycoprotein found on the surface of the SARS-CoV-2 virion that performs multiple functions in the transmission of COVID-19 viral infection, including host receptor interaction, cell tropism, and pathogenesis (Sigrist et al., 2020). The S protein is also a primary target of the host immune system. According to an investigation, these proteins are virulence determinants and potent immunogenic molecules capable of eliciting a humoral immune response, as well as attractive epitopes for vaccine development and antibody-based therapeutic approaches (Lv et al., 2020; Sigrist et al., 2020). The S protein plays an important role in virus attachment and penetration into host cells. In reality, the high affinity and mutability contact between the RBD on the S1 subunit of the S protein and the ACE2 receptor causes multiple structural rearrangements and conformational changes in the S protein, exposing a proteolytic site. This is broken by the host cellular serine protease TMPRSS27, resulting in the dissociation of the S1 subunit and the change of the S2 subunit to a postfusion state, allowing the virus to be endocytosed (Letko et al., 2020; Walls et al., 2020). Molecules that can disrupt and destabilize the interaction between the SARS-CoV-2 spike protein and the ACE2 receptor, thereby inhibiting membrane fusion and viral nucleocapsid transfer, could be effective therapeutics for blocking viral host cell attachment and endocytosis. (Bongini et al., n.d.) Following enlisted natural molecules could play a beneficial role in the inhibition of SARS CoV-2 infection by targeting the spike protein binding site.

Emodin: Emodin is a trihydroxyanthraquinone (9,10-anthraquinone) with hydroxy groups at positions 1, 3, and 8 and a methyl group at position 6. It can be found in the roots and barks of many plants, molds, and lichens. It is an active constituent in several Chinese herbs. It functions as a tyrosine kinase inhibitor, antineoplastic agent, laxative, and plant metabolite. It could be extracted from the *Rheum palmatum* and known to interact with the spike protein of SARS-CoV to inhibit its mechanism of action (Ho et al., 2007).

Luteolin: Luteolin is a flavonoid that occurs naturally and has antioxidant, antiinflammatory, apoptosis-inducing, and chemopreventive properties. Lutein scavenges free radicals, shields cells from reactive oxygen species-induced damage, and promotes direct cell cycle arrest and apoptosis in tumor cells after treatment. This prevents tumor cell proliferation and metastasis. It could be extracted from *Galla Chinensis* and is nowadays recognized for its efficacious role in the inhibition of coronavirus by avidly binding with the surface of the spike protein of SARS-CoV leading to its inhibition (Yi et al., 2004).

Iridoid: Iridoid has a major source of extraction from *Veronica linariifolia*, plays a vital role in the prevention of infection of novel coronavirus. It attaches to the spike protein binding site of the SARS-CoV 2 virus which as a result leads to inhibition of viral entry of the virus into the host organism (Xiong et al., 2013).

Fisetin: Fisetin is a 7-hydroxyflavonoid containing hydroxy groups at positions 3, 3', and 4'. It functions as a DNA topoisomerase (ATP-hydrolysis) inhibitor, antioxidant, anti-inflammatory agent, metabolite, and plant metabolite. It contains 3'-hydroxyflavonoid, 7-hydroxyflavonol, and tetrahydroxyflavone. It interacts with THR 778, HIS 1058, and SER 730 residues via H-bonding exhibiting hydrophobic interaction with PRO 880, THR 732, and ILE 870 residues of the S2 domain of the spike protein (Pandey et al., 2020).

Quercetin: Quercetin is a flavonoid that can be found in a variety of foods and herbs and is an important part of a healthy diet. Quercetin extracts have been used to treat or prevent a variety of ailments, including cardiovascular disease, hypercholesterolemia, rheumatoid arthritis, infections, and cancer. Quercetin also has anti-inflammatory and antiallergy properties that are mediated through the inhibition of the lipoxygenase and cyclooxygenase pathways, reducing the synthesis of proinflammatory mediators. It forms hydrogen bonds with LEU 861, GLY 1059, LYS 733, MET 731, SER 730, PRO 1057, HIS 1058, and ALA 1056 residues, displaying hydrophobic interaction with MET 730, ILE 870, ASP 867, PRO 863, and VAL 860 resulting in inhibition of binding of spike protein (Pandey et al., 2020).

Hydroxychloroquine: Hydroxychloroquine is a chloroquine aminoquinoline with one of the N-ethyl groups hydroxylated at position 2. It functions as an antimalarial, antirheumatic, dermatologic, and anticoronaviral agent. It is an organochlorine compound, an aminoquinoline, primary alcohol, a secondary amino compound, and a tertiary amino compound. It is derived from the drug chloroquine. It interacts with GLN564, ARG 567, ALA 520, HIS 519, and PHE 565 residues through hydrogen bond formation, forms the hydrophobic interaction with CYS 391, ALA 522, LEU 517, LEU 546, and LEU 518 by targeting the spike protein binding site of SARS CoV 2 (Pandey et al., 2020).

7.2 Natural molecules targeting TMPRSS2

The SARS-CoV-2 enters the host cell in two stages: first, it makes contact with the angiotensin-converting enzyme 2 (ACE2) via its spike's RBD, and then the transmembrane protein serine 2 (TMPRSS2) cleaves viral S protein, causing an irreversible conformational change that leads to viral S protein fusion with the host cell membrane. The S2 subunit drives the cleavage of the S protein, which permits the viral and host cell membranes to merge (Glowacka et al., 2011; Matsuyama et al., 2010; Shulla et al., 2011). TMPRSS2 is involved in the entry of the SARS-CoV-2 virus into the host cell. It appears to have no vital role in the host organ system, but it does provide some redundancy. As a result, it has emerged as the preferred target for wide therapeutic use against SARS-CoV-2 (Chikhale et al., 2020). The transmembrane protease serine 2 (TMPRSS2) is a type II transmembrane serine protease (TTSP) that is involved in the SARS-CoV infection. Targeting TMPRSS2 could be a potential antiviral target to treat coronaviruses, as shown by a study in the case of the Middle East respiratory syndrome-associated coronavirus (MERS-CoV) and Asian H7N9 influenza virus, as well as several H1N1 subtypes influenza-A viruses infections (Zhang et al., 2020). TMPRSS2 is an androgen-regulated type II transmembrane serine protease found in respiratory, gastrointestinal, and urogenital epithelial cells, with significant levels of expression in the prostate and colon

(Bertram et al., 2012; Bugge et al., 2009; Hatesuer et al., 2013; Lucas et al., 2014). In the animal model after infection with SARS-CoV and MERS-CoV, the absence of TMPRSS2 in the airways lowers the severity of lung disease (Zhu et al., 2009). Inhibiting TMPRSS2 may be a promising method to minimize the initial site of SARS-CoV-2 infection. A TMPRSS2 inhibitor in clinical use has previously been approved and accepted as a way to limit entry and could be an effective therapeutic option for COVID-19. The TMPRSS2 could be a significant target for developing inhibitors that have a distinct advantage in blocking this host protease (Hoffmann et al., 2020). Several investigations that have reported the role of phytochemicals which could potentially target TMPRSS2 and thus be helpful to combat SARS-CoV 2 are mentioned below.

Geniposide: Geniposide which has a major source *Gardenia jasminoides*. It interacts with the TMPRSS2 forming 10 hydrogen bonds with the active site residues of the receptor protein resulting in the inhibition of entry of viral antigen into the host body (Pandey et al., 2020; Rahman et al., 2020).

Withanone: Ashwagandha could be termed as the major source of withanone. It could play a crucial role in preventing the infection from SARS CoV 2 as it showcases a mechanism of downregulation of TMPRSS2 leading to the blockage of TMPRSS2 via dual potential resulting in the inhibition of entry of the virus into the host body (Boukhatem & Setzer, 2020).

Withaferin-A: *Physalis longifolia* is the major source for the extraction of Withaferin-A. It binds and at the same time interacts stably at the catalytic site of TMPRSS2 which results in the blockage of insertion of viral antigen into the host cell resulting in the inhibition of the infection (Boukhatem & Setzer, 2020).

7.3 Natural molecules targeting RdRp

RdRp, also known as nsp12, is a key component of the replication and transcription machinery of SARS-CoV-2. This enzyme catalyzes the production of viral RNA with the help of cofactors nsp7 and nsp8, and plays a key role in viral replication and transcription. Indeed, this is a prominent target for therapeutic investigations, and compounds that might disrupt its activity could be evaluated as potential COVID-19 viral infection treatments (Gao et al., 2020; Yu et al., 2020). RdRp aids in the synthesis of SARS-CoV-2, which is important for its survival and transmission. RdRp could be a pharmacological target for a number of medications employing to eradicate the complication led by the viral infection. Gao et al. studied the structure of the RdRp from SARS-CoV-2 in 2020, emphasizing its importance as a useful target for controlling the outbreak by limiting virus replication (Gao et al., 2020). The nonstructural proteins (nsp) generated form a multisubunit replication/transcription machinery that facilitates viral replication and transcription. The nsp12 is a critical enzyme that catalyzes the manufacture of a complementary RNA strand from the virus's RNA template with the help of cofactors nsp7 and nsp8 (Huang et al., 2020). Subgenomic RNA is synthesized from genomic RNA, which leads to the production of structural (S, E, M, and N) and auxiliary proteins. That was then transferred to the endoplasmic reticulum-Golgi intermediate compartment after

being insulated in the endoplasmic reticulum (ERGIC). Finally, through the secretory pathway, the formed virions are discharged (Astuti & Ysrafil, 2020). Researchers have screened various phytochemicals for targeting RdRp of SARS-CoV-2, some of potential molecules are enlisted as follows.

Quercetin: Quercetin is a flavonoid present in a number of foods and herbs and is an essential component of a healthy diet. Quercetin extracts have shown potential therapeutic efficacy for various disease conditions which include cardiovascular disease, hypercholesterolemia, rheumatoid arthritis, infections, and cancer. It could be extracted from *Houttuynia cordata* and is found to block viral RNA-dependent RNA polymerase activity resulting in the prevention of infection caused by the SARS CoV 2 (Lau et al., 2008).

Theaflavin: Theaflavin which can be obtained from black tea has been investigated and it was observed to strongly bind to the catalytic site of SARS-CoV-2 RNA dependent RNA polymerase resulting in the blocking of the further replication via inhibiting RdRp mediated transcription process (Singh et al., 2020).

Theaflavin-3'-O-gallate: Theaflavin-3'-O-gallate could be extracted from tea, german camomile, and peppermint which plays a crucial role in inhibiting the further transcription of the virus by blocking the replication of RNA by binding to the catalytic site of SARS-CoV-2 RdRp (Singh et al., 2020).

Theaflavin-3'-gallate: It is a phytochemical investigated for its efficacy to prevent the spread of infection into the host body. It binds with the catalytic site of the SARS-CoV-2 RdRp and prevents the replication of RNA resulting in the omission of further infection (Singh et al., 2020).

Theaflavin 3, 3'-digallate: Natural molecules like Theaflavin 3,3'-digallate have been studied and investigated for its binding potential with the catalytic site of SARS-CoV-2 RNA dependent RNA polymerase activity. Studies revealed that it inhibits the transcription phenomena of SARS-CoV-2 by restricting the replication of RNA (Singh et al., 2020).

Hesperidin: Hesperetin is a disaccharide derivative in which a 6-O-(alpha-L-rhamnopyranosyl)-beta-D-glucopyranosyl moiety is substituted at position 7 via a glycosidic bond. It functions as a mutagen. It's a disaccharide derivative, a 3'-hydroxyflavanone, a dihydroxyflavanone, a monomethoxyflavanone, a monomethoxyflavanone, a flavanone glycoside, a 4'-methoxyflavanone, and a rutoside. It is made from hesperidin. It has been studied to function in the inhibition of the transcription phenomena of SARS-CoV-2 by restricting the replication of RNA by binding with the SARS-CoV 2 RdRp (Singh et al., 2020).

Epigallocatechin gallate: Epigallocatechin gallate could be extracted from green tea extract, caffeine, and various herbal, fruit, and vegetable extracts, has been investigated as an important phytochemical for the inhibition of the viral infection into the host body by preventing the RNA to replicate. It basically works by targeting the RNA-dependent Rna polymerase the SARS-CoV 2 resulting in the restriction of further replication of RNA (Singh et al., 2020).

Myricetin: Myricetin, extracted from *M. rubra*, has been investigated to strongly bind to the catalytic site of SARS-CoV-2 RNA dependent RNA polymerase activity resulting in the blocking of the replication of further RNA of the virus preventing viral transcription process (Singh et al., 2020).

7.3.1 Natural molecules targeting main protease

The SARS-CoV-2 genome encodes 3CLpro, also known as the Mpro. This enzyme is required for the proteolytic maturation of viral polyproteins (pp1a and pp1ab) in order to create the RNA replicase-transcriptase complex, which is required for both viral transcription and replication processes (Elmezayen et al., 2020). Among many CoVs, this protease possesses a highly conserved three-dimensional structure and is exclusively active in a dimeric state (the individual monomers of SARS-CoV Mpro are enzymatically inactive). The 3CLpro structural and catalytic properties make it a selective target for therapeutic development. Indeed, a variety of approaches could be used to produce inhibitors for this enzyme. For starters, because Mpro is highly conserved, a mutation in the Mpro genome is frequently deadly to the virus. Additionally, the catalytic activity of this enzyme could be changed by the fixing of a molecule in the substrate-binding pocket or the use of dimerization inhibitors (Chen, Yao, et al., 2020; Goyal & Goyal, 2020). Thus, compounds targeting the Mpro enzyme may represent prospective medicines with broad antiviral activity capable of stopping the posttranslational processing of SARS-CoV-2 polypeptides and reducing the possibility of mutation-mediated treatment resistance. Because of its importance in the viral replication cycle, PLpro is another important druggable target. This enzyme is involved in the cleavage of N-terminal viral polyproteins in order to produce numerous Nsps (Nsp1, Nsp2, and Nsp3) (Mhatre et al., 2021).

It is also critical in alienating the host cells' inherent immunity. Indeed, SARS-CoV viruses employ PLpro as an antagonist to block the activation of the interferon regulatory factor-3 pathway (IRF3-route) in order to limit interferon production, which is well known for its antiviral properties (Chen et al., 2014; Yuan et al., 2015). Inhibiting the PLpro enzyme would ordinarily trigger a strong interferon-mediated response, engage the immune system and the host cells' antiviral response, and disrupt the replication cycle (Mouffouk et al., 2021). In flavonoid skeletons, the absence of a 2,3-double bond and a carbonyl group at the C-4 position in the C ring, as well as galloyl moiety and the presence of a hydroxyl group at the C-5' position of the B ring, reduces chemical interactions, hydrogen bond formation, and electrostatic interactions with the active site of 3CLpro. In comparison to other types of flavonoids, these findings suggest the bioactivity of flavanols with a carbonyl function (C-4) and a double bond in position C2–C3 (Nguyen et al., 2012). Following enlisted phytochemicals are known to target the main protease of the coronavirus and can be used to combat its pathological effects:

Glycyrrhetic acid (GA): glycyrrhizic acid (GA) is a key bioactive component derived from *Rhizoma Glycyrrhizae*. It has clear pharmacological effects, including detoxifying, cough-relieving, antiinflammatory, anticancer and antibacterial activity. It inhibits SARS-3 CL pro activity resulting in the inhibition of viral entry into the host organism (Chen, Yang, et al., 2020).

Indole-3-carboxaldehyde: Indole-3-carbaldehyde is a heteroarene-carbaldehyde that is indole with a formyl group in place of the hydrogen at position 3. It's a plant metabolite that could be extracted from *Isatis indigotica*, a human xenobiotic metabolite, a bacterial metabolite, and a marine metabolite, among other things. It's a heteroarene-carbaldehyde, an indole alkaloid, and a part of the indoles family of

alkaloids. It inhibits the cleavage activity of SARS-3CL pro enzyme resulting in the prevention of entry of the virus into the host organism leading to inhibition of infection (Campagna & Rivas, 2010; Docherty et al., 2005; Lin et al., 2017; Zhao et al., 2017).

Isaindigotone: It is known to be extracted from *I. indigotica*. It has a major function to inhibit the cleavage activity of SARS-3CL pro enzyme which helps inhibit the mechanism of entry of the viral antigen into the host body as a result it prevents viral infection (Lin et al., 2005).

Lectin: The major source of lectin could be *Astragalus membranaceus*. It is known to impede the cleavage activity of SARS-3CL pro activity similar to isandigotone and hence could contribute as a cure for SARS-CoV-2 (Yang et al., 2020).

Calceolarioside B: Ahydroxycinnamic acid, calceolarioside B is a hydroxycinnamic acid which could be extracted from *Fraxinus sieboldiana*, performs the function of a metabolite [124]. It Inhibit 3CLpro interacting through His41, Gly143, Cys145, Glu166, Thr24, Thr25 H-bonding hence, resulting in the blockage in the viral entry process (Tahir ul Qamar et al., 2020).

Myricitrin: Myricitrin which could be extracted from *Myrica cerifera*, apart from the activities for targeting the ACE 2 receptor is known to Inhibit 3CLpro interacting through H bonding with Gly143, Cys145, His41, Thr24, Thr25, Thr26 residue resulting in the prevention of the viral particle entry into the host organism (Tahir ul Qamar et al., 2020).

Methyl rosmarinat: Methyl rosmarinat which could be extracted from *Hyptis atrorubens* Poit, is investigated to Inhibit 3CLpro interacting through H-bonding with Cys145, His41, Thr24, Thr25, Thr26 residues which as a result lead to viral inhibition (Tahir ul Qamar et al., 2020).

Amaranthin: *Amaranthus tricolor* is the major source of amaranthin which plays a key role in imedeton of the viral entry into the host organism as it's H-bonding with Thr26, Glu166, Cys145, His41, and Thr24 inhibits 3CLpro interaction (Tahir ul Qamar et al., 2020).

Licoleafol: Licoleafol which is known to be extracted from *Glycyrrhiza uralensis* functions to Inhibit 3CLpro interacting through H bonding with Cys145, His41, Thr24, Thr25, Thr26 thereby leading in the inhibition of further infection (Tahir ul Qamar et al., 2020).

7.3.2 Natural molecules targeting endoribonuclease

Among the several Nsps, Nsp15 is an intriguing enzyme that belongs to the EndoU family and is a nidoviral RNA uridylyate-specific endoribonuclease (NendoU) with a C-terminal catalytic domain (Posthuma et al., 2006). The NendoU protein has been discovered to be conserved in arteriviruses, toroviruses, and coronaviruses. Initially, it was considered that Nsp15 simply participated in viral replication; however, it was later shown that Nsp15-deficient coronaviruses were both viable and capable of replication, raising questions regarding its biological function (Deng et al., 2017). It was also assumed that Nsp15 degrades viral RNA in order to protect it from host defenses and work independently as an endonuclease (Kim et al., 2020). Aside from the endoribonuclease activity that Nsp15 exhibits, an animal model experiment indicated that it has immunomodulating effects during early viral infection (Deng et al., 2017). Furthermore, as a unique nidoviral genetic marker, small molecules that modulate the biological role of SARS-CoV-2, Nsp15

can be predicted to block its close homolog of SARS-CoV or MERS-CoV Nsp15 as well. Nonetheless, Nsp15 is crucial in coronavirus biology, and therefore approach to block Nsp15 of SARS-CoV-2 could lead to a powerful therapeutic option against COVID-19 (Kumar et al., 2021). The phytochemicals which show a key role in targeting the endoribonuclease as a therapeutic target for the prevention of SARS-CoV 2 are enlisted below.

Demethoxycurcumin: Demethoxycurcumin could be extracted from *Curcuma zedoaria* and *Etingera elatior* as these are the major sources of it. It has a binding affinity of -7.51 Kcal/mol and forms five hydrogen bonds with Lys-290, Gly-248, His-235, Thr-341, and Glu-340 amino acid residue and thereby blocking the viral entry resulting in the prevention of further infection (Sharma et al., 2020).

Scutellarin: Scutellarin could be extracted from *Scutellaria lateriflora*, *Scutellaria lateriflora* which are known as its major sources. It has the function to bind to the target with a binding affinity of -6.97 Kcal/mol with Lys-290, His-250, Gly-248, and Glu-340 amino acids formed four hydrogen bonds and hence prevent viral infection and related consequences (Sharma et al., 2020).

Bisdemethoxycurcumin: Bisdemethoxycurcumin which could be extracted from *Curcuma longa* has a binding affinity of -6.56 Kcal/mol and it forms one hydrogen bond with Lys-290 thereby blocking the viral entry by targeting the endoribonuclease site, that is, nsp15 (Sharma et al., 2020).

7.3.3 Current challenges and future prospects

Herbal concoctions have been used for centuries as traditional medicines to treat a variety of ailments. Virus replication was found to be inhibited by several plant extracts. While medicinal plants and aromatic herbs-based phytochemicals have antibacterial and antifungal effects, there is currently inadequate scientific evidence to evaluate safe and effective antiviral treatments (Zhu et al., 2009). Certain chemicals that work on different viral biosynthetic routes are the best possibilities for effective antiviral chemotherapeutics. They suppress different steps in the viral replication cycle, resulting in little or no viral progeny. These drugs may be effective at modest dosages that do not harm the host cell. They will prevent viruses from replicating, healing the infected cells in the long run. Replicating viruses, unfortunately, can evolve resistance to these treatments. Virucidal drugs, on the other hand, interact with the enveloped virus's membrane shell and dissolve viral structural glycoproteins (Cheng et al., 2006; Lau et al., 2008; Ryu et al., 2010). Natural bioactives' complicated metabolism is at the heart of a number of therapeutic medicines and has aided in the development of novel antivirals. Herbal antiviral treatments have been understudied in comparison to insecticides. However, some scientific investigations have begun to assess their efficacy in greater detail. Antiviral activities of medicinal plants and their separated components have been observed against specific coronaviruses, and the mechanism of action of these traditional supplements is mostly viral replication inhibition (Cheng et al., 2006; Jassim & Naji, 2003; Li et al., 2005).

Efforts are continuing to develop efficient antiviral chemotherapeutics that are cost-effective and have few side effects, as well as those that may be used in conjunction with other medications to improve the treatment of coronavirus-infected patients. Due to the

lack of preventive vaccines and active antiviral medications for the treatment of various viruses, eradicating these diseases appears difficult and problematic. Natural products, on the other hand, provide a rich source of biodiversity for the development of novel antivirals, new structure–activity connections, and effective medical and therapeutic approaches to viral diseases (Asres et al., 2001). Although most studies in this area are still in the early stages, more research on the identification of active substances, the description of underlying mechanisms, as well as the analysis of efficacy and potential in vivo applications, is recommended to aid in the discovery of effective antiviral chemotherapeutics (Asres et al., 2001). Additional studies should look into combining these treatments with other natural substances or regular medicines since a multitarget solution could help reduce the likelihood for drug-resistant virus strains to infect people (Hudson, 1990). Natural remedies including aromatic herbs, essential oils generated from medicinal plants, and phytochemicals, we believe, will continue to play an important role in the creation and enhancement of anticoronavirus medications.

7.4 Concluding remarks

Phytochemicals are a valuable and strong source of chemical molecules with antiviral characteristics that exist naturally. In this chapter we have enlisted a few phytochemicals which are known to target various binding sites which play a vital role in the inhibition of the viral entry into the cells of the host organism. Myricetin, Rutin, Thioflexibilolide A, candidate, Baicalin and Geranium are some phytochemicals that were investigated to target the ACE2 receptor protein binding site resulting in the inhibition of the viral entry of the antigen into the host. Emodin, Luteolin, Iridoid, Fisetin, Quercetin, Hydroxychloroquine are some phytochemicals investigated to target the spike protein binding site of the SARS-CoV-2 leading to the destruction of the entry pathway by blocking the entry of SARS-CoV-2 into the body. Some phytochemicals such as Geniposide, Withanone, and Withaferin-A were investigated to target the TMPRSS2 which is yet another known binding site that plays an efficacious role in the blockage of the viral entry by binding onto its particular binding surface. These natural molecules interact to their specified binding site resulting in inhibition of aforesaid havoc named as coronavirus. Quercetin which is known for its key roles in the treatment of various viruses has a potential aspect to target the spike protein binding site as well as it has functions to target efficiently the RdRp. RdRp refers to RNA-dependent RNA polymerase activity which is been targeted by the natural products cum phytochemicals such as epigallocatechin gallate, myricetin, theaflavin, theaflavin-3'-O-gallate, hesperidin, theaflavin-3'-gallate, and theaflavin 3,3'-digallate which strongly bind to the catalytic site of the SARS-CoV-2 RdRp and are expected to inhibit the RdRp activity. The SARS-CoV-2 genome encodes 3CLpro, also known as the Mpro which is yet another binding which is been targeted by GA, indole-3-carboxaldehyde, isaindigotone, lectin, Calceolarioside B, Myricitrin, Methyl rosmarinat, Amaranthin and Licoleafol. Demethoxycurcumin, scutellarin, and bisdemethoxycurcumin are some of the phytochemicals which target the endoribonuclease binding site which is nsp15 belonging to EndoU family.

The phytochemicals-based therapy have the potential to be used as a promising treatment of coronavirus in humans. These natural molecules could be used as a therapeutic cure to combat COVID-19 which is wreaking havoc. Several clinical trials have been registered to study the potential of natural products to slow the progression of disease (Costanzo et al., 2020). As per overall investigations, these natural molecules could be considered as therapeutic medications for COVID-19 treatment and can be helpful to reduce mortality rate and COVID-19 associated comorbidities.

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