Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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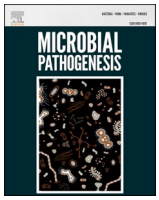

Multifaceted roles of plant derived small molecule inhibitors on replication cycle of SARS-CoV-2

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is an illness caused by the new coronavirus severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). It has affected public health and the economy globally. Currently approved vaccines and other drug candidates could be associated with several drawbacks which urges developing alternative therapeutic approaches.
Aim: To provide a comprehensive review of anti-SARS-CoV-2 activities of plants and their bioactive compounds.
Methods: Information was gathered from diverse bibliographic platforms such as PubMed, Google Scholar, and ClinicalTrials.gov registry.
Results: The present review highlights the potential roles of crude extracts of plants as well as plant-derived small molecules in inhibiting SARS-CoV-2 infection by targeting viral or host factors essential for viral entry, polyprotein processing, replication, assembly and release. Their anti-inflammatory and antioxidant properties as well as plant-based therapies that are under development in the clinical trial phases-1 to 3 are also covered.
Conclusion: This knowledge could further help understanding SARS-CoV-2 infection and anti-viral mechanisms of plant-based therapeutics.

1. Introduction

A newly emerged pandemic of COVID-19, caused by an infectious coronavirus SARS-CoV-2, has severely affected the entire world and remains a health threat. The emergence of new strains that evade immune responses generated by the vaccines suggests an urgent need for developing alternative therapeutic approaches to cut down the COVID-19 infection rate and related morbidity and mortalities.

COVID-19 is currently being treated with several plausible drugs including antimalarial drugs [28], antiviral drugs [83], certain immunosuppressors [70], and convalescent plasma therapy. However, these kinds of treatments are associated with several concerns, especially in patients with severe disease conditions [90]. For example, severe adverse effects such as renal impairment and hypotension were observed in critically ill patients receiving remdesivir therapy [30]. Additionally, several case studies have reported that these standard drugs exhibit drug-drug or nutrition-drug interactions into the severely infected COVID-19 patients resulting in the unrecognized source of medication errors and negative effects [2]. Therefore, it is essential to use an alternative and safer approach, such as plant-derived compounds.

Numerous scientific reports have documented the ability of plants and their secondary metabolites against SARS-CoV [91]. Despite being new virus, there are multiple *in-silico* studies suggesting anti-SARS-CoV-2 capability of plant-based small compounds. Additionally, *in-vitro*, cell culture and *in-vivo* clinical trials further validate and strengthen their COVID-19 suppressing potential.

2. Scope of the review

This review article aims to collect data on anti-SARS-CoV-2 activity and therapeutic potential of natural plant extracts and phytocompounds primarily based on *in-silico* (molecular docking and molecular dynamics) studies. An attempt has also been made to highlight *in-vitro,* cell culture, *in-vivo* and clinical trial (phase 1 to 3) studies. Several bibliographic platforms such as PubMed, Science-Direct, Google Scholar, and

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Abbreviations

RBD	receptor-binding domain
RBM	receptor-binding motif
aa	amino acids
nsp	non-structural protein
E	envelope protein
M	membrane protein
N	nucleocapsid
NTD	N-terminal domain
CTD	C-terminal domain
ACE2	angiotensin-converting enzyme 2
TMPRSS2	transmembrane protease serine 2
RNA	ribonucleic acid
sgRNAs	sub-genomic RNAs
gRNA	genomic RNA
ERGIC	endoplasmic reticulum-Golgi intermediate complex
LDLRA	low density lipoprotein receptor class A
SRDR	scavenger receptor cysteine-rich domain
RdRp	RNA dependent RNA polymerase
kb	kilobases
PLpro	papain-like protease
3-CLpro	3 chymotrypsin-like protease
EGCG	Epigallocatechin 3-gallate
TF	theaflavin
SF-1	superfamily-1
ADMET	absorption, digestion, metabolism, excretion, and toxicity
QGRG	Quercetin 3-glucosyl rhamnosyl galactoside
2′-O-MTase	2′-O- methyltransferase
kDa	kilodalton

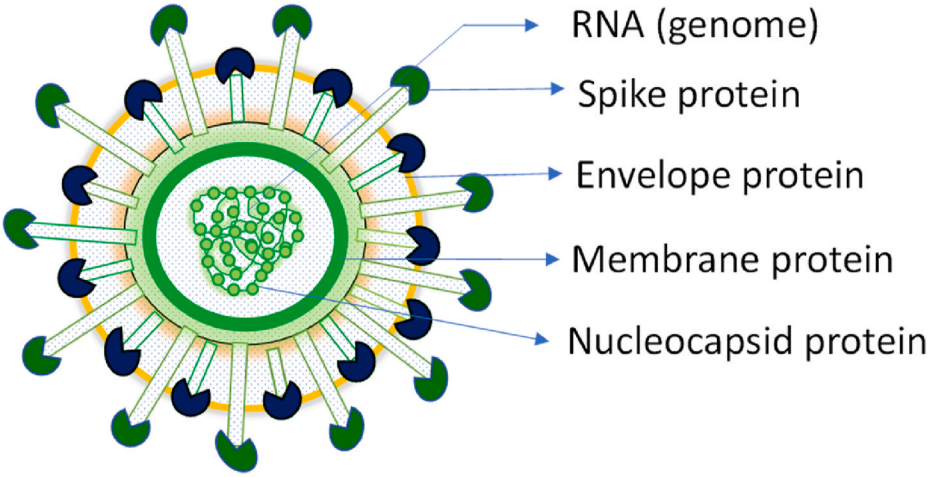

Fig. 1. Structure of the SARS-CoV-2 virus: Spike (S) is the surface glycoprotein that mediates the interaction of SARS-CoV-2 with the cell surface receptor angiotensin-converting enzyme 2 (ACE2). The membrane glycoprotein (M) and envelope (E) are embedded in the host cell-derived lipid membrane which encapsulates the viral nucleocapsid.

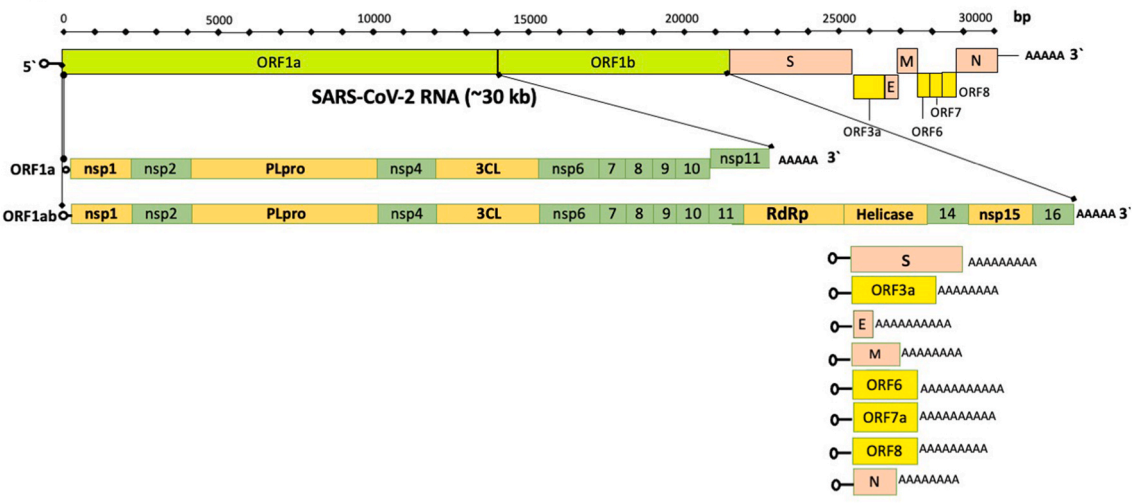

Fig. 2. Genome organization of SARS-CoV-2. Approximately 30 kb long viral genome comprises 10 open reading frames (ORFs) encoding 27 viral proteins. The ORF1ab encompasses about 67% of the total viral genome and encodes 16 non-structural proteins (nsps). Whereas the accessory and structural proteins are encoded by the remaining ORFs(adapted from Kim et al., 2020[116] with some modifications)

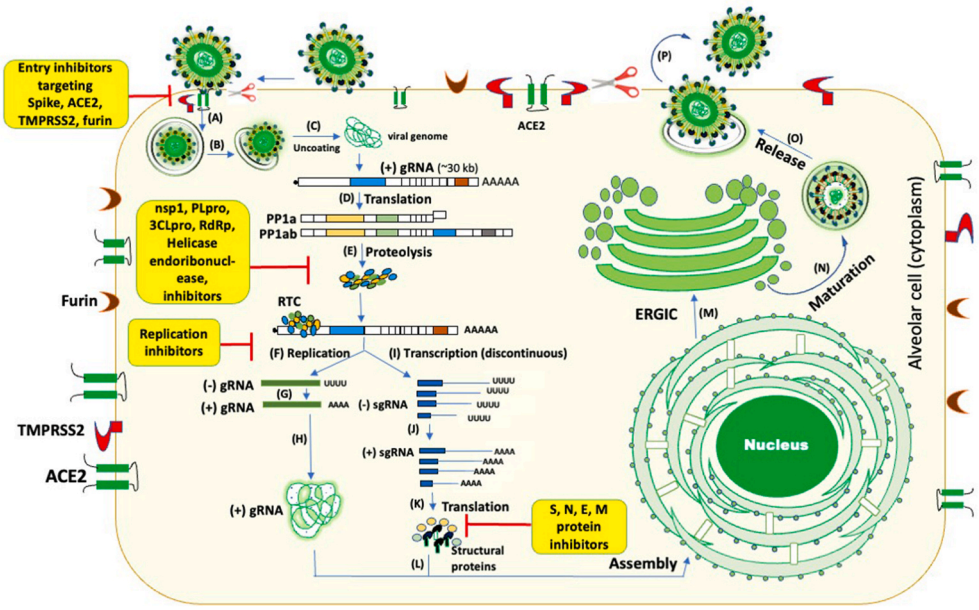

Fig. 3. The life cycle of SARS-CoV-2 and potential targets of plant-derived small molecule inhibitors (A-B) SARS-CoV- 2 spike protein binding to ACE2 followed by internalization of the virus (C) uncoating of the viral genome and its release into the cytoplasm (D-E) translation of replicase proteins (ORF1a/ab) followed by proteolysis (F–K) Replication/transcription of the viral genome. Incoming positive-strand genome generates full-length negative-strand RNA and sub-genomic RNA (sgRNAs). sgRNA translation results in both structural proteins and accessory proteins. (L–P) Structural proteins S (spike), M (membrane), E (envelope), and viral nucleocapsid complex get inserted into the ER-Golgi intermediate compartment (ERGIC) for virion assembly and release. Plant-based inhibitors (highlighted in yellow boxes) can target the majority of these steps as marked in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.) (adapted from de Vries 2020 [117] with some modifications)

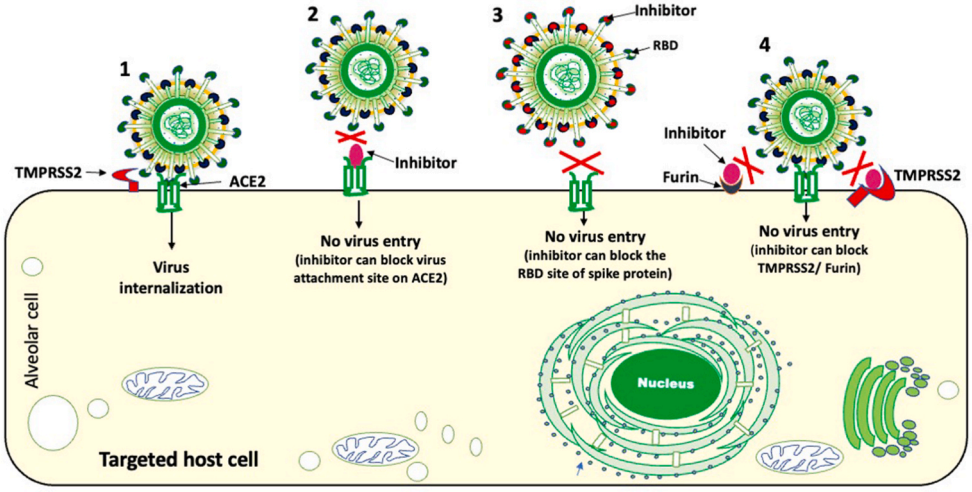

Fig. 4. Spike, ACE2, TMPRSS2 and Furin are the targets of viral entry inhibition. Plant-based inhibitors utilize several mechanisms to block SARS-CoV-2 entry.

ClinicalTrials.gov registry were used to gather research findings and to summarize them methodically as a review.

3. Fundamentals of SARS-CoV-2 genome organization and life cycle

SARS-CoV-2 infects human lung epithelial cells by binding to the cell surface located angiotensin-converting enzyme 2 (ACE2) receptor with the help of the receptor-binding domain (RBD) of spike protein (S protein). The transmembrane serine protease 2 (TMPRSS2) is required for the priming/activation of the S-protein [35]. A high expression of ACE2 and TMPRSS2 in the gastrointestinal tract has been reported to be associated with gastrointestinal symptoms seen in COVID-19 patients. There are also a few studies describing changes in the gut microbiome of these patients compared to healthy persons [32].

More recently, it has been found that the cleavage of a multibasic site present between two subunits (S1 and S2) of S protein by furin protease is also involved in S-protein mediated efficient membrane fusion, viral entry and the transmission of SARS-CoV-2 [36,65]. The virus is internalized via directly through RBD- ACE2 interaction or membrane fusion which requires TMPRSS2 proteolytic activity [9]. It is followed by uncoating of its genome and release into the host cell cytoplasm, which undergoes translation to produce viral proteins. Non-structural proteins (NSPs) 2–16 contain RNA synthesis, proof reading, cofactor and host immune evasion activities [76,88]. A negative-sense RNA intermediate is generated for the synthesis of positive-sense strand genomic RNA (gRNA) as well as a set of shorter sub-genomic RNAs (sgRNAs). Finally, the gRNA is packaged and assembled into progeny virions at the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). The sgRNAs encode structural proteins such as envelope (E), membrane (M), and nucleocapsid (N) and several accessory proteins (ORF3a, ORF6, ORF7a, ORF7b, ORF8, and other ORFs) [9,59,68,74]. (Figs. 1–3).

4. Virus-host interactions: Potential antiviral targets

The virus-host interactions during the virus entry, replication, and pathogenesis play a crucial role in the virus life cycle. Several viral and cellular factors facilitate this process in a coordinated manner. In SARS-CoV-2 infection, the viral spike protein interaction with host ACE2, TMPRSS2, and furin facilitate virus entry, which are thepotential drug

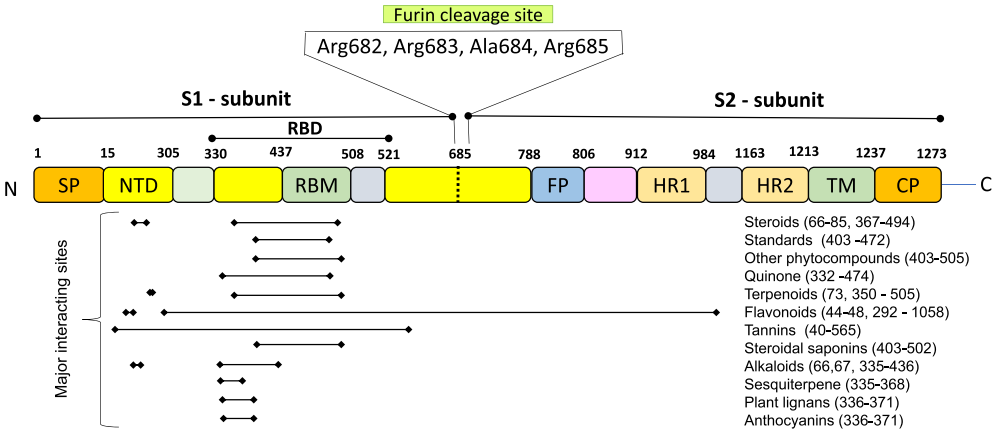

Fig. 5. Molecular structure of spike protein of SARS-CoV-2 and interactions with plant-based drugs. A furin cleavage site is present at the interface between S1 and S2 subunits of the spike protein. Amino acid positions of spike protein that can be interacted by different groups of plant-based inhibitors (steroids, quinones, terpenoids, flavonoids, and tannins) are also shown. Please refer **Table-1** for precise details. SP-signal peptide; RBD- Receptor binding domain; RBM- Receptor binding motif; TM-transmembrane motif; FP- fusion peptide; HR1-Heptad repeat-1, HR2-heptad repeat-2; NTD- N-terminal domain, CP- cytoplasmic domain(adapted from Joshi et al., 2020[40] with some modifications).

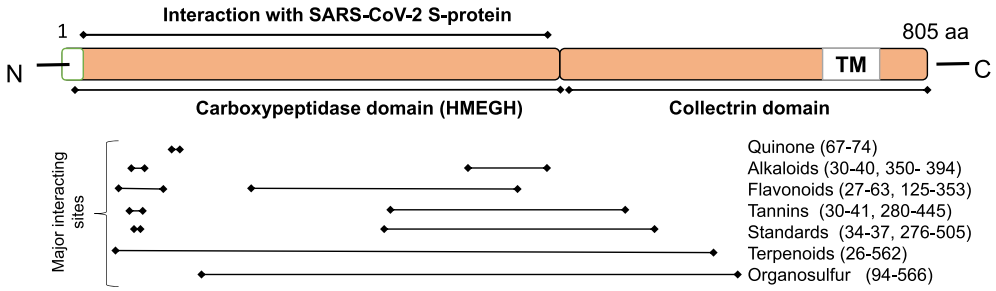

Fig. 6. Molecular organization of host ACE-2 monomer showing the interaction sites of different classes of phytocompounds (quinones, alkaloids, flavonoids, tannins, terpenoids, and organosulphur compounds) on the HEMGH/SARS CoV-2 spike protein binding domain and the collectrin domain (adapted from Bian and Li, 2021[118]).

targets for developing SARS-CoV-2 antivirals (Figure-4) and are discussed below in detail.

4.1. Spike (S) protein

Spike is a trimeric glycoprotein that mediates the binding of the virus to host cell surface-specific receptors and virus-cell membrane fusion [122]. It plays a vital role in determining host tropism and the diversity of coronaviruses (CoVs). SARS-CoV-2 is more contagious than SARS-CoV as SARS-CoV-2 spike protein interacts with ACE2 with 10–20 folds higher affinity than SARS-CoV. The receptor-binding motif (RBM) (437–508 amino acids) present in the RBD (319–541 amino acids) of the S1 subunit (13–685 amino acids) of the spike protein is majorly responsible for the binding of the virus to ACE2 [7,8,89] (Figure-5). *In-silico* docking results showed that the phytocompounds enlisted under the spike section in Table-1 interact well with the hot-spot residues of the RBD of spike glycoprotein of SARS-CoV-2.

4.2. Angiotensin-Converting Enzyme 2 (ACE2)

ACE2 is a single-pass type-1 transmembrane protein of 805 amino acids with an extracellular N-terminal peptidase domain and an intracellular C-terminus collectrin-like domain (CLD) [23]. The N- terminus has a zinc metallopeptidase binding motif (374–378 amino acids, HEMGH) essential for the interaction with SARS-CoV-2 S-protein (Figure - 6). Histochemical and single-cell RNA sequencing techniques revealed that ACE2 is primarily expressed in type-II lung alveolar epithelial cells [33,95].

A recent study, using bioinformatics, cheminformatics, and molecular docking, has demonstrated that tea flavonoids (epigallocatechin gallate, EGCG, and theaflavin gallate) have higher atomic contact energy value, dissociation constant (Ki)-value, surface area, ligand efficiency, and higher number of amino acid interactions with spike protein than synthetic hydroxychloroquine [53]). Another study showed that daturaolone, gallotannins, taraxerol, tinosporide, withanolide-A, deoxytubulosine, withametelin form strong hydrogen and non-bonding interactions with the amino acids of spike protein (between Arg 403 to Tyr 505) and have drug-likeliness properties based on Lipinski's rule of five. Moreover, these bioactive compounds have lower toxic effects and better gastrointestinal absorption than standards [56]. A simulation study using the crystal structure of SARS-CoV-2 S protein demonstrated that saikosaponin-U and saikosaponin-V, oleanane derivatives found in Chinese medicinal plants, can also interact with the spike glycoprotein *via* their octadecahydropicene and oxane rings [75]. Using molecular docking and conceptual density functional theory approaches, Kulkarni et al. showed that components of essential oils (monoterpenes, terpenoid phenols and phenyl propanoids) have the potential to interact with the RBD [47]. The phytocompounds punicalagin and punicalin (from Pomegranate), tenufolin, cinnamtannin-B1, pavetannin-C1, 6-glucopyranosyl procyanidin B1, procyanidin-B7, proanthocyanidin-A2 and Kaempferol-3-alpha-L-arabinoside-7-rhamnoside (from Cinnamon), frieldlin, and stigmasterol (from *Clerodendrum* spp) were also found to be effective candidates exhibiting important interactions with the targeted S protein [41,66,79], suggesting that they could serve as possible candidates for further *in-vitro* and *in-vivo* evaluations. Additionally, a molecular dynamics simulation study of the complex of RBD of S-protein with taraxerol for a time scale of 40 ns revealed its potent anti-SARS-CoV-2 activity [41]. Tellimagrandin-II and O-demethyl-deoxy curcumin isolated from plants used in Indian traditional medicine demonstrated stable intramolecular interactions with Asn343, which could be an important hit to affect host-immune evasion by inhibiting S-protein glycosylation [85].

The complex between viral S protein and human ACE2 has also been explored to identify antiviral phytochemicals. Using molecular

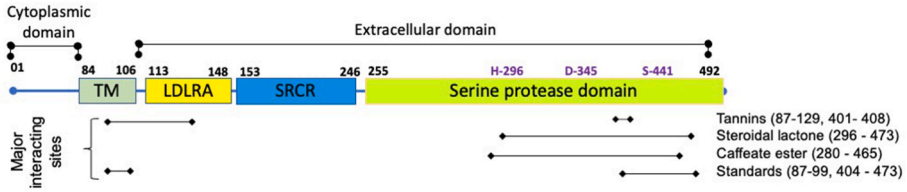

Fig. 7. Molecular structure of transmembrane protease serine-2 (TMPRSS2) and the interaction sites of tannins, steroidal lactone, and caffeate ester in its domains. H-296, D-345 and S-441 are the catalytic residues present in the serine protease domain (adapted from Paoloni-Giacobino et al, 1997 [63] and Mahmoud and Jarrar, 2021[119])

dynamics, hesperidin, a major flavonoid present in citrus fruits, has been demonstrated to interact with this complex noncompetitively at a site different from that of S-protein. Further, the antiviral activity of hesperidin was validated by a quantitative structure-activity relationship study [12]. Another study, using virtual screening followed by protein-ligand interaction approach, showed that phytochemicals like glycyrrhizinic acid, maslinic acid, ursolic acid, corosolic acid, 2-hydroxyseneganolide, gedunin, and oleanane can bind firmly with the active site and other important amino residues of S protein and ACE2 through multiple noncovalent interactions [87]. Of particular interest, His-34 is an important amino acid of ACE2 receptor as it lies on the surface and exhibits crucial interactions with the S protein. One of the molecular dynamic studies revealed that the andrographolide and pterostilbene could negatively affect SARS-CoV-2 by interacting with the His-34 [10]. Rilapladib, a quinoline, can interrupt the spike-ACE2 complex [11]. Natural compounds such as isothymol, thymol, p-cymene, limonene, and gamma-terpinene (from *Ammoides verticillata*), and 17- organosulfur compounds (from garlic) were also found to be potential inhibitors of ACE2 receptor [1,82]. Further, xanthones, proanthocyanidins, secoiridoids, naringenin, hesperetin, baicalin and neohesperidin, scutellarin, nicotinamin, and glycyrinodin could exhibit ACE2 inhibition activity [58]. Hesperidin can modulate the binding energy of ACE2-spike protein complex and affects the stability of viral-host interaction [12]. At the binding contact of the spike-ACE2 complex, the di-hydroflavone moiety of hesperidin has been predicted to be parallel to the β-6 sheet of RBD [92]. Apart from this, punicalin and punicalagin from pomegranate peel are predicted to interact with ACE2 and block entry of SARS-CoV-2 into host cells [79]. Several bioactive compounds shown in research article by Mondal *et al* can interact with hot-spot binding residues (Lys31 and Lys353) of the ACE2 receptor through hydrogen bond or non-bonded interactions [56]. Besides these, geranium and lemon essential oils downregulate the expression of ACE2 in human colon adenocarcinoma cells as observed by western blot experiments [48]. More details of *in-silico* studies, including types of interactions, binding energy values, as well as identity and position of interacting amino acids with different phytocompounds are presented in Table-1.

4.3. Transmembrane Serine Protease-2

Human TMPRSS2 is a 492 amino acid type-II transmembrane protein that belongs to the serine protease family. The N-terminal half consists of a predicted transmembrane domain (84–106 amino acids), a low-density lipoprotein receptor class A domain (LDLRA, 113–148 amino acids), and a scavenger receptor cysteine-rich domain (SRCR, 149–242 amino acids), whereas the C-terminus half contains a serine protease domain (255–492 amino acids) [63] (Figure-7). For priming of the viral spike protein, TMPRSS2 cleaves off the spike protein at two sites, Arg-685/Ser-686 and Arg-815/Ser-816. The catalytic site of TMPRSS2 consists of amino acid residues Ser-441, His-296, and Asp-345, whereas the substrate-binding sites include Asp-435, Ser-460, and Gly-462 [34]. Molecular docking studies showed that the bioactive constituents of different plants enlisted under the TMPRSS2 section in Table-1 and presented in Figure-7 display significant interactions with the amino acid residues of the serine protease domain (255–492), particularly with the amino acids of catalytic and substrate binding sites.

The phytocompounds withaferin-A, withanolide-N, punicalin, punicalagin, ellagic acid and gallic acid could interact well with the important amino acid residues of TMPRSS2 [49,79]. Withanolide-N not only showed stronger interactions compared to withaferin-A, but it could also downregulate the expression of TMPRSS2 mRNA in human breast cancer cell line. This observation led authors to predict its dual role in inhibiting SARS-CoV-2 entry. The disruption of substrate binding was most likely due to interactions of withanolide-N with the Ser-441 [49].

4.4. Furin

Furin is a subtilisin-like proprotein convertase located in the *trans*-Golgi network. It cleaves a precursor protein with a specific amino acid pattern (Arg-X-X-Arg). The furin-like cleavage site, a 12-nt insertion at S1/S2 junction in the spike coding sequence, is absent in other members of the same clade [13,19]. Furin cleavage site enhances receptor affinity and facilitates membrane fusion. The cleavage of this site occurs via priming of S protein which could provide a gain-of-function benefit to the SARS-CoV-2 for an efficient human to human transmission compared to other members of beta coronaviruses [13,19,54]. *In-silico* analyses suggested that punicalagin, punicalin, ellagic acid and gallic acid from pomegranate could interact with the active site residues and other crucial amino acid residues of furin (**Table-1**) and form more stable complexes than sulconazole (control) [80]).

5. SARS CoV-2 replication inhibitors

The replication and transcription of the SARS-CoV-2 RNA genome (~ 30 kb) is catalyzed by an RNA-dependent RNA polymerase (RdRp) domain located at the C-terminus of non-structural protein 12 (nsp12) in association with other non-structural proteins such as nsp3 (papain-like protease), nsp5 (3-chymotrypsin-like protease), nsp15 (endoribonuclease) and nsp16 (2-O' MTase).

Fig. 8. Location of amino acid interaction site (89–264) of tannins and flavonoids on SARS-CoV-2 nsp3 papain-like protease monomer(adapted from Joshi et al., 2020 [40]).

Table 1
Interactions of plant-based small molecules with targeted SARS-CoV-2 or host proteins.

Spike Glycoprotein (viral protein)			
Class	Small molecule inhibitors	Interacting amino acids with different classes of phytocompounds	References
Tannins	**Punicalin** (3-IR and −7.406 BE), **punicalagin** (6-IR and −7.312 BE), **Pedunculagin** (4-HB, 6 NBI and −7.7 BE), **punigluconin** (7-HB, 5-NBI and −7.9 BE), **chebulagic acid** (5-HB, 5-NBI and −7.5 BE), **chebulinic acid** (5-HB, 7-NBI and −6.5 BE), **cinnamtannin-B1** (3-HB, 3-HP and −10.2 BE), **6-Glucopyranosyl procyanidin-B1** (8-HB, 1-EI and −9.9 BE), **Procyanidin-B7** (2-HB, 3-HP, 2-EI and −9.6 BE), **proanthocyanidin-A2** (5-HxB, 1-HP, 2-EI and −9.4 BE), **ellagic acid** (3 IR and −6.114 BE), **gallic acid** (2 IR and −4.808 BE), **gallotannins** (6 HB, 7-NBI, −7.4 BE).	Phe40, Leu95, Gln102, Asn103, Lys187, Asp206, Val209, Asn210, Leu335, Phe342, Asn343, Pro346, Thr347, Trp349, Val367, Leu368, Tyr369, Asn370, Ser371, Ala372, Phe374, Phe377, Asp382, Phe390, Arg393, Asn394, Glu398, Gln493, Ala396, His401, Glu402, Arg403, Glu406, Gln409, Lys417, Tyr449, Tyr453, Leu455, Phe456, Tyr489, Phe490, Leu492, Gln493, Ser494, Tyr495, Gln496, Asn501, Tyr505, Asp509, Arg514, Tyr515, Lys562, Lys562, Pro565	[56,66,79].
Terpenoids	**Geraniol** (2-HB and-5.0 BE), **L-4-terpineol** (2-HB and −5.1 BE), **carvacrol** (1-HB and −5.2 BE), **limonene** (12-HPI and −5.1 BE), **thymol** (-5.4 BE), **tinosporide** (2HB, 6-NBI and −6.4 BE), **taraxerol** (7-NBI and −7.9 BE), **daturaolone** (8 NBI and −7.5 BE), **glycyrrhizin** (7-HB, 3-NBI, −7.1 BE), **friedelin** (1-HB, 2-IR and −7.3 BE), **tenuifolin** (4-HB, 2-HP and −8.7 BE), **ϒ-terpinene** (−4.8 BE), **α-terpinene** (−5.0 BE), camphene (2-HPI and −5.2 BE), **camphor** (2-HPI and −4.8 BE).	Leu73, Asp350, Tyr385, Phe390, Asn394, Arg403, Asp405, Glu406, Arg408, Gln409, Gly416, Lys417, Tyr449, Tyr451, Leu452, Tyr453, Leu455, Phe-456, Lys458, Ser-459, Leu461, Ile468, Thr470, Ile472, Glu484, Tyr489, Phe490, Pro491, Leu492, Gln493, Ser494, Tyr495, Gly496, Asn501, Tyr505	[47,56,66]
Flavonoids	**Pavetannin-C1** (9-HB, 4-HP, 1-EI and −11.1 BE), **hesperidin** (5 IR and −8.99), **chrysin** (9 IR and −6.87), **querceitin 3-O-robinobioside** (5-HB, 6-NBI, −7.9 BE), **kaempferol 3 - alpha-L-arabinofuranoside 7-rhamnoside** (7-HB, 2-HP and −8.7 BE), catechin gallate (5 HB, 3 HP and −6.1 BE), **cinnamaldehyde** (2-HB and −5.0 BE), Anthranol (1 HB, 2 HP and-9.08 BE),Apigenin (5 HB, 2 HP and -10.09 BE)Derrisin (2 HB, 2 HP and -11.04 BE)Jaceidin (2 HB, 2 HP and -10.54 BE),Lupiwighteone (1 HB, 3 HP and -9.92 BE), Luteolin (2 HB, 2 HP and -10.92 BE), Mundulinol (2 HB, 1 HP and -11.08 BE), Naringenin (2 HB, 2 HP and -10.12 BE), Rhamnetin (2 HB, 2 HP and -10.15 BE), Tamarixetin (2 HB, 1 HP and -10.33 BE), Cannflavin (1 HB, 2 HP and -9.11 BE), Methylglovanon (1 HB, 1 HP and -9.43 BE)	Ser44, Leu48, Ala292,Cys301, Leu303, Ile312, Tyr313, Thr315, Asn317, Phe318, Arg319, His345, Thr347, Ala348, Trp349, Asp350, His374, Glu375, His378, Asp382, Tyr385, Gly395, Asn397, Glu398, His401, Arg403, Glu406, Tyr410, Lys417, Arg443, Ser448, Asn449, Tyr453, Arg454, Leu455, Phe456, Ser459, Glu471, Val472, Glu473, Gly474, Phe475, Phe486, Tyr484, Thr487, Asn488, Ser494, Tyr495, Gly496, Phe497, Tyr505, Tyr510, Arg514, Tyr515, Gln516, Leu517, His519, Ala520, Ala522, Asn544, Gly545, Leu546, Val595, Pro665, Ser730, Met731, Lys733, Gln762, Arg765, Ala766, Asn856, Val860, Pro863, Asp867, Asp867, Lys964, Leu966, Ser967, Phe970, Asn969, His1058.	[12,47,56,57, 25,66]
Steroids	**Withametelin** (8 NBI and −8.0 BE), **withanolide-A** (1-HB, 7-NBI and −7.7 BE), **echinacin** (2-HB, 6-NBI and −7.9 BE), **stigmasterol** (2-IR and −7.2 BE), withanolide G (4 HB, 2 HP and −8.4 BE)	Asp66, Arg67, Gln85, Val367, Asn370, Phe374, Tyr449, Leu452, Leu455, Phe456, Glu484, Tyr489, Phe490, Leu492, Gln493, Ser494.	[41,56,57]
Quinone	**Emodin** (4 IR and −6.19), **rhein** (5 IR and −8.73)	Asn332, Thr333, Asn353, Ser388, Val401, Asn448, Ala464, Val472, Gly474,	[12]
Steroidal saponins	**Asparoside-C** (5 HB and −7.54 BE), **asparoside-D** (6 HB and −7.06 BE), **shatavarin-I** (Asparoside-B) (5 HB and −6.52 BE), **shatavarin-X** (6 HB and −6.43 BE), **racemoside-A** (3 HB and −6.23)	Arg403, Glu406, Gln409, Gln414, Thr415, Lys417, Asp420, Lys444, Gly447, Tyr449, Tyr453, Glu484, Ser494, Gly496, Gly496, Gln498, Gly502	[16]
Alkaloid	Chelidimerine (2 HB, 3 HP and −8.2 BE), Withanone (1 HB, 5 HP and −7.8 BE), Norsanguinarine (3 HB, 3 HP and −7.0 BE), Sanguinarine (1 HB, 4 HP and −6.8 BE), Adlumidine (3 HB, 4 HP and −6.8 BE), Somniferine (2 HB, 4 HP and −6.7 BE), Fumariline (1 HB, 3 HP and −6.4 BE)	Asp66, Arg67, Leu335, Phe338, Gly339, Phe342, Asn343, Asp364, Val367, Leu368, Leu368, Asn370, Ser371, Phe374, Trp436	[57]
Sesquiterpene	Badrakemin acetate (3 HB, 5 HP, and −8.0 BE), Samarcandin (2 HB, 3 HP, and −7.4 BE)	Leu335, Phe338, Gly339, Glu340, Asn343, Asp364, Val367, Leu368	[57]
Plant lignans	Pinoresinol-4-O-b-D- glucopyranoside (4 HB, 3 HP, and −4.9 BE)	Cys336, Phe338, Asn343, Asp364, Val367, Leu368, Ser371	[57]
Anthocyanin	Pelargonidin 3-glucoside (4 HB, 3 HP and −6.2 BE)	Cys336, Phe338, Asn343, Asn364, Val367, Leu368, Ser371	[57]
Other compounds	**Cinnamyl acetate** (3-HB and −5.2 BE), **barlerinoside** (7-HB, 9-NBI and −7.4 BE), **deoxytubulosine** (1-HB, 8-NBI and −7.2 BE)	Arg403, Asp405, Glu406, Gln409, Lys417, Tyr449, Tyr453, Arg454, Leu455, Phe456, Ser469, Glu471, Glu484, Gly485, Tyr489, Phe490, Leu492, Gln493, Ser494, Gly496, Asn501, Tyr505	[47,56]
Standards	**Remidesvir** (3 IR and −5.94 BE), **chloroquine** (3 IR and −8.98), **hydroxychloroquine** (4 IR and −7.82 BE)	Arg403, Glu406, Tyr453, Thr467, Pro468, Cys469, Gly471, Val472	[12,16,41] [16]
ACE2 (host protein acting as CoV-2 receptor)			
Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Organo-sulfur	**Allyl disulfide** (3 IR and −12.84 BE), **allyl trisulfide** (2 IR and −12.76 BE), **allyl (E)-1-propenyl disulfide** (2 IR and −9.07 BE), **allyl methyl trisulfide** (2 IR and −12.50 BE), **diallyl tetrasulfide** (4 IR and −14.06 BE), **1,2-dithiole** (2 IR and −13.21 BE), **1,2-dithiole** (1 IR and −7.89), **allyl (Z)-1-propenyl disulfide** (T7) (2 IR and −9.04 BE), **2-vinyl-4H-1,3-dithiine** (3 IR and −11.83 BE), **3-vinyl-1,2-dithiacyclohex-4-ene** (3 IR and −10.57 BE), **carvone** (2 IR and −8.58 BE), **trisulfide, 2-propenyl propyl** (4 IR and −14.01 BE), **methyl allyl disulfide** (3 IR and −10.32 BE), **diacetonalcohol** (2 IR and −9.71 BE), **trisulfide, (1E)-1-propenyl 2- propenyl** (2 IR and −9.57 BE), **allyl sulfide** (3 IR and −9.38 BE), **1-propenyl methyl disulfide** (2 IR and −8.06 BE), **trisulfide, (1Z)-1-propenyl 2-propenyl** (2 IR and −8.06 BE).	Lys94, Gln98, Gln101, Gln102, Asn103, Gly205, Asp206, Glu208, Val209, Asn210, Ala396, Lys562, Ser563, Pro565, Trp566	[82]
Tannins	**Punicalin** (5 IR and −7.353 BE), **punicalagin** (4 IR and −7.144 BE), **ellagic acid** (4 IR and −6.85 BE), **gallic acid** (4 IR and −5.24 BE),	Asp30, Asn33, His34, Glu35, Glu37, Asp38, Tyr41, Ser280, Pro289, Asn290, Ile291, Asp292, Arg393, Lys353, Asp367,	[79]

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Table 1 (*continued*)

	pedunculagin (4 HB, 4 HPI and −7.2 BE), **punigluconin** (5 HB, 5 HPI and −6.6 BE), **chebulagic acid** (1 HB, 6 HPI and −6.6 BE), **chebulinic acid** (4 HB, 3 HPI and −6.8 BE), gallotannins (4 HB, 7 HPI and −7.1 BE).	Ala386, Ala387, Gln388, Pro389, Arg393, Phe428, Lys441, Gln442, Thr445.	
Flavonoid	**Hesperidin** (4 IR and −9.167 BE), **chrysin** (3 IR and −7.146 BE), **rutin** (6 IR and −3.41 BE), **vitexin** (7 IR and −5.71 BE), **apigenin** (5 IR and −3.75 BE), **quercetin** (5 IR and −4.11 BE)	Thr27, Lys31, His34, Glu35, Glu37, Asp38, Gln42, Asn63, Thr125, Ile126, Thr129, Asn137, Pro138, Gly139, Lys353	[12,100]
Quinone	**Emodin** (3 IR and −9.83 BE), **Rhein** (- 7.423 BE)	Asp67, Ala71, Lys74	[12]
Terpenoid	**Thymol** and **iso-thymol** (1 H-donor and −4.74 BE), **m-eugenol** (4 IR and −2.53 BE), **p-thymol** (3 IR and −2.75 BE), **carvacrol** (7 IR and −3.31 BE), **costunolide** (4 IR and −4.0 BE), **cynaropicrin** (5 IR and −3.06 BE), **bharangin** (4 IR and −4.36 BE), **andrographolide** (6 IR and −4.53 BE), **beta-pinene** (5 IR and −5.22 BE), **spathulenol** (6 IR and −4.98 BE), **vetiverol** (6 IR and - 4.96 BE), **cucurbitacin B** (6 IR and −5.36 BE), **alpha-bisabolol** (7 IR and −5.69 BE), **6-shogaol** (6 IR and −3.33 BE), **6-gingerol** (6 IR and −3.49 BE), **beta-sitosterol** (7 IR and −4.88 BE), **linoleic acid** (6 IR and −2.07 BE), **glycyrrhizinic acid** (4 HB, 2 Pi-Alkyl, 1CHB, 9 VDW and −9.5 BE), **maslinic acid** (4 HB, 3 Pi-Alkyl, 5 VDW and −8.5 BE), **obacunone** (1 HB, 1 Pi-sigma, 1 Pi-Pi T shaped, 2 Pi-Alkyl, 8 VSW and −8.1 BE), **epoxyazadiradione** (2 Alkyl/Pi-Alkyl, 1 Pi-Sigma, 7 VDW and −8.0 BE), **azadiradionolide** (3 HB, 3 Alkyl/Pi-Alkyl, 6 VDW and −8.0 BE), **Ursolic acid** (3 HB, 3 Pi-Alkyl, 7 VDW and −7.4 BE), **gedunin** (1 HB, 3 Alkyl/Pi-Alkyl, 1 Pi-Sigma, 1 CHB, 7 VDW and −7.3 BE).	Lys26, Thr27, Asp30, Lys31, Asn33, His34, Glu35, Asp38, Glu37, Leu39, Phe40, Gln42, Asn90, Thr92, Val93, Gln96, Tyr127, Ser128, Glu145, Asn 149, Trp271, Arg273, Phe274, His345, Pro346, Thr347, Ala348, Trp349, Asp350, Lys353, Asp367, Lue370, Thr371, His373, His374, Glu375, Asp382, Tyr385, Ala387, Gln388, Pro389, Phe390, Arg393, Asn394, His401, Glu402, Glu406, Ser409, Gln442, Thr445, Leu503, Phe504, His505, Asn508, Arg514, Tyr515, Lys562	[1,87,100]
Alkaloids	**Pellitorine** (5 IR and −3.4 BE), **vasicine** (5 IR and −6.21 BE), **piperidine** (9 IR and −4.31 BE), **piperine** (5 IR and −4.1 BE)	Asp30, Lys31, Asn33, His34, Glu35, Glu37, Asp38, Phe40, Asp350, Lys353, Pro389, Phe390, Arg393, Asn394,	[100]
Standards	**Lopinavir** (9 IR and −7.5 BE), **umifenovir** (7 IR and −6.5 BE), Hydroxychloroquine (10 IR and −7.1 BE)	His34, Glu37, Thr276, Asn290, Ile291, Met366, Asp367, Leu370, Gln388, Pro389, Arg393, Lys403, Glu406, Ser409, Leu410, Ala413, Lys441, Thr445, Ser494, Tyr495, Gly496, Tyr505	[10,79]

TMPRSS2 (host protease)

Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Tannins	**Punicalin** (5 IR and −8.168 BE), **punicalagin** (6 IR and −7.358 BE), **ellagic acid** (2 IR and −6.829 BE), **gallic acid** (5 IR and −5.709 BE)	Arg87, Ala88, Arg91, Asp92, Asn97, Asp129, Tyr401, Met404, Arg405, Gly408	[79]
Steroidal lactone	**Withaferin-A** (2 HB, 19 IR and −5.60 BE), **Withanone** (1 HB; 18 HP and −4.30 BE)	His296, Glu299, Tyr337, Lys342, Glu389, Asp435, Ser436, Cys437, Gln438, Asp440, Ser441, Thr459, Ser460, Trp461, Gly462, Ser463. Gly464, Cys465, Ala466, Gly472, Val473	[49]
Caffeate ester	**Caffeic acid phenethyl ester** (2 HB; 17 HP and −6.20 BE)	Cys281, Val280, His296, Cys297, Glu299, Leu302, Asp435, Ser436, Cys437, Gln438, Gly439, Asp440, Ser441, Thr459, Ser460, Trp461, Gly462, Gly464, Cys465	[49]
Standards	**Camostat** (5 IR and −7.069 BE), **Camostat mesylate** (1 HB and 20 HPI and -5.9 BE)	Arg87, Asn97, Phe99, Met404, Arg405, Val275, Gln276, Val278, Val 280, His296, Cys297, Leu302, Asp435, Ser436, Cys437, Gln438, Gly439, Ser441, Thr459, Trp461, Gly462, Cys465, Ala466, Gly472, Val473	[79] [49]

Furin (host protein)

Class	Small molecule inhibitors		References
Tannins	**Punicalin** (7 IR and −9.725 BE), **punicalagin** (4 IR and −9.385 BE), **ellagic acid** (5 IR and −7.801 BE	His194, Gly255, Pro256, Pro256, Glu257, Asp258, Asp259, Thr262, Arg298, Cys303, Asp306, Gly307, Ser311, Gly366, Ser368, Thr365, Arg 490, Trp531, Ala532,	[79]
Standards	**Sulcanozole** (4 IR and −6.923 BE)	Val263, Phe528, Trp531, Ala532	[79]

Papain-like protease/nsp3 (viral protease)

Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Terpenoid, Flavonoid	Oleonolic acid (4 IR and −10 BE), ursolic acid (5 IR and −9.7 BE), 3β-acetoxyolean-12-en-27-ioc acid (3 IR and −9.5 BE), Isovitexin (5 IR and −9.3 BE)	His89, Trp106, Ala107, Asp108, Asn109, Val159, Gly160, Gu161, Leu162, Pro248, Tyr264	[55]

3 Chymotrypsin-like protease/nsp5 (viral protease)

Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Flavonoid	**Epigallocatechin** (6 IR and −7.0 BE), **gallocatechin** (6 IR and −7.1 BE) **catechin** (6 IR and −7.1 BE), **epicatechin** (6 IR and −7.2 BE), **catechin gallate** (6 IR and −7.2 BE), **epigallocatechin gallate** (9 IR and −7.6 BE), **epicatechin gallate** (10 IR and −8.2 BE), **gallocatechin-3-gallate** (9 IR and −9.0 BE), **kaempferol** (4 HB, 6 HPI and −8.58 BE), **quercetin** (8 IR and −6.58), **luteolin-7-glucoside** (10 IR and −8.17 BE), **myricetin** (4 IR and −6.15 BE), **scutellarin** (2 IR and −7.13 BE), **isoflavone** (2 IR and −5.69 BE), **Quercetin-3-O-rutinose** (6 HB, 1 PS and −9.2 BE), **Quercetin-7-O-glucuronide** (6 HB, 1 PC, 1 PS, 1 PP, 1 Pal and −8.4 BE), **quercetin-3′-O-glucuronide** (6 HB, 1 PS, 2 Pal and −8.5 BE), **quercetin-3-O-glucuronide** (3 HB, 1 PS, 1 PC, 1 Pal and −8.5 BE), **quercetin-7-O-sulfate** (6 HB, 1 PS, 1 Pal and −8.4 BE), **quercetin-3-O-sulfate** (4 HB, 1 PS, 1 Pal and −7.6 BE), **quercetin-3′-O-sulfate** (6 HB, 1 PC, 3 PS	Lys5, Thr24, Thr25, Thr26, Leu27, His41, Cys44, Thr45, Ser46, Met49, Tyr53, Tyr54, Pro108, Lys137, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu-166, Leu-167, Pro168, His172, Asp187, Arg188, Gln189, Thr190, Ala191, Gln192, Gly195, Asp197, Thr199, Asn238, Tyr239, His246, Leu271, Leu272, Leu286, Leu287, Glu288, Asp289.	[20,57,66,67, 73,109]

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Table 1 (*continued*)

	and −8.1 BE), **quercetin** (4 HB; 1 PS, 2 Pal and −7.5 BE), kaempferol-3-O-rutinose (nicotiflorin) (4 HB, 1 PS, 1 Psi, 1 PP and −8.9 BE), **kaempferol-4′-O-glucuronide** (4 HB, 3 Pal and −8.0 BE), **kaempferol-3-O-glucuronide** (6 HB, 1 PS, 1 PP, 1 Psi and −8.3 BE), **kaempferol-7-O- glucuronide** (4 HB, 2 PS, 1 Psi, 2 Pal and −8.3 BE), **kaempferol-7-O-sulfate** (3 HB, 1 PS, 1 PP, 2 Pal and −8.3 BE), **kaempferol-4′-O-sulfate** (4 HB, 1 Pal and −8.2 BE), **kaempferol-3-O-sulfate** (3 HB, 1 PS, 1 Pal and −7.3 BE), **kaempferol** (1 HB, 2 PS, 2 Pal and −7.2 BE), **5,7,3′4' - tetrahydroxy2'-(3,3- dimethylallyl) isoflavone** (14 IR and −16.35 BE), **myricitrin** (16 IR and −15.64 BE), **methyl rosmarinate** (16 IR and −15.44 BE), **3,5,7,3′,4′,5′-hexahydroxy flavanone – 3 – O – beta – D glucopyranoside** (13 IR and −14.42 BE), **(2S)-eriodictyol 7-O-(6″-Ogalloyl)-beta-D-glucopyranoside**, (15 IR and −14.41 BE), **calceolarioside B** (16 IR and −19.87 BE), **myricetin 3-Obeta-D-glucopyranoside** (17 IR and −13.70 BE); **licoleafol** (13 IR and −13.63 BE), **amaranthin** (16 IR and −12.67 BE), **peonidin 3-O-glucoside** (5 HB, 7 HP and −9.4 BE), **kaempferol 3-O-β –rutinoside** (4 HB, 6 HP and −9.3 BE), rutin (2 HB, 6 HP and −9.2 BE), **4 - (3, 4 - Dihydroxyphenyl) – 7 – methoxy - 5 - [(6 – O – b – D – xylopyranosyl – b – D - glucopyranosyl) oxy] - 2H-1-benzopyran – 2 - one** (5 HB and 7 HP), **quercetin-3-D-xyloside** (7 HB, 5 HP and −9.1 BE), **quercetin 3-O-a-L-arabinopyranoside** (4 HB, 6 IR and −9.0 BE), **kaempferol 3-rutinoside 40-glucoside** (9 HB, 6 HP and −8.9 BE), **quercetin 3-O-(6″-O-malonyl)-b-D-glucoside** (3 HB, 8 HP and −8.8 BE), **idaein** (2 HB and 8 HP), **callistephin** (3 HB and 8 HP); **malvin** (4 HB, 8 HP and −8.7 BE), **luteolin 7-rutinoside** (2 HB; 9 HP; −8.6 BE), **cyanin** (4 HB; 4 HP; −8.5 BE), **kaempferol 7-O-neohesperidoside** (5HB, 7 HP and −8.4 BE), **rhamnetin 3 sophoroside** (5 HB, 4 HP and −8.3 BE), **myricetin 3-O-b-D-galactopyranoside** (5 HB, 2 HP and −8.2 BE), **2″-O-alpha-L-rhamnopyranosyl-isovitexin** (3 HB, 10 HP and −8.2 BE), **hesperidin methylchalcone** (5 HB, 4 HP and −8.0 BE), **procyanidin-B7** (4 HB, 1 HP, 1 EI and −8.2 BE), **kaempferol 3-alpha-L-arabinofuranoside-7-rhamnoside** (3 HB, 1 HP, 1 EI and −8.1 BE), **proanthocyanidin-A2** (1 HB, 1 HP, 1 EI and −8.0 BE), **6-glucopyranosyl procyanidin B1** (5 HB, 1 HP, and −7.6 BE), **pavetannin-C1** (4 HB, 1 HP, 1 EI and −7.3 BE), **querceitin 3-O-robinobioside** (6 HB, 8 NBI and −8.8 BE).		
Organosulfur	**Allyl disulfide** (6 IR and −15.32 BE), **allyl trisulfide** (4 IR and −15.02 BE), **allyl (E)-1-propenyl disulfide** (2 IR and −13.25 BE), **allyl methyl trisulfide** (4 IR and −14.36 BE), **diallyl tetrasulfide** (4 IR and −14.47 BE), **1,2-dithiole (T6-ACE2) (2 IR and -13.21 BE), allyl (Z)-1-propenyl disulfide** (2 IR and −12.60 BE), **2-vinyl-4H-1,3-dithiine** (4 IR and −14.04 BE), **3-vinyl-1,2-dithiacyclohex-4-ene** (3 IR and −13.83 BE), **carvone** (1 IR and −12.36 BE), **trisulfide, 2-propenyl propyl** (5 IR and −14.36 BE), **methyl allyl disulfide** (3 IR and −13.56 BE), **diacetonalcohol** (2 IR and −13.26 BE); **trisulfide, (1E)-1-propenyl 2- propenyl (2 IR and −12.00 BE); (1Z)-1-propenyl 2- propenyl** (1 IR and −11.68 BE)	Leu141, Asn142, Gly143, Ser144, Cys145, His163, Met165, Glu166	[82]
Terpenoids	**Glycyrrhizic acid** (4 HB, 3 CHB, 12 VDW and −8.7 BE), **6-oxoisoiguesterin** (5 IR and −9.1 BE), **daturaolone** (10 NBI and −7.3 BE), **glycyrrhizin** (7 HB; 7 NBI and −8.2 BE), **calendulaglycoside B** (16 IR and −8.2 BE), **calenduloside** (15 IR and −7.9), **tenuifolin** (6 HB, HP-2 and 8.8 BE), **7-Deacetyl-7-benzoylgedunin L** (1 CHB, 2 HB, 10 VDW, 1 Pi-Pi T shaped, 1 alkyl, 1 Pi-alkyl, −9.1), **glycyrrhizic acid** (4 HB, 3 CHB, 12 VDW, −8.7), **limonin**: 3 HB, 1 pi-donor, 1 CHB, 4 VDW, −8.7), **Obacunone** (3 HB, 1 pi-donor, 1 pi-alkyl, 5 VDW, −7.5), **Dihydroartemisinin** (2 HB, 2A, 1 PA and −7.0 BE)	Thr24, Thr25, Thr26, Leu27, His41, Cys44, Thr45, Ser46, Met49 Leu50, Tyr118, Arg131, Lys137, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, His172, Asp187, Arg188, Gln189, Thr190, Ala191, Tyr239, Leu275, Leu286, Leu287	[21,31,51,56,87]
Sesquiterpene	**Badrakemin acetate** (2 HB, 5 HP and −8.6 BE), **Samarcandin** (3 HB, 2 HP and −8.5 BE)	His41, Gly143, Cys145, His163, Glu166, Leu167, Pro168, Gln192	[57]
Iridoid glycoside	**Harpagoside** (3 HB, 3 HP and −6.1 BE)	His41, Met49, Leu141, Asn142, Met165, Glu166	[57]
Beta-diketone	**demethoxycurcumin** (1 IR and −7.02 BE), **curcumin** (2 IR and −6.04 BE); **bisdemethoxycurcumin** (5 IR and −7.3 BE)	His41, Asn119, Phe140, Cys145, His163	[73]
Beta-hydroxy ketone	**Zingerol** (5 IR and −5.40 BE) and **gingerol** (5 IR and −5.38 BE)	Met49, His163, Met165, Glu166, Pro168, Asp187, Arg188, Gln189, Thr190	[43]
Furanocoumarin	**Bergapten (5-methoxypsoralens)** (2 IR and −5.98 BE)	Phe140, His163	[73]
Anthocyanins	**Delphinidin 3-Sambubioside-5-Glucoside** (27 IR and −12.37 BE); **Delphinidin 3,3′-Di-Glucoside-5-(6-P-Coumarylglucoside)** (28 IR and −11.59 BE), **2-(3,4,5-Trihydroxyphenyl)-3- [6- [(E)-3-(4-hydroxyphenyl) acryloyl] -beta-D-galactopyranosyloxy] -5,7-dihydroxy-1-**	Thr24, Thr25, Thr26, Leu27, His41, Cys44, Met49, Leu50, Pro52, Tyr54, Gly138, Ser139, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, Thr169, Gly170, His 172, Val186, Asp187, Arg188, Gln189, Thr190, Ala191, Gln192	[27,57]

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Table 1 (*continued*)

	benzopyrylium 2-(3,4,5- Trihydroxyphenyl)-3- [6- [(Z)-3-(4-hydroxyphenyl) acryloyl] -beta-D-galactopyranosyloxy] -5,7-dihydroxy-1-benzopyrylium (27 IR and −10.94 BE), **3-O- [b-D-Glucopyranosyl-(1->2)- [4-hydroxycinnamoyl-(->6)] -b-D-glucopyranoside] (E-), 5-O-(6-O-malonyl-b-D-glucopyranoside) Pelargonidin 3-O- [b-D-Glucopyranosyl-(1->2)- [4-hydroxycinnamoyl-(->6)] -b-D-glucopyranoside] (E-) 5-O-(6-O-malonyl-b-D-glucopyranoside** (25 IR and −10.30 BE), **3-< [4,5-dihydroxy-6-(hydroxymethyl)-3- [(3,4,5-trihydroxy-6-< [hydroxy(4-oxocyclohexa-2,5-dien-1-ylidene)methoxy] methyl > oxan-2- yl)oxy] oxan-2-yl] oxy>-2-(3,4-dihydroxyphenyl)-7-hydroxy-5-< [3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl] oxy>-1lambda-chromen-1-ylium** (25 IR and −13.59 BE), **Cyanidin 3-(60 '-p-coumarylsambubioside)** (22 and −9.58 BE), **Pelargonidin 3-glucoside** (4 HB, 5 HP and −8.1 BE), **Cyanidin 3,5-di-O-glucoside** (4 HB, 6 HP and −6.9 BE), **Cyanidin 3-O-rutinoside** (7 HB, 4 HP and −6.9 BE)		
Steroidal lactone	**Withanoside-II** (20 IR and −11.30 BE), **withanoside IV** (20 IR and 11.02 BE), **withanoside-V** (27 IR and −8.96 BE), **sitoindoside IX** (24 IR and −8.37 BE), Withanolide G (4 HB, 4 HP and −8.6 BE)	Thr24, Thr25, Thr26, Leu27, His41, Cys44, Thr45, Ser46, Met49, Leu50, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His163, His164, Met165, Glu166, Leu167, Pro168, Arg188, Gln189, Thr190, Ala191, Gln192	[57,84]
Alkaloid	**10-Hydroxyusambarensine** (10 IR and −10.1 BE), **cryptoquindoline** (3 IR and −9.7 BE); **6-Oxoisoiguesterin** (1 HB, 4 IR and −9.1 BE), N-[(5-methylisoxazole - 3-yl) carbonyl] alanyl-l-valyl-n1- ((1r,2z)-4-(benzyloxy) – 4 – oxo -1- [(3r)-2-oxopyrrolidin-3-yl] methyl] but-2-enyl)-l-leucinamide (3 HB, 3 HPI, −7.4 BE), **22-hydroxyhopan-3-one** (1 HB, 4 IR and −8.6 BE), Chelidimerine (2 HB, 6 HP and −10.2 BE), Somniferine (3 HB, 3 HP and −8.3 BE), Adlumidine (5 HB, 2 HP and −8.2 BE), Withanone (4 HB, 3 HP and −8.2 BE), Fumariline (3 HB, 5HP and −7.8 BE), Sanguinarine (5 HB, 3 HP and −7.7 BE), Norsanguinarine (3 HB, 5 HP and −7.5 BE)	His41, Met49, Tyr54, Lys137, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, Cys148, Met49, His163, Met165, Glu166, Leu167, Pro168, Asp187, Gln189, Gln192, Thr199, Tyr239, Tyr273, Leu275 Leu286, Leu287	[31,57]
Tannins	**Pedunculagin** (5 HB, 9 NBI and −8.9 BE), **punigluconin** (6 HB, 12 NBI and −8.5 BE), **taraxerol** (11 NBI and −7.2 BE), **withametelin** (8 NBI and −7.9 BE), **tinosporide** (2 HB, 12 NBI and −8.5 BE), **chebulagic acid** (6 HB, 3 NBI and −6.5 BE), **chebulinic acid** (9 HB, 9 NBI and −8.6 BE), **gallotannins** (5 HB, 10 NBI and −8.3 BE), **cinnamtannin-B1** (3 HB, 4 HP and −8.4 BE), **barlerinoside** (7 HB, 10 NBI and −7.5 BE)	Thr24, Thr25, Thr26, His41, Cys44, Thr45, Ser46, Tyr54, Cys145, His163, Thr25, Met49, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, His164, Met165, Glu166, His172, Ala285, Asp187, Arg188, Gln189, Asp197, Thr199, Tyr239, Met276, Leu287, Leu286	[41,56,66]
Phenylpropanoids	Hydroxycinnamic acid (3 HB, 2A, 1 PA, and −7.5 BE)	His41, His164, Gln192, Thr190, Pro168, Met165, Arg188, Arg187, Val186, Thr190, Gln192, Met49, Met165, Pro168	[51]
Aromatic alcohol	Phenethyl alcohol (6 HB, 2 PA, −7.3 BE)		[51]
Standards	**N3 inhibitor (native cocrystal ligand)** (8 HB, 6 HPI and −7.9 BE/28 IR and −9.47 BE/23 IR and −8.12 BE), **nelfinavir** (9 IR and −12.20 BE); **prulifloxacin** (10 IR and −11.32 BE) and **colistin** (18 IR and −13.73 BE), **x77** (4 HB, 2 PS, 1 Pal, 1 Pam, 1 PP and −8.4 BE), **ribavirin** (5 IR and −5.43 BE), **lopinavir** (3 HB, 3 HP and −9.41 BE), **ritonavir** (2 HB, 3 IR and −6.8 BE), l X77 (4 HB, 2 PS, 1 PA1, 1 Pam, 1 PP and −8.4 BE)	Thr24, Thr25, Thr26, Leu27, His41, Cys44, Thr45, Ser46, Glua47, Met49, Leu50, Pro52, Tyr54, Val104, Gln110, Ile106, Asp153, Phe140, Leu141, Asn142, Gly143, Ser144, Cys145, Ser158, His163, His164, Met165, Glu166, Leu167, Pro168, Gly170, Hie172, Asp187, Arg188, Gln189, Thr190, Ala191, Gln192, Val202, Ile249, Pro293, Phe294 Val297.	[20,27,31,67, 73,84,109]

RNA dependent RNA polymerase/nsp12 (viral replicase)

Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Flavonoid	**Theaflavin** (8 HB, 2 PA and −9.1 BE), **quercetin-3-O- (rutin)** (9 HB, 1 Psi and −8.5 BE), **quercetin-7-O-glucuronide** (6 HB, 1 PA and −8.2 BE), **quercetin-3′-O-glucuronide** (5 HB; 1 PAm; −8.2 BE), **quercetin-3-O-glucuronide** (6 HB; 2 PA; 1 Pal; −8.0 BE), **quercetin-7-O-sulfate** (6 HB, 1 PC, 1 Pal, and −8.0 BE), **quercetin-3-O-sulfate** (2 HB, 2 PA and −7.1 BE), **quercetin-3′-O-sulfate** (6 HB, 1 PC, 1 Pal and −8.1 BE), **quercetin** (3 HB, 2 Psi and −7.4 BE), **kaempferol-3-O-rutinose** (4 HB, 2 PA and −9.2 BE), **kaempferol -4′-O-glucuronide** (6 HB, 1 PC and −8.3 BE), **kaempferol-3-O-glucuronide** (6 HB, 2 PA, 2 Pal and −7.9 BE), **kaempferol-7-O-glucuronide** (8 HB, 1 PC and −7.9 BE), **kaempferol-7-O-sulfate** (4 HB, 1 PC, 2 PA, 2 Pal and −7.3 BE), **kaempferol-4′-O-sulfate** (1 HB, 2 PA and −6.7 BE), **kaempferol-3-O-sulfate** (1 HB, 2 PA and −6.7 BE), **kaempferol** (2 HB, 2 Psi and −7.2 BE)	Asp452, Lys545, Arg553, Ala554, Arg555, Thr556, Met615, Trp617, Asp618, Tyr619, Pro620, Lys621, Cys622, Asp623, Arg624, Thr687, Asn691, Ser759, Asp760, Asp761, Ser778, Ile779, Glu796, Lys798, Cys799, Trp800, Thr801, Glu811, Cys813, Ser814	[20]
Terpenoids	**Glycyrrhizic acid** (7 HB, 1 CHB, 1 pi-alkyl, 16 VDW and −9.9 BE), **limonin** (2 HB, 2 pi-alkyl, 1 pi-pi T shaped, 10 VDW and −8.2 BE), **7-Deacetyl-7-benzoylgedunin** (1 HB, 1 Alkyl/pi-alkyl, 2 CHB, 1 pi-anion, 3 pi-cation, 6 VDW and −8.2 BE), **limonin glucoside** (3 HB, 1 CHB, 4 Alkyl/Pi-Alkyl, 9 VDW and −8.2 BE), 7- -deacetylgedunin (1 HB, 2 CHB, 1 Pi-Alkyl, 1 Pi-sigma, 1 Pi-anion, 5 VDW and −8.1 BE), **obacunone** (2 HB, 1 Alkyl, 1 Pi-Anion, 8 VDW and −7.8 BE)	His439, Asp452, Tyr456, Met542, Lys545, Ala547, Ile548, Ser 549, Ala550, Lys551, Arg553, Ala554, Arg555, Thr556, Val557, Ala558, Gly616, Trp617, Asp618, Tyr619, Pro620, Cys622, Asp623, Arg624, Ser682, Asp760, Asp761, Ala762, Val763, Ala797, Lys798, Trp800, His810, Glu 811, Phe812, Ser814, Arg836	[87]
Standards	**Remdesivir** (3 IR and −6.3 BE), **favipiravir** (3 IR and −3.6 BE)	Lys551, Arg553, Arg555, Asp623, Ser682	[41]

Helicase/nsp13 (viral protein)

Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Flavonoids			[46]

(*continued on next page*)

Table 1 (*continued*)

	Tomentodiplacone B (9 IR and −8.4 BE), **osajin** (4 IR and −8.2 BE), **sesquiterpene glycoside** (9 IR and −8.2 BE), **rhamnetin** (9 IR and −8.1 BE), **silydianin** (6 IR and −8.1 BE)	Val6, Asn9, Arg21, Arg22, Pro23, Phe24, Glu128, Arg129, Leu132, Phe133, Glu136, Arg178, Asn179, Pro234, Pro238, Ser310, Pro406, Ala407, Pro408, Asp534, Arg560	
Standards	**Nelfinavir** (6 IR and −6.2 BE), **remdesivir** (8 IR and −6.8 BE), **prulifloxacin** (7 IR and −8.1 BE)	Val6, Arg21, Arg129, Leu132, Glu136, Lys139, Glu142, Asn177, Asn179, Tyr180, Pro234, Pro238, Cys309, Met378, Asp383, Pro406, Ala407, Pro408, Arg409, Thr410, Leu412, Leu417, Arg560	[46]
Endoribonuclease/nsp15 (viral protein)			
Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Flavonoid	**Naringin** (5 IR and −7.8 BE), **taxifolin** (6 IR and −7.2 BE), **luteolin** (5 IR and −7.2 BE), **apigenin** (4 IR and −7.2 BE), **myricetin** (4 IR and −7.0 BE), **wogonin** (3 IR and −6.9 BE), **epigallocatechin** (3 IR and −6.8 BE), **chlorogenic acid** (6 IR and −6.8 BE), **afromosin** (4 IR and −6.7 BE), **rutin** (5 IR and −7.8 BE), **silymarin** (IR and −8.0 BE).	His235, ASP240, Gln245, Gly248, His250, Lys290, Val292, Ser294, Val339, Glu 340, Thr341, Tyr343, Pro344, Leu346	[106]
Beta-diketone	**Demethoxycurcumin** (5 IR and −7.51 BE), **quercetin** (4 IR and −6.49 BE), **bisdemethoxycurcumin** (1 IR and −6.56 BE), **curcumin** (1 IR and −6.48 BE), **myricetin** (4 IR and −6.52 BE), **bergapten** (4 IR and −5.92 BE), **scutellarin** (4 IR and −6.97 BE), **isoflavone** (2 IR and −5.47 BE)	His235, Glu340, Thr341, His250, Lys290; Ser294, Gly248	[73]
Terpenoid	**Saikosaponin-V** (8 HB, 9 HP and −8.35 BE), **saikosaponin-U** (8 HB, 8 HP and −7.27 BE), **saikosaponin-C** (6 HB, 9 HP and −6.98 BE), **saikosaponin-K** (5 HB, 10 HP and −6.79 BE), **saikosaponin-1b** (4 HB, 8 HP and −6.36 BE), **alpha-amyrin** (1 IR and −8.1 BE), **pomolic acid** (2 IR and −7.9 BE), **carnosol** (2 IR and −7.8 BE), **arjunolic acid** (1 IR and −7.6), **asiatic acid** (5 IR and −7.4 BE), **betulinic acid** (1 IR and −7.3 BE), **platanic acid** (5 IR and −7.3 BE), **alphitolic acid** (1 IR and −7.2), **Asiatic acid** (5 IR and −7.4), **ursonic acid** (5 IR and −8.4 BE).	Gly230, Ala232, Glu234, Hip235, Asp240, Gly245, Leu246, Gly247, Gly248, His250, Asn278, Lys290, Cys291, Val292, Cys293, Met331, Ala232, Trp333, Val339, Glu340, Thr341, Tyr343, Pro344, Leu346	[75,106]
Coumarin	**Beta sitosterol** (1 IR and −8.1 BE), **gliotoxin** (3 IR and −6.7 BE), **psoralen** (5 IR and −6.7 BE), **carinatine** (4 IR and −6.6 BE), **rhinacanthin** (6 IR and −6.5 BE), **caffeic acid** (4 IR and −6.3 BE), **coriandrin** (3 IR and −6.2 BE), **scopoletin** (5 IR and −6.1 BE), **cordycepin** (4 IR and −5.6 BE), **ricinoleic acid** (3 IR and −5.0 BE), **alpha asarone** (1 IR and −4.9 BE), **valproic acid** (4 IR and −4.6 BE)	His235, Gly248, His250, Lys290, Val292, Cys293, Ser294, Thr341, Tyr343.	[106]
Organosulfur	**allicin** (3 IR and −3.8 BE)	His235, Thr341, His250	[106]
Alkaloid	**Taspine** (4 IR and −7.3 BE), **ajmalicine** (5 IR and −8.1 BE), **reserpine** (4 IR and −7.4)	His235, Thr341, Gly248, His250, Lys290, Glu340	[106]
Steroids	**Asparoside-C** (5 HB and −7.16 BE), **asparoside-F** (7 HB and −6.6 BE), **asparoside-D** (6 HB and −6.4 BE), **rutin** (5 HB), **racemoside-A** (4 HB and −5.99)	Gly230, Ala232, Glu234, Hip235, Val339, Asp240, His243, Gln245, His250, Asn278, Val292, Glu340, Thr341, Leu346	[16]
Standards	**Hydroxychloroquine** (4 IR and −5.8 BE), Nelfinavir (4 IR and −7.3 BE), **ribavirin** (9 IR and −5.84)	Thr26, **His235, His250, Gly248, Lys290, Val-292, Ser294, Thr341, Tyr 343, Pro344,**	[73,106]
2′-O- methyl transferase/nsp16 (viral protein)			
Class	Small molecule inhibitors	Interacting residues with different classes of phytocompounds	References
Flavonoids, Alkaloids, others	**Eryvarin-M** (9 IR and −8.6 BE), **silydianin** (9 IR and −8.5), **osajin** (6 IR and −8.2 BE), **raddeanine** (8 IR and −8.2 BE)	Asp6873, Asn6899, Asp6897, Amet6929, Leu6898, Asn6841, Lys6844, Cys6913, Lys6968, Phe6947, Lys6944, Asn6899, Asp6928, Cys6913, Gly6911, Leu6898, Met6929, Asp6897, Asp6928, Met6929, Cys6913, Leu6898, Gly6869, Cys6898, Asp6928, Asp6897, Asp6912, Cys6913, Leu6898, Asp6897, Gly6871, Asn6811, Met6929, Phe6947.	[46]
Standards	**Nelfinavir** (9 IR and −8.2 BE), **remdesivir** (9 IR and −7.0 BE), **prulifloxacin** (12 IR and −7.6 BE)	Leu6898, Tyr6930, Gly6871, Pro6932, Lys6968, Lys6844, Gly6911, Met6929, GLy6969, Pro6932, Lys6968, Lys6844, Leu6898, Lys6996, Glu7001, Lys6844, Lys6844, Lys6968, Asp6928, Met6929, Cys6913, Asp6897, Asn6841, Gly6871, Leu6898, Phe6947, Tyr6930, Asp6897, Asn6899, Pro6932, Asp6931	[46]

Note: BE - binding energy, HB - hydrogen bond, HP/HPI - hydrophobic interactions, NBI = non-bonding interactions, IR-interacting residues, EI- electrostatic interactions, CHB –carbon-hydrogen bond, VDW – van der Waals interactions. PS: π-sulfur; Pal: π-alkyl; PP: π-π; PA: π-anion; PC: π-cation; Psi: π-sigma; Pam: π-amide; Pi-H = π-hydrogen bond, PA- π-alkyl; A-alkyl.

5.1. *Papain-like protease (PLpro)/nsp3*

Papain-like protease (PLpro)/nsp3 is a multidomain transmembrane protein with an active site containing catalytic triad residues (Cys-111, His-272 and Asp-286) in between thumb and palm protein domains (Figure-8**).** This protein is autocleaved from nsp3 protein via its intrinsic proteolytic activity. PLpro can also perform deISGylation of host proteins which could lead to inhibition of host innate immune response [18, 40]. Due to its key role in viral replication and disease pathogenesis, it represents a promising drug target [52]. The docking score and the prediction of the molecular interactions showed that phytochemicals oleanolic acid, 3β-acetoxyolean-12-en-27-oic, and isovitexin could efficiently interact with the PLpro mainly by hydrogen bond [55]. Another study showed that catechins from green tea can interact to the S1 ubiquitin-binding site of PLpro which might lead to inhibition of its protease enzymatic function as well as abrogation of SARS-CoV-2 inhibitory role on interferon-stimulated gene system [18](Table 1**).**

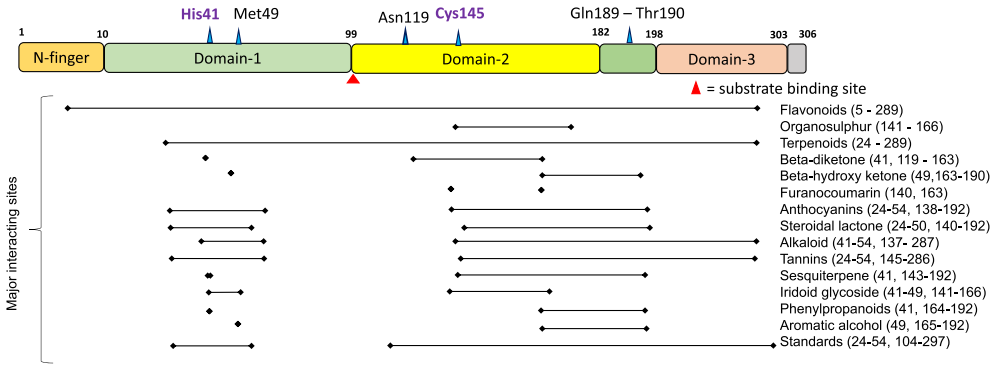

Fig. 9. The interaction sites of several classes of phytocompounds on different domains of SARS-CoV-2 3-chymotrypsin like protease (3CLpro) including the catalytic dyad residues (His-41 and Cys-145; shown in purple). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.) (3CLpro domain organization is adapted from Joshi et al., 2020 [40])

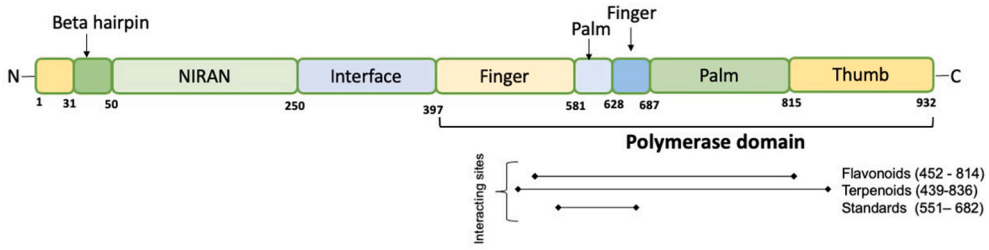

Fig. 10. Molecular structure of SARS-CoV-2 RNA dependent RNA polymerase (RdRp) and the interaction sites of flavonoids and and terpenoids on its different domains(protein domain organization is adapted from Zhang et al., 2020[120])

5.2. 3-chymotrypsin-like protease (3-CL pro)/nsp5

The 3CLpro, also called as viral main protease (or nsp5), consists of N-terminal finger domain (1–9 amino acids), domain-1 (10–99 amino acids), domain-2 (100–182 amino acids) and the C-terminal domain-3 (amino acid residues 198–303) [40,94]. The catalytic dyad consists of His-41 and Cys-145 (Fig. 9). The dimerization of 3-CLpro is required for its proteolytic activity.

In-silico screening followed by molecular docking analyses suggested that the phytochemicals bisdemethoxycurcumin, scutellarin, desmethoxycurcumin, quercetin, myricetin, luteolin and mundulinol could potentially inhibit 3-CL pro as these compounds exhibit low binding energy [25,73]. Another study recommended certain compounds such as catechin, naringenin, kaempferol, glucosides, quercetin, and epicatechin-gallate as potential inhibitors of 3CLpro [43]. The phytocompounds like melitric acid-A, salvianolic acid-A, withanoside-V, and a few bioactive compounds from *Calendula officinalis* showed higher binding affinities with 3-CLpro than the N3 and lopinavir (standards). Also, they could have important interactions with the amino acid residues of the catalytic dyad [20,21,24,56,84]. In another study, a database of medicinal plants consisting of more than 30,000 potential anti-viral phytochemicals was screened, and the top hits that could inhibit SARS-CoV-2 3CLpro function and viral RNA replication were selected. These hits include myricitrin, 5,7,3′,4′-tetrahydroxy2'-(3,3- dimethylallyl) isoflavone, methyl rosmarinate, (2S)-eriodictyol 7-O-(6″-O-galloyl)-beta-D-glucopyranoside, calceolarioside B, 3,5,7,3′, 4′,5′-hexahydroxy flavanone-3-O-beta-D-glucopyranoside, myricetin 3-O-beta-D-glucopyranoside, licoleafol, amaranthine, colistin, nelfinavir, and prulifloxacin [67]. Terpenoids (6-Oxoisoiguesterin and 22-hydroxyhopan-3-one) and some anthocyanin derivatives could stably interact with catalytic dyad and other crucial residues via hydrogen and hydrophobic interactions [27,31].Epigallocatechin, gallocatechin, and epicatechin from green tea also showed the potential to restrict the activity of 3-CL pro (Ghosh et al., 2020[101]). Similarly, several phytocompounds bind firmly at the catalytic dyad (Cys-145 and His-41) and other crucial amino acid residues (Phe-140, Leu-141, Asn-142, Gly-143, Ser-144, Glu-166, His-163, His-164, Met-165, Leu-167, Pro-168, His-172, Asp-187, Arg-188) of 3-CL pro via making hydrogen bonds, hydrophobic bonds and other interactions (like Pi-alkyl and Pi-Pi T-shaped, van der Waals etc). Phytocompounds extracted from *Avincennia officinalis* and Iranian medicinal plants have also been proposed as inhibitors of 3-CLpro [51,57]. Tanshinones, a class of natural phytocompounds have been found to inhibit 3-CLpro activity of SARS-CoV *in-vitro* enzymatic assay studies (Park et al., 2012[115]). Likewise, as listed in Table-1 and shown in Figure-9, several phytocompounds have ability to block 3-CLpro preferentially by interacting with its domain-1 and domain-2.

5.3. RNA dependent RNA polymerase/nsp12

With the help of accessory subunits nsp7 and nsp8, the catalytic subunit nsp12 of RdRp plays a crucial role in the transcription cycle of SARS-CoV-2 [88]. Its structure is highly similar to SARS-CoV. The nucleotide triphosphate (NTP) entry channel comprises positively charged amino acid residues Lys-545, Arg-553, and Arg-555. The right hand-like structure of the RdRp domain is further divided into a finger-domain (398–581 and 628–687 amino acids), a palm-domain (582–627 amino acids and 688–815 amino acids), and a thumb domain (816–919 amino acids). Two Zn ions are also required to stabilize three-dimensional structure of the RdRp [3,45] (Figure-10). Tyr-618, Asn-691, Met-755, Ile-756, Leu-757, Ser-759, Asp-760, Asp-761, Val-763, Phe-812, Cys-813 and Ser-814 are some of the amino acids residues that are crucial in interacting with the nsp7/8 complex. In addition, Asp-761 and Asp-762 are active site residues [3].

Several compounds have been analyzed *in-silico* against these important sites to investigate their possible antiviral viral targets for the SARS-CoV-2. Green tea polyphenols EGCG and theaflavin gallates including theaflavin-3-O-gallate (TF2a), theaflavin-3′-digallate (TF2b)

Table 2
Effect of phytocompounds on targeted SARS-CoV-2 proteins/replication/infection in cell-free and cell-based studies.

Sl no	Crude extract/compound	Virus/RNA/enzyme inhibition/cytotoxicity	Inhibitory assay	Dosage ($IC_{50}/EC_{50}/CC_{50}$)		References
Flavonoid						
01	Baicalein	3CLpro -	*Invitro*	IC_{50}	0.39 ± 0.11 μM	[50]
		SARS-CoV-2 replication	Vero cells	EC_{50}	2.92 ± 0.06 μM	[50]
		Cytotoxicity	Vero cells	CC_{50}	>500 μM	[50]
02	Baicalin	3CLpro	*In-vitro*	IC_{50}	83.4 ± 0.9 μM	[50]
03	Scutellarein	3CLpro	*In-vitro*	IC_{50}	5.80 ± 0.22 μM	[50]
04	Dihydromyricetin	3CLpro	*In-vitro*	IC_{50}	1.20 ± 0.09 μM	[50]
05	Quercetagetin	3CLpro	*In-vitro*	IC_{50}	1.24 ± 0.14 μM	[50]
06	Myricetin	3CLpro	*In-vitro*	IC_{50}	2.86 ± 0.23 μM	[50]
07	Baicalin	3CLpro (FRET)	*In-vitro*	IC_{50}	6.41 ± 0.95 μM	[78]
		Replication inhibition	Vero E6	EC_{50}	27.87 ± 12.95 μM	[78]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[78]
08	Baicalein	3CLpro (FRET)	*In-vitro*	IC_{50}	0.94 ± 0.20 μM	[78]
		Replication	Vero E6	EC_{50}	2.94 ± 1.19 μM	[78]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[78]
09	Theaflavin	3CLpro (FRET)	*In-vitro*	IC_{50}	8.44 μg/mL	[39]
		Cytotoxicity	HEK293T	CC_{50}	>40 μg/mL	[39]
10	Myricetin	3CLpro (FRET)	*In-vitro*	IC_{50}	0.2 μM	[107]
11	Baicalin	3CLpro (FRET)	*In-vitro*	IC_{50}	34.71 μM	[103]
12	Herbacetin	3CLpro (FRET)	*In-vitro*	IC_{50}	53.90 μM	[103]
13	Pectolinarin	3CLpro (FRET)	*In-vitro*	IC_{50}	51.64 μM	[103]
Terpenoids						
14	Glycycrrhizin (triterpenoid saponin)	3CLpro	*In-vitro*	IC_{50}	30 μM (0.024 mg/mL)	[86]
		Virus titer tit	Vero cells	$TCID_{50}$	0.44 mg/mL	[86]
		Cytotoxicity	Vero cells		4 mg/mL (no cytotoxicity)	[86]
15	Δ9-Tetrahydro cannabinol	Antiviral activity	Vero cells	EC_{50}	13.17 μM	[97]
		Cytotoxicity	Vero cells	CC_{50}	29.34 μM	[97]
16	Δ^9 -THC	Antiviral activity	Vero cells	EC_{50}	10.25 μM	[97]
		Cytotoxicity	Vero cells	CC_{50}	25.79 μM	[97]
17	CBN	Antiviral activity	Vero cells	EC_{50}	11.07 μM	[97]
		Cytotoxicity	Vero cells	CC_{50}	19.9 μM	[97]
18	CBD	Antiviral activity	Vero cells	EC_{50}	7.91 μM	[97]
		Cytotoxicity	Vero cells	CC_{50}	16.72 μM	[97]
19	CBDA	Antiviral activity	Vero cells	EC_{50}	37.61 μM	[97]
		Cytotoxicity	Vero cells	CC_{50}	59.53 μM	[97]
20	Andrographolide	SARS-CoV2 infection in-vitro	Vero E6	EC_{50}	6.58 μM	[42]
		Plaque reduction	Vero E6	EC_{50}	0.28 μM	
		Cytotoxicity		CC_{50}	27.77 μM	
21	Andrographolide	Plaque reduction	Calu-3 cells	EC_{50}	0.034 (μM)	[72]
		Cytotoxicity	a) HepG2	CC_{50}	a) 81.52 μM	
			b) imHC	CC_5	b) 44.55 μM	
			c) HK-2	CC_5	c) 34.11 μM	
			d) Caco-2	CC_5	d) 52.30 μM	
			e) Calu-3	CC_5	e) 58.03 μM	
			f) SH-SY5Y	CC_5	f) 13.19 μM	
22	Arteether (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	31.86 ± 4.72 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[14]
23	Artemether (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	73.80 ± 26.91 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[14]
24	Artemisic acid (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	>100 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[14]
25	Artemisinin (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	64.45 ± 2.58 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[14]
26	Artemisone (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	49.64 ± 1.85 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	>200 μM	[14]
27	Dihydroartemisinin (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	13.31 ± 1.24 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	31.44 ± 0.73 μM	[14]
28	Artesunate (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	12.98 ± 5.30 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	55.08 ± 2.32 μM	[14]
29	Arteannuin (sesquiterpene lactone)	SARS-CoV-2 infection	Vero E6	EC_{50}	10.28 ± 1.12 μM	[14]
		Cytotoxicity	Vero E6	CC_{50}	71.13 ± 2.50 μM	[14]
30	Cannabidinol	SARS-CoV-2 infection	Vero E6	CC_{50}	71.13 ± 2.50 μM	[14]
		Cytotoxicity	A549-ACE2	EC_{50}	1.25 μM (SARS CoV2γ)	[61]
					0.85 μM (SARS CoV2α)	
					0.86 μM (SARS CoV2β)	
					0.63 μM (SARS CoV2)	
Tannins						
31	Punicalin	RBD-ACE2 binding assay (ELISA)	In*vitro*	IC_{50}	0.14 mg/mL	[80]
32	Corilagin	SARS-CoV-2 inhibition	Vero	EC_{50}	0.13 μmol/L	[108]
33	Corilagin	RBD-ACE2 binding assay	*In-vitro*	IC_{50}	24.9 μM	[93]
34	Corilagin (RAI-S-37)	(ELISA)	HEK293 cell	CC_{50}	>100	[93]
35	Corilagin (RAI-S-37) +	Cytotoxicity	LO2 cells	CC_{50}	>100	

(*continued on next page*)

Table 2 (*continued*)

Sl no	Crude extract/compound	Virus/RNA/enzyme inhibition/cytotoxicity	Inhibitory assay	Dosage (IC_{50}/EC_{50}/CC_{50})		References
Flavonoid						
36	Remidesivir	Cytotoxicity	Beas-2B cell	CC_{50}	>100	[108]
37	Corilagin (RAI-S-37)	Cytotoxicity	HEK293 cell transfected	EC_{50}	3.33 ± 0.52 μmol/L	[108]
38	Corilagin (RAI-S-37)	SARS-CoV-2 RdRp inhibition	with nsp7 + nsp8 + nsp12	EC_{50}	1.25 ± 0.52 μmol/L	[108]
	Corilagin (RAI-S-37)	SARS-CoV-2 RdRp inhibition	HEK293 transfected with	EC_{50}	3.65 ± 0.56 μmol/L	[108]
		SARS-CoV-2 RdRp inhibition	nsp7 + nsp8 + nsp12	EC_{50}	1.84 ± 0.27 μmol/L	
		SARS-CoV-2 RdRp inhibition	HEK293 transfected with	EC_{50}	0.13 μmol/L	
		SARS-CoV-2 infection	nsp7 + nsp8+nsp12/ nsp10+nsp14 HEK293 transfected with nsp7 + nsp8+nsp12/ nsp10+nsp14 Vero cells			
39	EGCG	3CLpro (FRET)	*In-vitro*	IC_{50}	7.58 μg/mL	[39]
		Cytotoxicity	HEK293T	CC_{50}	>40 μg/mL	
Others						
40	Cepharanthine (alkaloid)	SARS-CoV2 infection	Vero cells	EC_{50}	2.8 μM	[38]
				CC_{50}	12.9 μM	
41	Emetine (alkaloid)	SARS-CoV2 infection	Vero cells	EC_{50}	0.000397 μM	[38]
				CC_{50}	1.53 e + 6 μM	
42	6-Gingerol (beta-hydroxy ketone)	SARS-CoV2 infection	Vero E6	EC_{50}	>100 μM	[42]
		Cytotxicity	Vero E6	CC_{50}	>100 μM	
43	Panduratin A (Diarylheptanoid)	SARS-CoV2 post infection	Vero E6	EC_{50}	0.81 μM	[42]
			Vero E6	CC_{50}	14.71 μM	
		SARS-CoV2 pre-entry	Vero E6	EC_{50}	5.30 μM	
			Vero E6	CC_{50}	43.47 μM	
		Plaque reduction	Vero E6	EC_{50}	0.078 μM	
		SARS-CoV2 infection	Calu3	EC_{50}	2.04 μM	
		Cytotoxicity	Calu3	CC_{50}	43.92 μM	
		Plaque reduction	Calu3	EC_{50}	0.53 μM	
44	Emetine hydrochloride (alkaloid)	SARS-CoV-2 virus reduction	Vero E6	EC_{50}	0.46 μM	[111]
		CPE inhibition	Vero E6	EC_{50}	1.5625 μM	[111]
		Cytotoxicity	Vero E6	CC_{50}	56.46 μM	[111]
45	Phillyrin (KD-1) Lignan)	Anti-HCoV-229E	Vero E6	EC_{50}	64.53 μg/ml	[113]
		Cytopathic effect	Vero E6	EC_{50}	63.90 μg/ml	[113]
		Cytotoxicity	Vero E6	CC_{50}	1959 μg/ml	[113]
			Huh7	CC_{50}	1034 μg/ml	[113]
		Reduce the production of proinflammatory cytokines	Vero E6	–CPE (cytopathic effect)	(250, 125, and 62.5 μg/ml of KD1) TNF-α, IL-6, IL-1β, MCP-1, and IP-10) at the mRNA levels.	[113]
46	Cepharanthine (bisbenzylisoquinoline	SARS-CoV-2 RNA	VeroE6/TMPRSS2	EC_{50}	0.35 μM,	[114]
		Cytotoxicity	VeroE6/TMPRSS2	CC_{50}	25.1 μM	[114]
47	alkaloid) Lycorine (alkaloid)	SARS-CoV-2 infection	Vero cells	EC_{50}	0.878 μM	[112]
48	Digoxin (cardiotonic glycoside)	SARS-CoV-2 infection	Vero cells	EC_{50}	0.043 μM	[110]
		Cytotoxicity	Vero cells	CC_{50}	>10 μM	[110]
49	Ouabain (Cardiac glycoside similar to digitoxin)	SARS-CoV-2 infection	Vero cells	EC_{50}	0.024 μM	[110]
		Cytotoxicity	Vero cells	CC_{50}	>10 μM	[110]
50	Herbacetin	3CLpro (FRET)		IC_{50}	33.17 μM	[71]
51	Pectolinarin	3Clpro (FRET)	in-vitro	IC_{50}	27.45 μM	
52	Rhoifolin	3CLLpro (FRET)	in-vitro in-vitro	IC_{50}	37.78 μM	
Crude extracts						
53	*Andrographis paniculata* extract	SARS-CoV2 infection	Vero E6	EC_{50}	68.06 μg/ml	[42]
		Cytotoxicity		CC_{50}	>100 μg/ml	
54	*Andrographis paniculata* extract	Plaque assay	Calu-3 cells	EC_{50}	0.036 (μg/mL)	[72]
55	*Zingiber officinale* rhizome extract	Inhibition of SARS-CoV2 infection	Vero E6	EC_{50}	29.19 μg/ml	[42]
		Cytotoxicity	Vero cells	CC_{50}	52.75 μg/ml	
		Plaque reduction	Vero cells	EC_{50}	1.45 μg/ml	
56	*Boesenbergia rotunda* (extract)	SARS-CoV2 infection	Vero cells	EC_{50}	3.62 μg/mL	[42]
			Vero cells	CC_{50}	28.06 μg/mL	
57	*Scutellaria baicalensis* extract	3CLpro assay	*In-vitro*	IC_{50}	8.52 ± 0.54 μg/mL	[50]
58	Pomegranate peel extract	SARS CoV2 RNA replication	Vero cells	EC_{50}	0.74 ± 0.36 μg/mL	[50]
		Cytotoxicity	Vero cells	CC_{50}	>500 μg/mL	
		RBD-ACE2 binding assay (ELISA)	*In-vitro*	IC_{50}	0.06 mg/mL	[80]

and theaflavin 3,3′-digallate (TF3) have the ability to form stable bound conformations with the RdRp protein and could interact with the catalytic site indicating their potential to serve as inhibitors [81].

Several alkaloids from *Argemone mexicana* and *Clerodendrum* spp. could be a potential inhibitory candidates against the SARS-CoV-2 RdRp protein [41,62] **(**Table-1**).**

5.4. RNA helicase (nsp13)

It is a multi-functional magnesium ion-dependent protein that belongs to the helicase superfamily-1 (SF-1) and has 5′ to 3' based RNA and DNA unwinding activities [121]. Compounds such as tomentodiplacone-B, sesquiterpene glycoside, rhamnetin, osajin, and silydianin have been shown to exhibit better docking results than those of remdesivir, nelfinavir, and prulifloxacin (standards) [46] **(Table-1).**

5.5. Endoribonuclease/nsp15

Endoribonuclease/nsp15 cleaves RNA genome into multiple subgenomic RNAs (sgRNAs). Based on the docking score, phytocompounds asparoside-C, asparoside-D, asparoside-F, racemoside-A, and rutin (from *Asparagus racemosus*) were found to be effective against nsp15 endoribonuclease [16]. The 100 nano-second based molecular dynamic simulation study and molecular mechanics-generalized born solvent accessibility calculations demonstrated that some phytoconstituents such as withanolide-N, ashwagandanolide, withanoside-X, and dihydrowithaferin-A from *Withania somnifera* could potentially suppress the nsp15 endoribonuclease activity of SARS-CoV-2 [17]. Another study revealed the binding capacity of silymarin, sarsasapogenin, ursonic acid, rosmarinic acid, curcumin, ajmalicine, novobiocin, aranotin, gingerol, and alpha terpinyl acetate to nsp15 protein [106].

5.6. 2′-O-methyltransferase (2′-O-MTase)/nsp16

This is a highly conserved protein of coronaviruses. It is known to play an essential role in viral replication and evasion of host cell innate immunity [64]. Phytocompounds like eryvarin-M, osajin, raddeanine, and silydianin have been found to exhibit the best docking results [46] (Table-1).

6. SARS-CoV-2 assembly inhibitors

Structural proteins, membrane, envelope and nucleocapsid, play essential roles in the assembly and formation of the infectious virion particles. Therefore, targeting these proteins could be a promising approach to inhibit virus multiplication and transmission.

6.1. Envelope protein

E protein (8–12 kDa) is involved in host cell binding, penetration, virion assembly, and budding. It is a transmembrane ion channel protein with an N-terminal ectodomain and an endodomain at C-terminus. Structural insights revealed that compounds from *Withania somnifera* could block the ion channel activity of E protein by binding to the pore region [5].

6.2. Nucleocapsid protein

N protein is a 419 amino acid protein with conserved N-terminal domain (NTD), Serine/Arginine rich motif (SR) domain, central linker region, and a C-terminal domain (CTD). It plays an essential role in viral genome packaging and efficient replication. The N protein is highly immunogenic and is produced in high amounts during infection [22,96].

An *in-silico* screening study revealed emodin, anthrarufin, alizarine, aloe-emodin, and dantron as phytocompounds with good binding affinity with the N-terminal domain of N protein. ADMET prediction revealed that anthrarufin, emodin, aloe-emodin, alizarine, and dantron could be potential candidate drugs to treat COVID-19 [69].

7. *In vitro* and *in vivo* anti-SARS-CoV-2 activities of plant-derived compounds

Plant-based polyphenols (such as phenolic acids, anthocyanins, lignans, flavonoids, and stilbenes) and carotenoids (such as xanthophylls and carotenes) are being used to generate antivirals against various coronaviruses. Recent data on plant-derived compounds showed their potent and significant SARS-CoV-2 inhibition activity *in-vitro* and *in-vivo*. A comprehensive study, conducted by Jia-Tsrong Jan et al., screened 190 supplements as well as traditional medicines from Chinese herbs to identify the SARS-CoV-2 infection inhibitors *in-vitro* in Vero-E6 cells. *in-vitro* enzymatic assays were coupled with *in-silico* modelling to confirm the antiviral activity against SARS-CoV-2 protease and RNA-dependent-RNA-polymerase (Jan et al., 2021). Further, the efficacy of these promising compounds was tested in a hamster challenge model. This study identified the anti-SARS-CoV-2 activity in nelfinavir, *Perilla frutescens*, mefloquine, and *Mentha haplocalyx* [38]. This observation is very encouraging and warrants an urgent need for testing several other potent phytocompounds in small animal models to speed up the process of developing COVID-19 therapeutics.

A wide range of natural compounds has been proposed to be used in treating COVID-19(either alone or in combination with FDA-approved drugs) including ginkgolic acid, shiraiachrome A, resveratrol, and baicalein. Moreover, ginkgolic acid is a specific covalent inhibitor of SARS-CoV-2 cysteine proteases, targeting PLpro and 3-CLpro *in-vitro* [93]; and [15] (please refer Table 2 and 3 for antiviral and immunomodulatory functions of small molecule inhibitors).

In another study, 122 Thai natural products for anti-SARS-CoV-2 activity were screened using fluorescence-based nucleoprotein detection combined with viral plaque reduction assay. This work showed that the extract of Boesenbergia rotunda and its phytochemical compound, panduratin A reduce SARS-CoV-2 infectivity in Vero E6 cells at pre-entry and post-infection phases [42]. Artemisinin B, an antimalarial drug derived from Chinese herbs, also showed anti-SARS-CoV-2 in these cells by blocking SARS-CoV-2 at the post-entry level [14].

Anti-SARS-CoV-2 activity evaluation of *Andrographis paniculata* extract and Andrographolide in human lung epithelial-carcinoma cell-line (Calu-3) using a high-content imaging platform in combination with plaque reduction assay showed potent inhibition of SARS-CoV-2 infection with minimal cytotoxicity [72]).

In another study, Glycyrrhizin showed potential antiviral activity against SARS-CoV-2 by inhibiting the viral 3-CL pro that is essential for viral replication [86]. Similarly, several other plant-derived compounds including tea polyphenols EGCG, theaflavin, baicalein, and shuanghuanglian inhibit 3-CLpro activity and the viral replication in Vero E6 cell line [39,50,78]. Overall, the potent antiviral and anti-inflammatory activities of plant-derived compounds further warrants need of developing phytochemical-based SARS-CoV-2 treatment options.

Table 3
Effect of small molecule inhibitors on host factors as well as on different cytokines (immunomodulatory functions)

Sl no	Compound/ plant	Properties	Biological/immune-action	Studies in *In-vivo* models	References
01	Quercetin	Impacts on ACE2 and Furin	a) Gene silencing b) Expression studies c) Transgenic mouse models	Quercetin affected ACE2 expression. In addition, it was found that it could alter the expression of 98 of 332 (30%) genes which encode human proteins that serve as target for the SARS-CoV-2	[29]
02	citral and lemon grass	anti-inflammatory action	Inhibits IL-6, IL-10, TNF-α, IL-4, IFNϒ and IL-1β, either release or production and NLRP3 inflammasome activation via blocking activites of proteins, NF-kB,p65, ATP-induced caspase-1	In macrophages challenges with LPS-induced mouse ASLN model	[98,104]
03	Ginsenoside	anti-inflammatory action	Down-regulates IL-6, TNF-α, mRNA expression via blocking the activation of NF-kB	II/R induced lung injury *in-vivo*	[102]
04	Withaferin-A	Immunosuppressant	Affect the release of TNF-α, IL-1α, IL-1β, IL-5, IL-3, IL-6, IL-8, IP-10, CCL2, MCP-1, SDF-1α, MIP-1α, MIP-1β and GM-CSF.	ATP-stimulated monocyte-derived THP-1 cells. Also mouse and human islet cells – *in vitro.*	[77,99]
05	Kaempferol	anti-inflammatory action	TNF-α, IL-1β, IL-6, IL-8 via inhibiting the activation of PKC θ	human mast cells	[105]
06	EGCG	Regulation of cytokine driven signaling pathways	Downregulating the IL-6 and IL-6 driven JAK-STAT pathway Similarly by affecting IL-1 driven MAPK pathway Reduced the protein levels of the receptors including CD11a, CXCR3, and CCR2 in human T-lymphocyte cells	Primary human melanocytes, human T cells or purified $CD8^+$ T cells from PBMC	[18,60]
		–	Prevents the cytokine storm and mucous hypersecretion in COVID-19		[81]
07	Cannabidol	anti-inflammatory and immunosuppressive	These effects are mediated by inhibition of pro-inflammatory cytokine release (e.g. tumor necrosis factor-a, Interferon-gamma, IL-1b, IL-6, and IL-17) and stimulation of several anti-inflammatory cytokine production (e.g. IL-4, IL-5, IL-10, and IL-13).	COVID 19 Patients	https://clinicaltrials.gov/ct2/show/NCT04731116
08	F_{THC}		Only low anti-inflammatory activity	Epithelial cancer cell lines (A549)	[6]
09	F_{CBD}		showed reduction of IL-6 and IL-8 secretion levels from lung epithelial cells with an IC50 values of 3.45 and 3.49 μg/mL respectively.	Epithelial cancer cell lines (A549)	[6]

7.1. Clinical evaluation of plant-based therapeutics

In-depth systemic randomized and non-randomized ongoing clinical trials of single plant species (*Tinospora cordifolia*, *Nigella sativa*, *Boswellia serrata*, Acai Palm Berry, *Caesalpinia spinosa*, *Cinchona/Stevia*, *Cannabis* sp, Brazilian Green Propolis), plant-based bioactive compounds (EGCG, quercetin, silymarin, hesperidin, escin, colchicine, resveratrol, cannabidiol, melatonin etc.), as well as poly-herbal formulations (ArtemiC, Drug – ADAPT-232, Dietary supplement: Inflammation-I, Inflammation-II, Inflammation-III, Tomeka, Shanshamani Vati Plus, Dietary Supplement: QuadraMune (TM), Ayurvedic formulation, Dietary Supplement: Cretan IAMA, Individualized-Chinese herbal medicine) showed their potential to interfere with COVID-19 pathogenesis via inhibiting virus replication, virus-mediated pneumonia as well as inmmune dysregulation such as cytokine storming **(**Supplementary Table**).** Certain anti-inflammatory herbal medicines from *Andrographis paniculata, Citrus* spp, and *Cuminum cyminum* can relieve fever and cough in COVID-19 patients [37]). Few other medicinal plants such as *Glycyrrhiza glabra, Thymus vulgaris, Allium sativum, Althea officinalis, Panax ginseng* and constituents of *Camellia sinensis* may modulate the immune system and provide supportive therapy against COVID-19 via upregulating levels of interleukins (IL-1α, IL-1β), monocytes, and lymphocytes in patients [4, 37]. Apart from these, green tea polyphenols can prevent airway blockage by reducing mucin hypersecretion, a phenomenon seen in COVID-19 patients [81]. Moreover, several plant species act as good source of expectorants as they can elevate the water contents of respiratory mucus or diluent of mucus and thus also contributing towards prohibiting airway blockage [26,44].

8. Conclusions

Since December 2019, SARS-CoV-2 infection and transmission have been a huge concern worldwide. Currently available therapies inhibit SARS-CoV-2, however, they could be associated with severe side effects as well as drug-nutrition interactions which could be harmful to severely infected patients.

On other hand, the complementary approach including plant-derived compounds could be used in controlling COVID-19 in the future. Our review herein presented a compilation of *in-silico, in-vitro,* cell culture , and *in-vivo* studies on numerous plants, plant formulations,

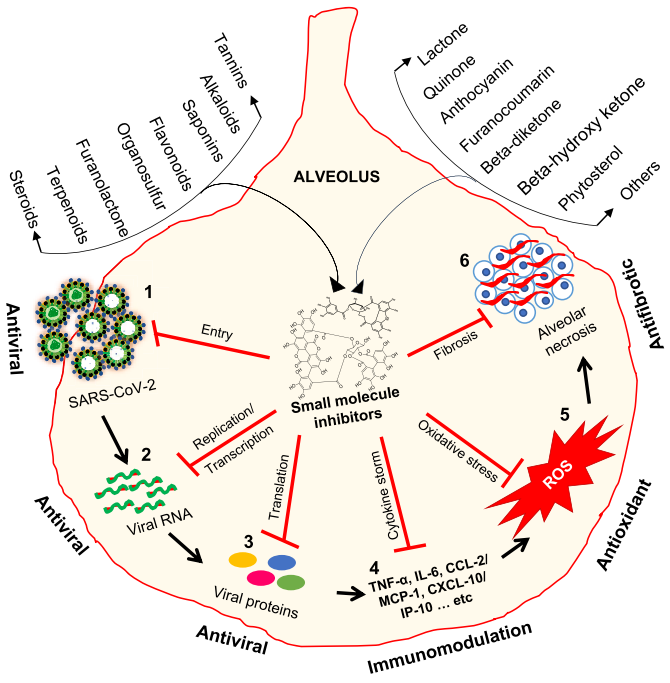

Fig. 11. The possible multifaceted roles of plant-derived small molecules in inhibiting SARS-CoV-2 mediated lung damage caused by viral replication and its related pathological consequences.

and their bioactive constituents that may block the life cycle of SARS-CoV-2 in all possible ways. Beyond the antiviral functions, plant-derived therapeutic drugs show diverse pharmacological actions (such as anti-inflammatory, antioxidant, anti-fibrotic activities), the remarkable tolerance, stability in the systemic circulation which could offer a greater advantage in reducing the risk of COVID-19 induced pathogenesis without much of side effects (Fig. 11). As a proof of concept, certain plant-based therapeutics are under different phases of clinical trials.

Taken together, this review article provides a summary of diverse mechanisms of action of plant-based therapeutics to mitigate COVID-19. The knowledge obtained here could be applied to further understand the COVID-19 replication cycle and related antiviral mechanisms.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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CRediT authorship contribution statement

B. Uma Reddy: Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Nanda Kishore Routhu:** Writing – review & editing, Writing – original draft. **Anuj Kumar:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing.

Data availability

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Appendix A. Supplementary data

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