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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
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 (nsp5). Whereas the accessory and structural proteins are encoded by the remaining ORFs (adapted from Kim et al., 2020[116] with some modifications).
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). sgRNA translation results in both structural proteins and 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 the potential drug

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.

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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 to host cell surface-specific receptors and virus-cell membrane fusion.

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 daturaoaline, 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-likeness 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 punica galin and punicalin (from Pomegranate), tenufolin, cinnamtannin-B1, proanthocyanidin-A2 and Kaempferol-3-alpha-pavetannin-C1, 6-glucopyranosyl procyanidin B1, procyanidin-B7, and are dis

**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]).
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).
### 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), puniglucin (7-HB, 5- NBI and -7.9 BE), cebulagic acid (5-HB, 5-NBI and -7.5 BE), cebulenic acid (5-HB, 7-NBI and -6.5 BE), cinnamannin-B1 (3-HB, 5-HP and -10.2 BE), 6-Glucopyranosyl prenylnanin-B1 (8-HB, 1-EI and -9.9 BE), Prenyl derivatives (2-HB, 3-HP, 2-EI and -9.6 BE), proanthocyanidin-A2 (5-Hb, 1-HP, 2-EI and -9.4 BE), ellagic acid (3 IR and -6.114 BE), gallic acid (2 IR and -4.808 BE), gallicotannins (6-HB, 7-NBI and -7.4 BE). | Ser44, Leu48, Ala292,Cys301, Leu303, Ile312, Tyr313, Thr315, Asn317, Phe318, Arg319, His345, Thr347, Asa434, | [12,47,56,57,25,66] |
| Terpenoids | Geraniol (2-HB and 5-1.0 BE), L-4-terpeniol (2-HB and 5.1 BE), carvacrol (1-HB and -5.2 BE), limone (12-HPI and -5.1 BE), thymol (5.4 BE), tinosporide (2HB, 6-NBI and -6.4 BE), taxaritol (7-NBI and -7.9 BE), daturaine (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), Y-typine (-4.9 BE), o-typine (-5.0 BE), camphene (2-HP and -5.2 BE), camphor (2-HPI and -4.8 BE). | Leu73, Arg350, Thr385, Phe390, Arg403, Arg405, Glu406, Arg408, Glu409, Gly416, Ile417, Ile449, Ile452, Tyr453, Leu455, Phe456, Ile458, Ser459, Leu461, Ille468, Thr470, Ille472, Glu484, Tyr489, Phe490, Pro491, Leu492, Glu493, Ser494, Tyr495, Gly496, Arg501, Tyr505, Asp509, Arg514, Tyr515, Lys562, Lys564, Pro565 | [47,56,66] |
| Flavonoids | Paveatannin-C1 (9-HB, 4-HP, 1-EI and -11.1 BE), hesperidin (5 IR and -8.99), chrysin (9 IR and -8.79), quercetin (3 O, 5-3 arabinofuranoside (5-HB, 6-NBI and -7.9 BE), kaempferol 3-alpha-L-arabinofuranose 7-hamnoside (7-HB, 2-HPI and -8.7 BE), catechin gallate (5 HB, 3 H and -6.1 BE), cinnamaldehyde (2 HB and -5.0 BE), Anthranol (1 HB, 2 H and -9.08 BE), Apigenin (5 HB and -10.09 BE), Derrisin (2 HB, 2 HP and -11.04 BE), Ile468, Thr470, Ile472, Glu484, Tyr489, Phe490, Pro491, Leu492, Glu493, Ser494, Tyr495, Gly496, Arg501, Tyr505, Asp509, Arg514, Tyr515, Lys562, Lys564, Pro565 | Ser44, Leu48, Ala292,Cys301, Leu303, Ile312, Tyr313, Thr315, Asn317, Phe318, Arg319, His345, Thr347, Asa434, | [12,47,56,57,25,66] |

#### References

1. [56,66,79]
2. [79]
3. [16]
| Class          | Small molecule inhibitors                                                                 | Interacting residues with different classes of phytocompounds                                                                 | References |
|----------------|-------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------|
| Flavonoid      | Hesperidin (4 IR and –1.167 BE), chrysins (3 IR and –7.146 BE), rutin (6 IR and –3.41 BE), | Th2r, Lys31, His34, Glu35, Glu37, Asp38, Glu42, Asn63, Thr125, Ile126, Thr129, Asn137, Pro138, Gly139, Lys353 | [12,100]   |
|                | vitexin (7 IR and –5.71 BE), apigenin (5 IR and –3.75 BE), quercetin (5 IR and –4.11 BE)   |                                                                              |            |
| Quinone        | Emodin (3 IR and –9.83 BE), Rhein (-7.423 BE)                                               |                                                                              |            |
| Terpenoid      | Thymol and isothymol (1 H-donor and –4.74 BE), m-eugenol (4 IR and –2.53 BE), carvacrol (7 |                                                                              | [1,87,100] |
|                | IR and –2.75 BE), (7 IR and –3.31 BE), cinnamaldehyde (4 IR and –4.0 BE), cinnamoyl (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), pathulenol (6 IR and –4.96 BE), vetiverol (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), linoic acid (6 IR and –2.07 BE), |                                                                              |            |
|                | p-coumaric acid (4 HB, 2 Pi-Alkyl, 1 CHB, 7 VDW and –8.0 BE), 5-hydroxy-2,4-dimethyl-|                                                                              |            |
|                | 3,7-dimethoxy-3H-pyrrole (4 HB; 11 HP and –10.86 BE), caffeic acid (5 HB, 11 CHB, 6 |                                                                              |            |
|                | VDW and –7.72 BE), ursofolic acid (3 HB, 1 Pi-Alkyl, 6 VDW and –8.0 BE), ellagic acid (4 |                                                                              |            |
|                | HB, 3 Alkyl/Pi-Alkyl, 1 Pi-Sigma, 1 CHB, 7 VDW and –7.3 BE), 8-vinyl-2H-chromen-2-one (2 |                                                                              |            |
|                | Alkyl/Pi-Alkyl, 1 Pi-Sigma, 2 VDW and –8.0 BE), 5,7-dimethoxypiperonal (5 IR and –5.08 BE), |                                                                              |            |
|                | and 5-hydroxy-6-methyl-2H-chromen-2-one (5 IR and –3.44 BE)                                |                                                                              |            |
| Standards      | Asp30, Lys31, Asn33, His34, Glu35, Glu37, Asp38, Phe40, Asp350, Lys353, Pro389, Phe390,     | His34, Glu37, Thr276, Asn290, Ile291, Met366, Asp367, Leu370, Glu388, Pro389, Asp393, Lys403, Gly406, Ser409, | [100]      |
|                | Arg393, Arg405, Val490, Trp495, Tyr495, Gly496, Tyr565                                     | Leu410, Ala413, Lys441, Thr445, Ser494, Tyr495, Gly496, Tyr565                                                             |            |
| Alkaloids      | Pettitorine (5 IR and –3.4 BE), vacinine (5 IR and –6.21 BE), piperidine (9 IR and –4.31 BE), |                                                                              |            |
|                | piperine (5 IR and –4.1 BE)                                                                |                                                                              | [10,79]    |
| Standards      | Minapin (9 IR and –7.5 BE), umifinovir (7 IR and –6.5 BE), 5-hydroxy-2H-chromen-2-one (10  |                                                                              |            |
|                | IR and –7.1 BE)                                                                            |                                                                              |            |
| TMRPSS2 (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 | Arg87, Ala88, Arg91, Asp90, Arg259, Asp395, Lys399, Arg405, Gly408                                                          | [79]       |
| Steroidal lactone | Withanifer-1 (2 HB, 19 IR and –5.60 BE), Withanone (1 HB; 18 HP and –4.30 BE)               | His296, Glu299, Tyr327, Lys342, Glu389, Asp435, Ser436, Cys347, Gln338, Asp440, Ser441, Arg393, Arg405, Val490,     | [49]       |
| Caffeate ester | Caffeic acid phenethyl ester (2 HB; 17 HP and –6.20 BE)                                     | Gln389, Asp440, Ser441, Ser442, Gln347, Gly348, Gln389, Asp440, Ser441, Thr445, Val370, Gly462, Val473, Gly464,       | [49]       |
| Standards      | Camostat (5 IR and –7.069 BE), Camostat mesylate (1 HB and 20 HPI and –5.95 BE)            | Gln347, Gly348, Gln389, Asp440, Ser441, Thr445, Val370, Gly462, Val473, Gly464, Val473, Gly465, Gly466,                | [49]       |
| Furin (host protein) |                                                                                         | Gln389, Asp440, Ser441, Thr445, Val370, Gly462, Val473, Gly464, Val473, Gly465, Gly466,                | [49]       |
| Class          | Small molecule inhibitors                                                                 | Interacting residues with different classes of phytocompounds                                                                 | References |
| Tannins        | Punicalin (7 IR and –9.725 BE), punicalagin (4 IR and –9.385 BE), ellagic acid (5 IR and | His100, Glu255, Pro256, Pro256, Glu257, Asp258, Asp259, Thr262, Arg298, Cys303, Asp306, Gly307, Ser311, Gly366, | [79]       |
| Standards      | (5 IR and –7.801 BE)                                                                       | Ser368, Thr365, Arg490, Trp531, Ala532, Val263, Phe528, Trp531, Ala532                                                     |            |
| Papain-like protease/ns3 (viral protease) |                                                                                         |                                                                              | [55]       |
| Class          | Small molecule inhibitors                                                                 | Interacting residues with different classes of phytocompounds                                                                 | References |
| Terpenoid, Flavonoid | Oleesinolic acid (4 IR and –10 BE), ursofolic acid (5 IR and –9.7 BE), 3p- | His89, Thr106, Ala107, Asp108, Asn109, Val159, Gly160, Gu161, Leu162, Pro248, Tyr264                           | [20,57,66,67,73,109] |
| Flavonoid      | Epigallocatechin (6 IR and –7.0 BE), gallolatechin (6 IR and –7.1 BE), catechin (6 IR and | Lys5, Thr24, Thr25, Thr26, Leu27, His41, Cys44, Thr45, Ser46, Met49, Tyr53, Tyr54, Pro108, Lys137, Phe410, Leu41, |            |
|                | –7.1 BE), epicatechin (6 IR and –7.2 BE), catechin gallate (6 IR and –7.2 BE), epigallocatechin | Arg345, Asp404, Ser441, Arg393, Arg405, Val490, Trp495, Tyr495, Gly496, Tyr565, Arg490, Trp531, Ala532, Val263, |            |
|                | gallate (9 IR and –7.6 BE), epicatechin gallate (10 IR and –8.2 BE), gallolatechin (3-| Arg298, Cys303, Asp306, Gly307, Ser311, Gly366, Ser368, Thr365, Arg490, Trp531, Ala532, Val263, Phe528, Trp531, Ala532 |            |
|                | gallate (9 IR and –9.0 BE), kaempferol (4 HB, 6 HPI and –8.58 BE), querectin (8 IR and | (continued on next page)                                                                                                      |            |
Table 1 (continued)

| Compounds                                                   | X-ray Localization |
|--------------------------------------------------------------|-------------------|
| **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-dithiolo (6H-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 −13.26 BE), trisulfide, 2-propanol propyl (5 IR and −14.36 BE), methyl allyl disulfide (3 IR and −13.56 BE), diacetoalkol (2 IR and −13.26 BE); trisulfide, (E)-1-propenyl 2-propenyl (2 IR and −12.00 BE); (1Z)-1-propenyl 2-propenyl (1 IR and −11.68 BE); |                   |
| **Terpenoids**                                               |                   |
| Glyceryl acid (4 H, 3 CH3, 12 DVA and −8.7 BE), 6-oxoisoquercetin (5 IR and −9.1 BE), daturaolone (10 NBI and −7.3 BE), glyceryl acid (7 H, 7 NBI and −8.2 BE), calenduloside B (16 IR and −8.2 BE), calenduloside B (15 IR and −7.9), tenuifolin (6 H, HP-2 and 8.8 BE), 7-Deacetyl-7-benzoylgedunin L (1 CHB, 2 H, 10 DVA, 1 PiPi T shaped, 1 allyl, 1 Pi-allyl, −9.1), glyceryl acid (4 H, 3 CHB, 12 DVA, −8.7), isinomin: 3 H, 1 pi-donor, 1 CHB, 4 DVA, −8.7), Obacunone (3 H, 1 pi-donor, 1 pi-allyl, 5 DVA, −7.5), Dihydrooartemisinin (2 H, 2A, 1 Pi and −7.0 BE) |                   |
| **Sesquiterpene**                                           |                   |
| Bdeakimacetin (2 H, 5 HBP and −8.6 BE), Samarcandin (3 H, 2 HP and −8.5 BE) |                   |
| 3-Deacetyl-7-benzoylgedunin L (1 CHB, 2 H, 10 DVA, 1 PiPi T shaped, 1 allyl, 1 Pi-allyl, −9.1), glyceryl acid (4 H, 3 CHB, 12 DVA, −8.7), isinomin: 3 H, 1 pi-donor, 1 CHB, 4 DVA, −8.7), Obacunone (3 H, 1 pi-donor, 1 pi-allyl, 5 DVA, −7.5), Dihydrooartemisinin (2 H, 2A, 1 Pi and −7.0 BE) |                   |
| Leu141, Asl142, Gly143, Ser144, Cys145, His163, Met165, Glu166 | [82]             |
| Leu141, Asl142, Gly143, Ser144, Cys145, His163, Met165, Glu166, Leu167, Pro168, His172, Asp187, Arg186, Glu189, Thr190, Ala191, Tyr239, Leu275, Leu286, Leu287 | [21,31,51,56,87] |
| **Furano coumarin**                                         |                   |
| Bergapten (5-methoxyxaraalen) (2 IR and −5.98 BE)            |                   |
| **Anthocyanins**                                            |                   |
| Delphinidin 3-Sambubioside-5-Glucoside (27 IR and −12.37 BE); |                   |
| Delphinidin 3,3′-Di-Glucoside (5-0-Coumarilglycoside) (28 IR |                   |
| and −11.59 BE), 2-(3,4,5-Trihydroxyphenyl)-3-[6-(3-H-Dihydroxy |                   |
| phenyl) beta-galactopyranosyl-5,7-dihydroxy-1- |                   |
| Zingerol (5 H and −5.40 BE) and gerrinol (5 IR and −5.38 BE)  |                   |
| Met49, His163, Met165, Glu166, Pro168, Asp187, Arg188, Glu189, Thr190 | [43]             |
| Phenol40, Gly138, Ser139, Phe40, Leu41, Ser44, Cys45, His163, Met165, Glu166, Leu167, Pro168, Gly170, His172, Val186, Asp187, Arg188, Glu189, Thr190, Ala191, Glu192 | [73]             |
| **Iridoid glycoside**                                       |                   |
| Harpagoside (3 H, 3 HP and −6.1 BE)                          |                   |
| **Beta-diketone**                                           |                   |
| demethoxycurcumin (1 IR and −7.02 BE), curcumin (2 IR and −6.04 BE), bisdemethoxycurcumin (5 IR and −7.3 BE) |                   |
| Met49, His163, Met165, Glu166, Pro168, Asp187, Arg188, Glu189, Thr190 | [43]             |
| **Beta-hydroxy ketone**                                     |                   |
| Zingerol (5 H and −5.40 BE) and gerrinol (5 IR and −5.38 BE)  |                   |
| Phe40, His163 | [73]             |
| **Iridoid glycoside**                                       |                   |
| Harpagoside (3 H, 3 HP and −6.1 BE)                          |                   |
| **Beta-diketone**                                           |                   |
| demethoxycurcumin (1 IR and −7.02 BE), curcumin (2 IR and −6.04 BE), bisdemethoxycurcumin (5 IR and −7.3 BE) |                   |
| Met49, His163, Met165, Glu166, Pro168, Asp187, Arg188, Glu189, Thr190 | [43]             |
| **Furano coumarin**                                         |                   |
| Bergapten (5-methoxyxaraalen) (2 IR and −5.98 BE)            |                   |
| **Anthocyanins**                                            |                   |
| Delphinidin 3-Sambubioside-5-Glucoside (27 IR and −12.37 BE); |                   |
| Delphinidin 3,3′-Di-Glucoside (5-0-Coumarilglycoside) (28 IR |                   |
| and −11.59 BE), 2-(3,4,5-Trihydroxyphenyl)-3-[6-(3-H-Dihydroxy |                   |
| phenyl) beta-galactopyranosyl-5,7-dihydroxy-1- |                   |
| Zingerol (5 H and −5.40 BE) and gerrinol (5 IR and −5.38 BE)  |                   |
| Met49, His163, Met165, Glu166, Pro168, Asp187, Arg188, Glu189, Thr190 | [43]             |
| Phenol40, Gly138, Ser139, Phe40, Leu41, Ser44, Cys45, His163, Met165, Glu166, Leu167, Pro168, Gly170, His172, Val186, Asp187, Arg188, Glu189, Thr190, Ala191, Glu192 | [73]             |
| **Iridoid glycoside**                                       |                   |
| Harpagoside (3 H, 3 HP and −6.1 BE)                          |                   |
| **Beta-diketone**                                           |                   |
| demethoxycurcumin (1 IR and −7.02 BE), curcumin (2 IR and −6.04 BE), bisdemethoxycurcumin (5 IR and −7.3 BE) |                   |
| Met49, His163, Met165, Glu166, Pro168, Asp187, Arg188, Glu189, Thr190 | [43]             |
| Phenol40, Gly138, Ser139, Phe40, Leu41, Ser44, Cys45, His163, Met165, Glu166, Leu167, Pro168, Gly170, His172, Val186, Asp187, Arg188, Glu189, Thr190, Ala191, Glu192 | [73]             |
Table 1 (continued)

| Class                              | Small molecule inhibitors                                                                 | Interacting residues with different classes of phytochemicals                                                                 | References |
|-----------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------|
| **Flavonoid**                      | Theaflavin (8 HB, 2 PA and -9.1 BE), quercetin-3-O- (rutina) (9 HB, 1 PA 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 Pal and -7.4 BE), kaempferol-3′-O-rutinoside (4 HB, 2 PA and -9.2 BE), kaempferol-4′-O-galloylglucoside (6 HB, 1 PC and -8.3 BE), kaempferol-3′-O-glucuronide (6 HB, 2 PA and -7.9 BE), kaempferol-7′-O-glucuronide (6 HB, 1 PC and -7.9 BE), kaempferol-7′-O-sulfate (6 HB, 2 PA and -7.3 BE), kaempferol-4′-O-sulfate (1 HB, 2 PA and -6.7 BE), kaempferol-3-0-sulfate (1 HB, 2 PA and -6.7 BE), kaempferol (2 HB, 2 Pal and -7.2 BE) | Asp452, Lys545, Arg553, Ala554, Arg555, Thr556, Met615, Trp617, Asp618, Tyr619, Lys622, Asp623, Arg624, Thr677, Asn691, Ser759, Asp760, Asp761, Ser778, Ile779, Glu796, Lys798, Cys799, Thr800, Thr801, Glu811, Cys813, Ser814 | [20]       |
| **Terpenoids**                     | Glycyrrhizic acid (7 HB, 1 CH3, 1 pi-alyl, 16 VDW and -9.9 BE), limonin (2 HB, 2 pi-alyl, 1 pi-pi T shaped, 10 VDW and -8.2 BE), 7-deacetyl-7-benzoylgedunin (1 HB, 1 Alky1-pi-alyl, 2 CH1, 1 pi-anion, 3 pi-cation, 6 VDW and -8.2 BE), limonin glucoside (3 HB, 1 CH4, 4 Alky1-Pi-Alky1, 9 VDW and -8.2 BE), 7-deacetylgedunin (1 HB, 2 CH1, 1 Pi-Alky1, 1 Pi-sigma, 1 Pi-anion, 5 VDW and -8.1 BE), abacunone (2 HB, 1 Alky1, 1 Pi-Anion, 8 VDW and -7.8 BE) | Asp452, Lys545, Arg553, Ala554, Arg555, Thr556, Met615, Trp617, Asp618, Tyr619, Lys622, Asp623, Arg624, Thr677, Asn691, Ser759, Asp760, Asp761, Ser778, Ile779, Glu796, Lys798, Cys799, Thr800, Thr801, Glu811, Cys813, Ser814 | [87]       |
| **Standard**                       | Remdesivir (3 IR and -6.3 BE), favipiravir (3 IR and -3.6 BE) | Lys551, Arg553, Arg555, Asp623, Ser682 | [41]       |
| **Helicase/nsp13 (viral protein)** | Small molecule inhibitors                                                                 | Interacting residues with different classes of phytochemicals                                                                 | References |
| **Flavonoids**                     |                                                                                           | Asp452, Lys545, Arg553, Ala554, Arg555, Thr556, Met615, Trp617, Asp618, Tyr619, Lys622, Asp623, Arg624, Thr677, Asn691, Ser759, Asp760, Asp761, Ser778, Ile779, Glu796, Lys798, Cys799, Thr800, Thr801, Glu811, Cys813, Ser814 | [46]       |

(continued on next page)
Figure-8 proteolytic activity. PLpro can also perform deISGylation of host pro-5.1. Papain-like protease (PLpro)/nsp3 interactions, CHB: BE - binding energy, HB - hydrogen bond, HP/HPI - hydrophobic interactions, NBI - binding interaction.

| Standards | Interacting residues with different classes of phytochemicals | References |
|-----------|-------------------------------------------------------------|------------|
| Nelfinavir (6 IR and –6.2 BE), remdesivir (8 IR and –6.8 BE), prulifloxacin (7 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 | [46] |

| Endonuclease/nsp15 (viral protein) | Class | Small molecule inhibitors | Interacting residues with different classes of phytochemicals | References |
|-----------------------------------|-------|--------------------------|-------------------------------------------------------------|------------|
| Flavonoid | Naringin (5 IR and –7.9 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). | Hic235, ASp240, GIn245, Gly248, Hic250, Lys290, Val292, Ser294, Val339, GIn340, 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). | Hic235, GIn340, Thr341, Hic250, Lys290, Ser294, GIn348, 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 –9.6 BE), saikosaponin-18 (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), arjunalic acid (1 IR and –7.6), asiatic acid (5 IR and –7.4 BE), betulonic acid (1 IR and –7.3 BE), platanic acid (5 IR and –7.3 BE), alpinol acid (1 IR and –7.2), asiatic acid (5 IR and –7.4), ursolic acid (5 IR and –8.4 BE). | GIn230, Ala232, Gln234, Hip235, Asp240, GIn345, Leu346, GIn247, Gly248, Hic250, Asn278, Lys290, Cys293, Val292, Cys293, Met331, Ala232, Trp333, Val339, GIn340, Thr341, Tyr343, Pro344, Leu346 | [75,106] |
| Coumarin | Beta sototol (1 IR and –8.1 BE), glitoxin (3 IR and –6.7 BE), psoralen (5 IR and –6.7 BE), carpinine (4 IR and –6.6 BE), rhinacanthin (5 IR and –6.5 BE), cinnamic acid (4 IR and –6.3 BE), coriandrin (5 IR and –6.2 BE), scopeolitin (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 HB and –4.5 BE). | Hic235, GIn348, Hic250, Lys290, Val292, Ser294, Thr341, Thr343, Gly248, Hic250, | [106] |
| Organsulfin | Allin (3 IR and –3.8 BE) | Hic235, Thr341, Hic250, Gly248, Hic250, Lys290, GIn346 | [106] |
| Alkaloid | Taspine (4 IR and –7.3 BE), ajmalicine (5 IR and –8.1 BE), reserpine (4 IR and –7.4). | Hic235, Thr341, Gly248, Hic250, Lys290, GIn346 | [106] |
| Steroids | Asposasodi-C (5 HB and –7.16 BE), asposasodi-F (7 HB and –6.6 BE), asposasodi-D (6 HB and –6.4 BE), rutin (5 HB), racemose-A (4 HB and –5.99). | Gly230, Ala232, Gln234, Hip235, Asn240, Hic243, Hic245, Hic250, Asn278, Val292, GIn340, Thr341, Leu346 | [16] |
| Standards | Hydroxycithorouglione (4 IR and –5.8 BE), Nelfinavir (4 IR and –7.3 BE), ribavirin (9 IR and –5.84). | Thr26, Hic235, Hic250, Gly248, Lys290, Val292, Ser294, Thr341, Tyr343, Pro344, Gly248, Lys290, Val292, Ser294, Thr341, Tyr343, Pro344, Leu346 | [73,106] |

| 2′-O- methyltransferase/nsp16 (viral protein) | Class | Small molecule inhibitors | Interacting residues with different classes of phytochemicals | References |
|-----------------------------------|-------|--------------------------|-------------------------------------------------------------|------------|
| Flavonoids, Alkaloids, others | Eryvin-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, Asn699, Asp6897, Amet6929, Leu6989, Asn6841, Lys6844, Cys913, Lys6968, Phe947, Lys6944, Asn6899, Asp6928, Cys913, Gly911, Leu6989, Met929, Asp6979, Asp6928, Met929, Cys913, Leu6898, Gly6869, Cys6898, Asp6928, Asp6928, Asp6928, Cys913, Leu6891, Leu6898, Asp6897, Gly6871, Asn6811, Met929, 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, Pro952, Leu6968, Lys6944, Lys6911, Met929, Gly6969, Pro952, Leu6968, Lys6944, Leu6989, Leu6996, Lys7001, Lys6844, Lys6944, Lys6968, Leu6928, Met929, Cys913, Asp6841, Gly6871, Leu6898, Phe947, Tyr6930, Asp6897, Asn6899, Pro952, Asp6931 | [46] |

| Table 1 (continued) | 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 deSylation 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-ol, 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).
These hits include myricitrin, 5,7,3′-SARS-CoV-2 3CLpro function and viral RNA replication were selected. The phytochemicals were screened, and the top hits that could inhibit binding affinities with 3-CLpro than the N3 and lopinavir (standards). In another study, a database of medicinal plants consisting of more than 30,000 potential anti-viral compounds 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 that are crucial in interacting with the nsp7/8 complex. In-silico screening followed by molecular docking analyses suggested that the phytochemicals bisdemethoxycurcumin, scutellarin, desmethoxycurcumin, quercetin, myricetin, luteolin and mundulinol could potentially inhibit 3-CLpro as these compounds exhibit low binding energy [25,73].

**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). Terpenoids (6-Oxoisoiguesterin and 7-O-(6′-lallyl) isoflavone, methyl rosmarinate, (2S)-eriodictyol-D-glucopyranoside, licoleafol, amaranthine, colistin, nelfinavir, and prulifloxacin [67]. Terpenoids (6-Oxoisooquesterin 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, gallatechin, and epicatechin from green tea also showed the potential to restrict the activity of 3-CL pro (Ghosh et al., 2020[101]). Similarly, several phytochemicals 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 Avinennia officinalis and Iranian medicinal plants have also been proposed as inhibitors of 3-CLpro [51,57]. Tanshinones, a class of natural phytochemicals 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.
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<sub>50</sub>/EC<sub>50</sub>/CC<sub>50</sub>) | References |
|-------|------------------------|-----------------------------------------|-----------------|---------------------------------------------|------------|
| 01    | Baicalein 3CLpro -     | in vitro                                | IC<sub>50</sub> | 0.39 ± 0.11 μM                             | [50]       |
| 02    | Baicalin 3CLpro        | in vitro                                | IC<sub>50</sub> | 83.4 ± 0.9 μM                              | [50]       |
| 03    | Scutellarein 3CLpro    | in vitro                                | IC<sub>50</sub> | 5.80 ± 0.22 μM                             | [50]       |
| 05    | Quercetagetin 3CLpro   | in vitro                                | IC<sub>50</sub> | 1.24 ± 0.14 μM                             | [50]       |
| 06    | Myricetin 3CLpro       | in vitro                                | IC<sub>50</sub> | 2.86 ± 0.23 μM                             | [50]       |
| 07    | Baicalin 3CLpro (FRET) | in vitro                                | IC<sub>50</sub> | 6.41 ± 0.95 μM                             | [78]       |
| 08    | Baicalein 3CLpro (FRET)| in vitro                                | IC<sub>50</sub> | 0.94 ± 0.20 μM                             | [78]       |
| 09    | Theaflavin 3CLpro (FRET)| in vitro                                | IC<sub>50</sub> | 8.44 μg/mL                                  | [39]       |
| 10    | Myricetin 3CLpro (FRET)| in vitro                                | IC<sub>50</sub> | 0.2 μM                                     | [107]      |
| 11    | Baicalin 3CLpro (FRET)| in vitro                                | IC<sub>50</sub> | 34.71 μM                                   | [103]      |
| 12    | Herbacetin 3CLpro (FRET)| in vitro                                | IC<sub>50</sub> | 53.90 μM                                   | [103]      |
| 13    | Pectolinarin 3CLpro (FRET)| in vitro                                | IC<sub>50</sub> | 51.64 μM                                   | [103]      |
| 14    | Glycyrrhizin (triterpenoid saponin) | 3CLpro | in vitro                                | IC<sub>50</sub> | 30 μM (0.024 mg/mL)                        | [86]       |
| 15    | Δ9-Tetrahydrocannabinol | Antiviral activity                       | EC<sub>50</sub> | 13.17 μM                                   | [97]       |
| 16    | Δ2 -THC                | Antiviral activity                       | EC<sub>50</sub> | 10.25 μM                                   | [97]       |
| 17    | CBN                    | Antiviral activity                       | EC<sub>50</sub> | 25.79 μM                                   | [97]       |
| 18    | CBD                    | Antiviral activity                       | EC<sub>50</sub> | 11.07 μM                                   | [97]       |
| 19    | CBDA                   | Antiviral activity                       | EC<sub>50</sub> | 19.9 μM                                    | [97]       |
| 20    | Andrographolide        | SARS-CoV2 infection in-vitro             | IC<sub>50</sub> | 50 μM (0.024 mg/mL)                        | [86]       |
| 21    | Andrographolide        | Plaque reduction                         | EC<sub>50</sub> | 4.72 μM                                    | [13]       |
| 22    | Arteether (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 31.86 ± 4.72 μM                           | [14]       |
| 23    | Artemether (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 73.80 ± 26.91 μM                          | [14]       |
| 24    | Artemisic acid (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 4.72 μM                                    | [14]       |
| 25    | Artemisinin (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 4.72 μM                                    | [14]       |
| 26    | Artemione (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 4.72 μM                                    | [14]       |
| 27    | Dihydrartemisinin (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 4.72 μM                                    | [14]       |
| 28    | Artesunate (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 4.72 μM                                    | [14]       |
| 29    | Artemannuin (sesquiterpene lactone) | SARS-CoV2 infection | Vero cells | 4.72 μM                                    | [14]       |
| 30    | Cannabidiol            | SARS-CoV2 infection                      | IC<sub>50</sub> | 1.25 μM (SARS CoV2γ)                       | [61]       |
| 31    | Punicalin (ELISA)      | RBD-AE2 binding assay                   | IC<sub>50</sub> | 0.14 mg/mL                                 | [80]       |
| 32    | Corilagin              | SARS-CoV2 inhibition                     | EC<sub>50</sub> | 0.13 μmol/L                                | [106]      |
| 33    | Corilagin (ELISA)      | RBD-AE2 binding assay                   | IC<sub>50</sub> | 24.9 μM                                    | [93]       |
| 34    | Corilagin (RAI-S-37)   | HEK293 cell                              | CC<sub>50</sub> | >100                                        | [93]       |
| 35    | Corilagin (RAI-S-37)   | Lyo2 cells                              | CC<sub>50</sub> | >100                                        | [93]       |

(continued on next page)
| Sl no | Crude extract/compound                  | Virus/RNA/enzyme inhibition/cytotoxicity | Inhibitory assay                  | Dosage (IC<sub>50</sub>/EC<sub>50</sub>/CC<sub>50</sub>) | References |
|------|----------------------------------------|-----------------------------------------|-----------------------------------|-------------------------------------------------|------------|
| 36   | Remdesivir                             | Cytotoxicity                            | in-vitro                          | IC<sub>50</sub> 7.58 μg/mL                      | [30]       |
| 37   | Corilagin (RAI-S-37)                   | Cytotoxicity                            | HEK293T                           | IC<sub>50</sub> 2.8 μM                         | [30]       |
| 38   | Corilagin (RAI-S-37)                   | SARS-CoV-2 RdRp inhibition              | Vero cells                        | EC<sub>50</sub> 1.53 ± 0.06 μmol/L             | [108]      |
|      | Corilagin (RAI-S-37)                   | SARS-CoV-2 RdRp inhibition              | Vero cells                        | EC<sub>50</sub> 1.35 ± 0.56 μmol/L             | [108]      |
|      | Corilagin (RAI-S-37)                   | SARS-CoV-2 RdRp inhibition              | Vero cells                        | EC<sub>50</sub> 1.98 ± 0.27 μmol/L             | [108]      |
|      | Corilagin (RAI-S-37)                   | SARS-CoV-2 RdRp inhibition              | Vero cells                        | EC<sub>50</sub> 0.13 μmol/L                    | [108]      |
| 39   | EGCG                                   | 3CLpro (FRET)                           | Vero cells                        | IC<sub>50</sub> 7.58 μg/mL                      | [30]       |
|      |                                        |                                        |                                   | C<sub>50</sub> >40 μg/mL                        |            |
| 40   | Cepharanthine (alkaloid)               | SARS-CoV-2 virus reduction              | Vero cells                        | EC<sub>50</sub> 0.46 μg/ml                      | [111]      |
| 41   | Emetine (alkaloid)                     | Cytotoxicity                            | Vero cells                        | EC<sub>50</sub> 1.5625 M                        | [111]      |
| 42   | 6-Gingerol (beta-hydroxy ketone)       | SARS-CoV-2 infection                    | Vero cells                        | EC<sub>50</sub> 1.471 μM                       | [111]      |
| 43   | Panduratin A (Diarylheptanoid)         | SARS-CoV-2 post infection               | Vero cells                        | EC<sub>50</sub> 1.471 μM                       | [111]      |
|      |                                        |                                        |                                   | C<sub>50</sub> 5.30 μg/ml                       | [113]      |
|      |                                        |                                        |                                   | C<sub>50</sub> 43.47 μM                        | [113]      |
| 44   | Emetine hydrochloride (alkaloid)       | SARS-CoV-2 virus reduction              | Vero cells                        | EC<sub>50</sub> 0.46 M                        | [111]      |
|      |                                        | Cytotoxicity                            | Vero cells                        | EC<sub>50</sub> 1.5625 μg/ml                    | [111]      |
| 45   | Phillyrin (KD-1) Lignan                 | Anti-HCoV-229E                          | Vero cells                        | EC<sub>50</sub> 64.53 μg/ml                     | [113]      |
|      |                                        | Cytotoxic effect                        | Vero cells                        | EC<sub>50</sub> 63.90 μg/ml                     | [113]      |
|      |                                        | Cytotoxicity                            | Vero cells                        | EC<sub>50</sub> 1959 μg/ml                      | [113]      |
|      |                                        | Plaque reduction                        | Calu3                             | IC<sub>50</sub> 1034 μg/ml                      | [113]      |
|      |                                        |                                        |                                   | C<sub>50</sub> 2.04 μg/ml                       | [113]      |
|      |                                        |                                        |                                   | C<sub>50</sub> 43.92 μM                        | [113]      |
| 46   | Cepharanthine (bisdemethoxyquinooline alkaloid) | SARS-CoV-2 RNA                          | Vero6/TMPRSS2                    | IC<sub>50</sub> 0.35 μM                        | [114]      |
| 47   | Lycorine (alkaloid)                    | SARS-CoV-2 infection                    | Vero cells                        | EC<sub>50</sub> 0.878 μM                       | [112]      |
| 48   | Digoxin (cardiotonic glycoside)         | SARS-CoV-2 infection                    | Vero cells                        | EC<sub>50</sub> 0.043 μM                       | [110]      |
| 49   | Osabain (Cardiac glycoside similar to digitoxin) | SARS-CoV-2 infection                    | Vero cells                        | EC<sub>50</sub> 0.024 μM                       | [110]      |
|      |                                        | Cytotoxicity                            | Vero cells                        | EC<sub>50</sub> 0.024 μM                       | [110]      |
|      |                                        |                                    | Vero cells                        | EC<sub>50</sub> >10 μM                         | [110]      |
| 50   | Herbacetin                             | 3CLpro (FRET)                           | Vero6/TMPRSS2                    | EC<sub>50</sub> 52.75 μg/ml                     | [110]      |
| 51   | Pectolinarin                           | 3CLpro (FRET)                           | in-vitro                          | IC<sub>50</sub> 33.16 μM                       | [71]       |
| 52   | Rhoifolin                              | 3CLpro (FRET)                           | in-vitro                          | IC<sub>50</sub> 27.45 μM                       | [71]       |
|      |                                        |                                        |                                   | IC<sub>50</sub> 37.78 μM                       |            |
| 53   | Andrographis paniculata extract        | SARS-CoV2 infection                     | Vero E6                           | IC<sub>50</sub> 68.06 μg/ml                     | [42]       |
| 54   | Andrographis paniculata extract        | Cytotoxicity                            | Calu-3 cells                      | EC<sub>50</sub> 1.006 μg/ml                     | [72]       |
| 55   | Zingiber officinalis rhizome extract   | Inhibition of SARS-CoV2 infection       | Vero E6                           | EC<sub>50</sub> 29.19 μg/ml                     | [42]       |
|      |                                        | Cytotoxicity                            | Vero cells                        | EC<sub>50</sub> 52.75 μg/ml                     | [110]      |
|      |                                        |                                    | Vero cells                        | EC<sub>50</sub> 1.45 μg/ml                      | [110]      |
| 56   | Boesenbergia rotunda (extract)         | SARS-CoV2 infection                     | Vero cells                        | EC<sub>50</sub> 3.62 μg/ml                      | [42]       |
| 57   | Scutellaria baicalensis extract        | 3CLpro assay                           | Vero cells                        | IC<sub>50</sub> 8.52 ± 0.54 μg/ml               | [50]       |
| 58   | Pomegranate peel extract               | SARS-CoV2 RNA replication               | Vero cells                        | IC<sub>50</sub> 0.74 ± 0.36 μg/ml               | [50]       |
|      |                                        | Cytotoxicity                            | Vero cells                        | IC<sub>50</sub> >500 μg/ml                      | [50]       |
|      |                                        |                                    | Vero cells                        | IC<sub>50</sub> 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 [12]. Compounds such as tomentidiploacne-B, sesiquiterpene glycoside, rhoaminetin, 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 sub-genomic RNAs (sgRNAs). Based on the docking score, phytocompounds asparagine- C, asparaginase-D, asparaginase-F, racemose-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 terpiny acetate to nsp15 protein [106].

5.6. 2′-O-methyltransferase (2′-OMTase)/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*, meliloquine, 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 bai-calein. Moreover, ginkgolic acid is a specific covalent inhibitor of SARS-CoV-2 cysteine proteases, targeting PRpro 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 phychochemical 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, baikaline, and shuan-ghuanglian 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

| 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) Tranogenic 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, IFN-γ and IL-1β, either release or production and NLRP3 inflammasome activation via blocking activities of proteins, NF-kB,p65, ATP-induced caspase-1 inflammasome activation via blocking activities 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-κB | IL-κB induced lung injury in vivo | [102] |
| 04    | Withaferin-A   | Immunosuppressant | Affect the release of TNF-α, IL-1β, IL-1α, IL-6, IL-8, IP-10, CCL2, MCP-1, SDF-1α, MIP-1β, MIP-1α 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 PKCθ | 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] |
| 07    | Cannabidiol    | anti-inflammatory and immunosuppressive | Prevents the cytokine storm and mucous hypersecretion in COVID-19  
These effects are mediated by inhibition of pro-inflammatory cytokine release (e.g. tumor necrosis factor-a, Interferon-gamma, IL-1β, 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 | [81] |
| 08    | F3HC           | Only low anti-inflammatory activity | 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] |
| 09    | FCRD           | Only low anti-inflammatory activity | | 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 immune 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,
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 pathological consequences 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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