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REVIEW ARTICLE

Repurposing of Plant-based Antiviral Molecules for the Treatment of COVID-19

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Abstract: COVID-19, stemming from SARS-CoV-2, poses a formidable threat to global healthcare, with a staggering 77 million confirmed cases and 690,067 deaths recorded till December 24, 2023. Given the absence of specific drugs for this viral infection, the exploration of novel antiviral compounds becomes imperative. High-throughput technologies are actively engaged in drug discovery, and there is a parallel effort to repurpose plant-based molecules with established antiviral properties. In this context, the review meticulously delves into the potential of plant-based folk remedies and existing molecules. These substances have showcased substantial viral inhibition in diverse *in vivo*, *in silico*, and *in vitro* studies, particularly against critical viral protein targets, including SARS-CoV-2. The findings position these plant-based molecules as promising antiviral drug candidates for the swift advancement of treatments for COVID-19. It is noteworthy that the inherent attributes of these plant-based molecules, such as their natural origin, potency, safety, and cost-effectiveness, contribute to their appeal as lead candidates. The review advocates for further exploration through comprehensive *in vivo* studies conducted on animal models, emphasizing the potential of plant-based compounds to help in the ongoing quest to develop effective antivirals against COVID-19.

Keywords: Medicinal plants, Drug molecules, SARS-CoV-2, Plant-based antivirals, COVID-19, Middle Eastern Respiratory Syndrome (MERS).

1. INTRODUCTION

Viruses perpetually pose a threat to humanity, causing numerous worldwide diseases [1]. Coronaviruses, characterized by their enveloped, non-segmented, positive-single-strand RNA structure and crown-like spikes, belong to the family Coronaviridae, exhibiting a genome size of 27-32 Kb [2]. Among the seven identified human coronaviruses (HCoVs), strains like 229E, NL03, OC43, and HKU1 typically induce mild infections like the common cold [2]. However, severe outbreaks like the 2012 Middle Eastern Respiratory Syndrome (MERS) in Saudi Arabia and the 2003 Severe Acute Respiratory Syndrome (SARS) pandemic in China's Guandong province resulted in death rates exceeding 10% and 35%, respectively [3-7]. MERS-CoV and SARS-CoV, originating from native bat populations and spread through intermediate hosts, caused these deadly outbreaks [8-10]. In December 2019, a novel coronavirus strain, SARS-CoV-2, appeared in Wuhan, Hubei Province, that was termed as coronavirus disease 2019 (COVID-19)

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by the World Health Organization (WHO) [11]. Evidence suggests that, akin to MERS-CoV and SARS-CoV, SARS-CoV-2 also has a bat origin [13, 14]. On March 11, 2020, COVID-19 was declared as global pandemic due to rapid dissemination of SARS-CoV-2 worldwide following its emergence [15]. As of November 26, 2023, the global administration of vaccine doses has reached 13.59 billion. Furthermore, as of December 24, 2023, 77,311,917,173 COVID-19 cases, with 69,900,067 fatalities, have been documented globally [15].

Effectively handling the COVID-19 pandemic presents difficulties owing to the heightened transmissibility of SARS-CoV-2 and the emergence of novel variants [16]. The international scientific community has demonstrated remarkable tenacity in rapidly developing vaccines and diagnostic procedures [16]. Ongoing efforts aim to create safe and effective vaccines that provide long-term immunity across various platforms, addressing the continuous emergence of variants, including Alpha, Delta, Omicron, BA.4, and BA.5, leading to surges in cases and hospitalizations [17]. The imperative for a variant-proof vaccine capable of safeguarding against all current and future SARS-CoV-2 strains remains high [18]. If achieved, this milestone could profoundly impact human health. While endeavors focus on developing antibodies that neutralize all variants, this process is time-consuming and requires rigorous safety and efficacy validations in clinical trials [17]. Hence, exploring drug discovery through repurposing existing antiviral drugs with potential effectiveness against viral diseases is a prudent alternative [19-21].

Furthermore, considering the genomic similarity of over 85% between MERS-CoV and SARS-CoV compared to SARS-CoV-2, there is an anticipation that drugs proven effective in treating SARS and MERS could also be beneficial in combatting COVID-19 [22]. No designated medication or therapeutic approach method is known for SARS-CoV-2 [23-25]. Different existing antiviral drugs, like imdevimab, sotrovimab, lopinavir/ritonavir, darunavir/umifenovir, oseltamivir, favipiravir, remdesivir, chloroquine, hydroxychloroquine, azithromycin, tocilizumab, and interferon-β, are undergoing different phases of clinical trials against SARS-CoV-2 [22, 26-29]. However, many of these drug molecules are associated with numerous adverse effects [24, 30-32]. Hence, an immediate requirement exists to discover effective and safe natural drugs to combat this formidable virus.

Given the current circumstances, drug repositioning/ repurposing emerges as the most suitable and effective strategy to promptly address the global challenge posed by COVID-19, considering the prolonged timeline of new drug development, often exceeding 10 years [19, 33]. Jeon *et al*. (2020) recently identified a set of 24 possible antiviral agents targeting SARS-CoV-2 from a pool of forty-eight FDA-accepted drugs. Among these, niclosamide and ciclesonide exhibited significant promise as antivirals, showing very low 50% inhibitory concentrations (IC_{50}s) [34]. Subsequent validation by Matsuyama *et al*. (2020) confirmed ciclesonide as a promising remedy for SARS-CoV-2, pinpointing NSP15, a viral endoribonuclease, as its molecular target [35]. In a comprehensive screening, Riva *et al*. (2020) assessed around 12,000 FDA-approved small molecules, identifying 100 antiviral compounds capable of inhibitingSARS-CoV-2 replication [36].

Natural molecules derived from fungi, plants, soil microorganisms, marine organisms, and various sources have a longstanding history of beneficial applications in disease treatment [33, 37]. These natural molecules also hold potential as primary compounds for derivatization, creating new compounds with enhanced pharmacological attributes [38]. Remarkably, chemical frameworks derived from natural sources have been pivotal in advancing drug development over the last five decades, with approximately three-quarters of globally used drugs for various diseases reported to be based on natural resources [37, 39-42]. Secondary metabolites exhibiting antiviral properties have been isolated from numerous medicinal plants, showcasing robust therapeutic potential against SARS-CoV-2 [43-49]. Many plants harbor diverse secondary metabolites that bind to viral proteins and enzyme targets, including ACE2 receptor, RdRp, Spike protein, Plpro, 3Clpro, TMPRSS2, and Cathepsin L, thereby impeding viral penetration and/or replication within host cells, curtailing viral multiplication (Fig. **1**) [31, 32, 50-53]. Notably, Boozari *et al*. (2021) emphasize contribution of medicinal plants and their extracts in COVID-19 treatment, with *Nigella sativa*, *Hypericum perforatum*, *Echinacea* spp, *Camellia sinensis*, *Allium sativum*, *Zingiber officinale*, *Glycyrrhiza glabra*, and *Scutellaria baicalensis* demonstrating potential to enhance immune responses against COVID-19 infections [54]. Furthermore, molecules like berberine, mangiferin, curcumin, nimbin, withaferin A, and rographolide, piperine, and the baine have been reported to successfully hinder the spike glycoprotein and its receptor's interaction [55]. The imperative for discovering safe and cost-effective herbal medicines with antiviral properties persists, encouraging exploration within traditional medicine systems like Ayurveda, Unani, Siddha, and Sowa-rigpa. This review aims to underscore potential natural antiviral molecules effective for SARS-CoV and MERS-CoV that might prove valuable as antivirals for SARS-CoV-2 and its mutation-laden novel strains such as Delta, Omicron, and potential future strains.

2. MECHANISMS OF SARS-COV-2 INFECTION IN HUMANS

2.1. Transmission

Like other coronaviruses, SARS-CoV-2 transmits *via* indirect or direct contact with infected carriers [56, 57]. Direct transmission may happen through respiratory droplets or aerosols, while indirect transmission involves respiratory droplets or secretions shed by infected individuals, forming fomites (contaminated surfaces). The virus can persist on surfaces for varying durations, ranging from hours to days, contingent upon ambient temperature and surface type. Consequently, the indirect transmission may also happen in contact with infected objects or surfaces in the immediate environment.

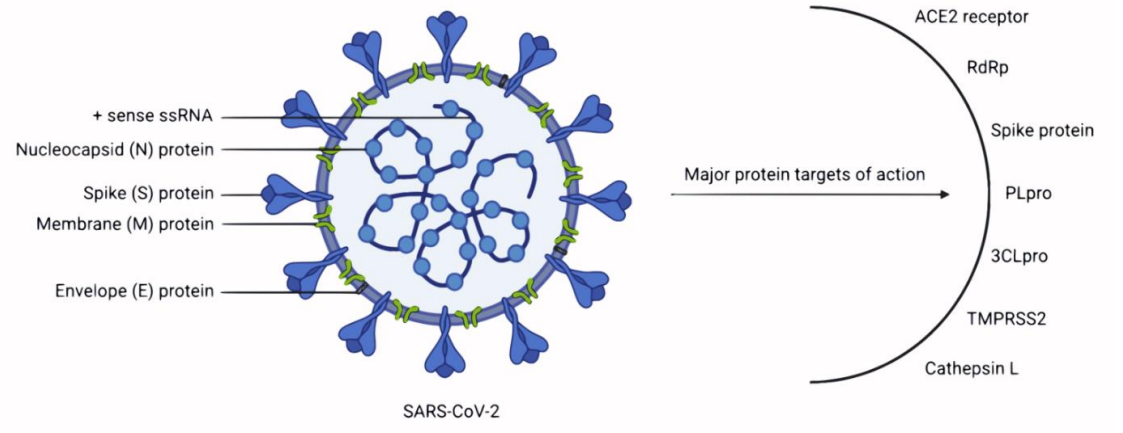


Fig. (1). Structure of coronavirus with major protein targets of action. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

2.2. SARS-CoV-2 Structure

SARS-CoV-2 is characterized as a single-stranded, non-segmented, positive-sense RNA virus [58]. The replicase gene constitutes two-thirds of its genetic makeup that encodes sixteen Non-structural Proteins (nSPs), crucial for RNA transcription and replication. The rest of the genome encodes Structural Proteins (SPs), such as Ncleocapsid (N), Membrane (M), Envelope proteins (E), and Spike glycoprotein (S) [60]. The spike protein enables viral binding to the host angiotensin-converting enzyme 2 (ACE-2) receptor, leading to subsequent entry. N proteins assemble into a helical capsid around the RNA genome, enclosed by a phospholipid bilayer envelope. Assembling of viruses is assisted by M and E proteins, with E proteins acting as ion channels and M proteins interacting with other SPs [61]. These functional proteins are crucial and represent significant targets for drug therapy development against this highly pathogenic virus [16]. Recent findings propose that C-type lectin receptors CD209L/L-SIGN and CD209/DSIGN may function as substitute receptors for human cell entrance of SARS-CoV-2.

2.3. Replication of the Virus and Identification of Target Proteins

Virus-host interactions significantly impact the viral entrance and replication within host cells. Upon receptor recognition, the S protein facilitates the virus's entry into cells by cleaving into S1 and S2 subunits. (Figs. **1** and **2**). The receptor-binding domain of the S1 subunit specifically interacts with ACE2, while the S2 subunit, housing the transmembrane domains and fusion peptide, facilitates the merging of host cell and viral membranes. This fusion requires priming by host proteases like cathepsin L and B, trypsin, furin, and TMPRSS2. Notably, these proteases present probable targets for antiviral drugs [35, 64]. Upon penetration, the RNA genome is freed into the cytoplasm, encompassing a replicase gene that is translated into polyprotein ppa and pp1ab, subsequently cleaved by viral proteases into sixteen individual nSPs, constituting the RNA replicase-transcriptase complex (RTC) [60, 65].

The RTC, formed using membranes derived from the rough endoplasmic reticulum (ER), facilitates the production of negative-sense RNAs.The viral RNA synthesis yields both genomic and sub-genomic RNAs, wherein full-length negative-sense RNAs act as templates for the generation of full-length (+) RNA genomes, and sub-genomic RNAs serve as templates for mRNA coding the virus's SPs. The translated mRNA produces S, N, M, and E proteins, subsequently integrating them into the ER and conveyed to the ER-Golgi Intermediate Complex (ERGIC). Within the ERGIC, encapsulating genomic RNA, the N protein combines with other SPs, resulting in viral buds [64]. The assembled genomic RNA and structural proteins constitute the viral nucleocapsid and envelope within the ERGIC, afterward liberated through exocytosis (Fig. **2**). In-depth knowledge of the virus's structure and replication, has unveiled critical protein targets, including the spike protein, ACE2, RdRp (RNA-dependent R.N.A. polymerase), host cell proteases, and viral proteases. Inhibiting these targets can effectively impede viral replication [66, 67]. Notably, catalytic sites in 2019-nCoV enzymes demonstrate significant sequence resemblance with known MERS-CoV and SARS-CoV enzymes, suggesting a conserved primary drug-binding pocket in SPs across the three viruses [68].

Repurposing established SARS-CoV and MERS-CoV antivirals for 2019-nCoV seems pragmatic. Preliminary investigations and clinical trials for various drugs have been initiated against this virus. Plant-based molecules with anti-SARS activity have been studied for their binding to key proteins in the virus-host interaction, demonstrating high affinity and inhibiting virus replication [31, 69]. Although many natural molecules were screened for inhibiting SARS-CoV after the 2003 outbreak, in-depth studies are needed to validate potential plant-based therapeutic agents.

3. PLANT-DERIVED MOLECULES WITH ANTI-SARS-COV ACTIVITY

The potent plant-based lead molecules and their potency, structure, and antiviral activity on various coronaviruses are presented in Table **1**. Some of the molecules are briefly discussed here.

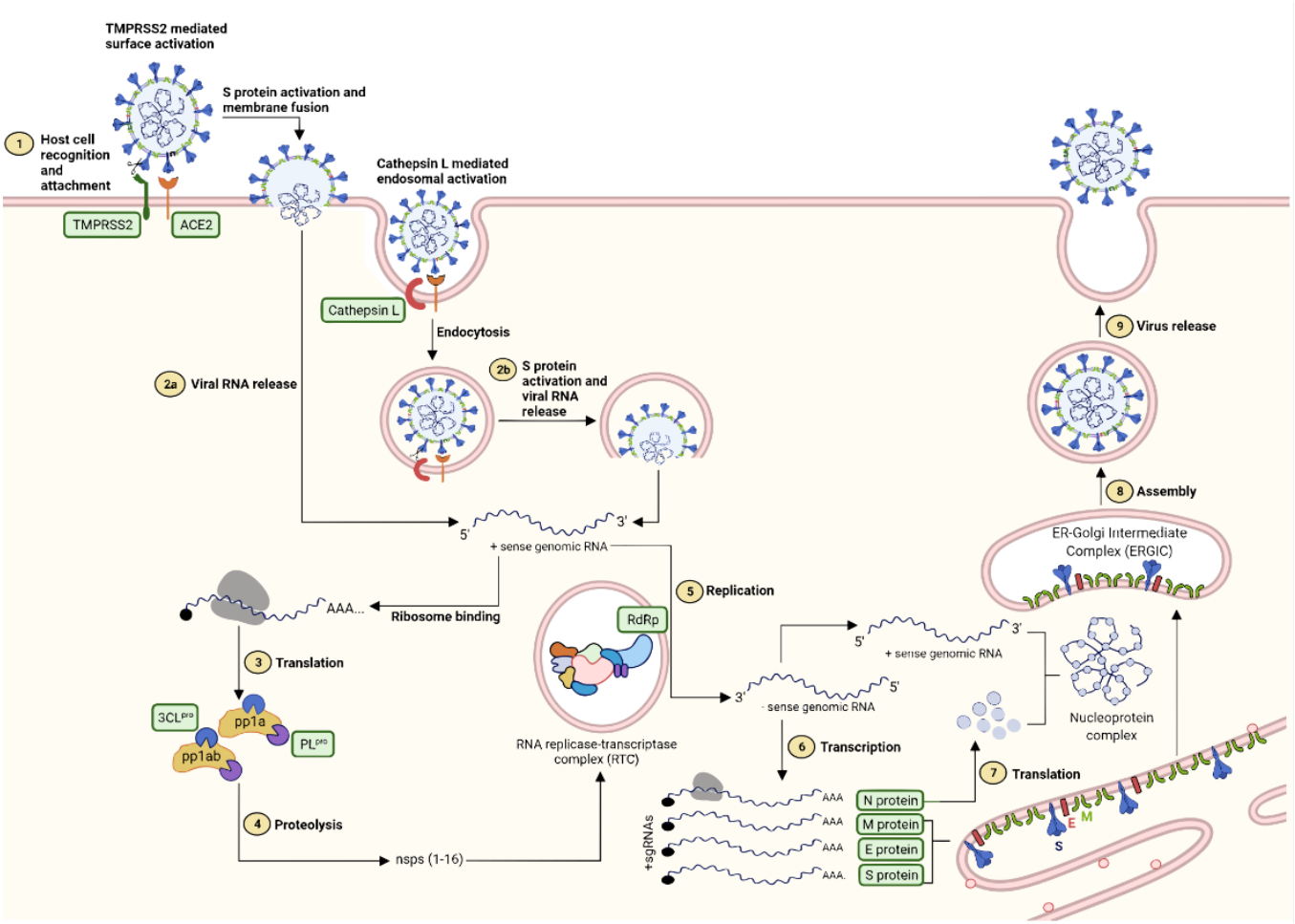
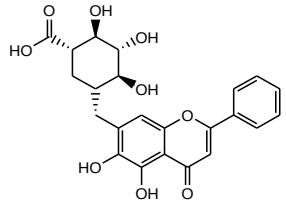
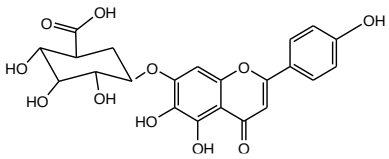
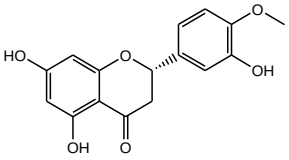
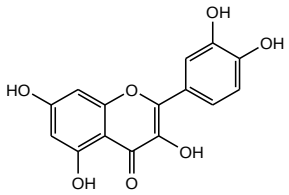
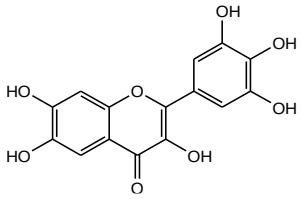
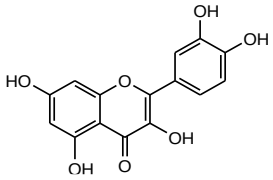
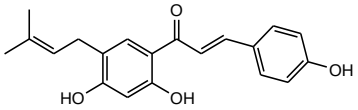
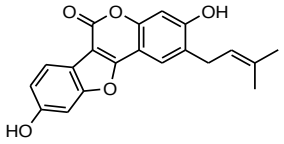
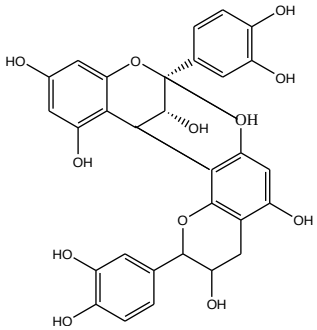
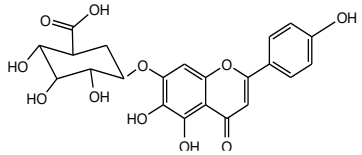
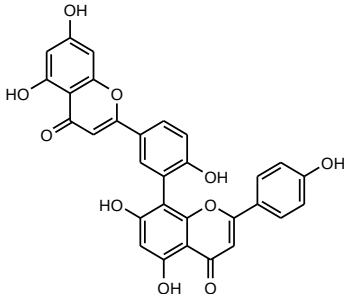


Fig. (2). Mode of entry of virus mediated by various proteins. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

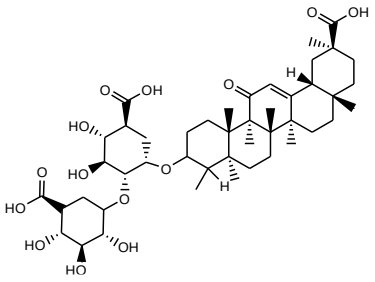
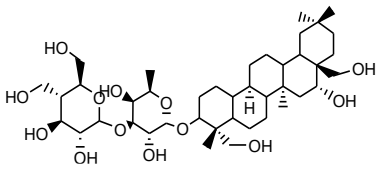
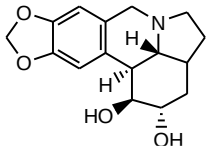
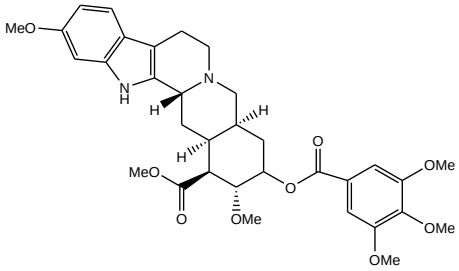
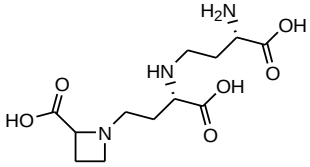
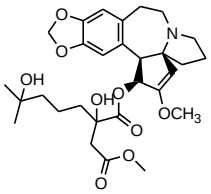
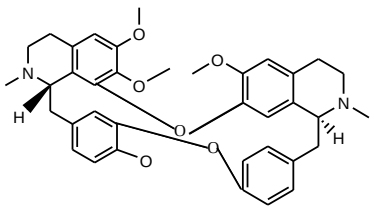
Table 1. Potent lead molecules from natural sources, their potency, structure, and antiviral activity on various types of coronaviruses.

Chemical Group	Plant Molecule	Source	Coronavirus Targeted	IC_{50}/EC_{50}	Structure
Flavonoid	Baicalin	*Scutellaria baicalensi*	SARS-CoV	IC_{50}= 2.24 µM	
	Scutellarin	*Scutellaria barbata*		IC_{50}= 48.1 µM	
	Hesperitin	*Citrus aurantium*		IC_{50}= 8.3 µM	

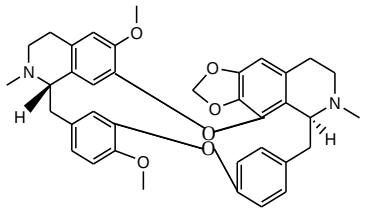
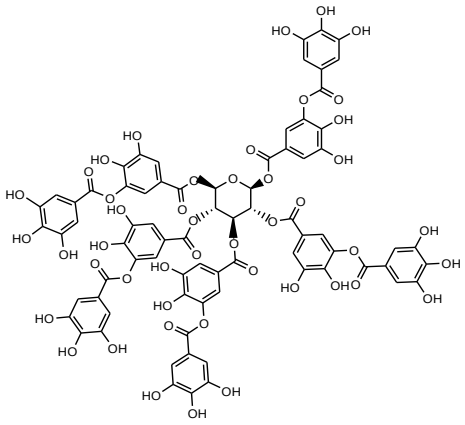
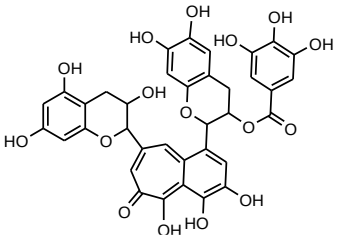
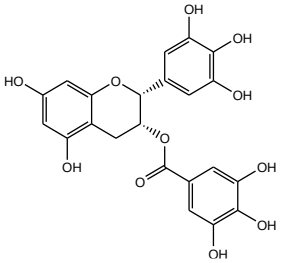
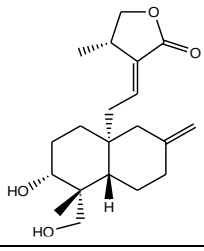
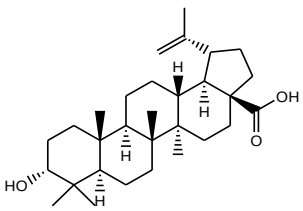
(Table 1) contd…

Chemical Group	Plant Molecule	Source	Coronavirus Targeted	IC_{50}/EC_{50}	Structure
-	Quercetin	Fruits and vegetables	-	IC_{50}= 8.6 µM	
	Myricetin	Beries and fruits		IC_{50}= 2.7 µM	
	Luteolin	*Torreya nucifera*		IC_{50}= 10.6 µM	
	Papyriflavonol A	*Broussonetia papyrifera*		IC_{50}= 3.7 µM	
	Psorolidin	*Psoralea corylifolia*		IC_{50}= 4.2 µM	
	Procyanidin A-2	*Cinnamomi Cortex*		IC_{50}= 29.9 µM	
	Scutellerin	*Scutellaria barbata*		IC_{50}= 0.86 µM	
-	Amentoflavone	-	-	IC_{50}= 8.3 µM	

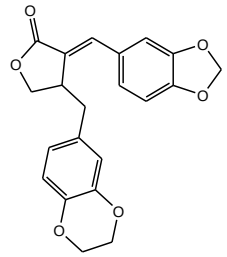
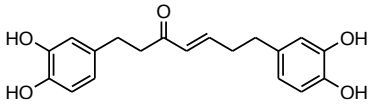
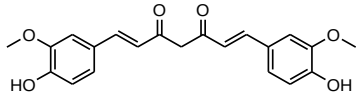
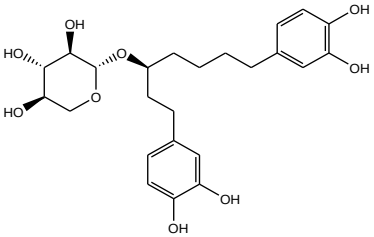
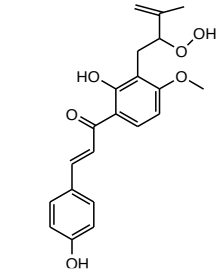
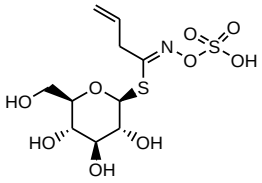
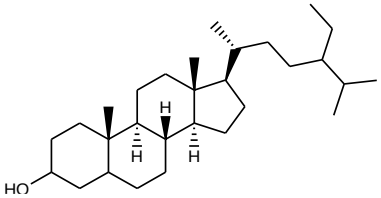
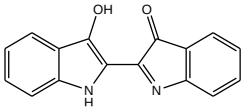
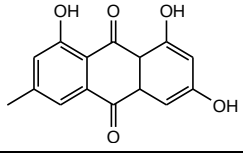
(Table 1) contd…

Chemical Group	Plant Molecule	Source	Coronavirus Targeted	IC_{50}/EC_{50}	Structure
Saponin	Glycyrrhizin	*Glycyrrhizin glabra*	-	IC_{50}= 364.5 µM	
	Saikasaponin A	*Bupleurum* spp.	HCoV-22E9	IC_{50}= 8.6 µM	-
	Saikasaponin B2	*Bupleurum* spp.		IC_{50}= 1.7 µM	
	Saikasaponin C	*Bupleurum* spp.		IC_{50}= 19.9 µM	-
	Saikasaponin D	*Bupleurum* spp.		IC_{50}= 13.2 µM	-
	Escin	*Aesculas bippocartanum*	SARS-CoV	EC_{50} = 6.0 µM	-
Alkaloid	Lycorine	*Lycoris radiata*		EC_{50}= 15.7 nM.	
	Reserpine	*Rawfolia* sp.		EC_{50}=3.4 µM	
	Nicotinamide	Higher plants		IC_{50}= 84 nM	
	Homoharring-tonine	*Cephalotoxus fortunei*	-	IC_{50}= 11.0 nM	
	Tetrandrine	*Stephania tetrandra*		IC_{50}= 0.33µM	

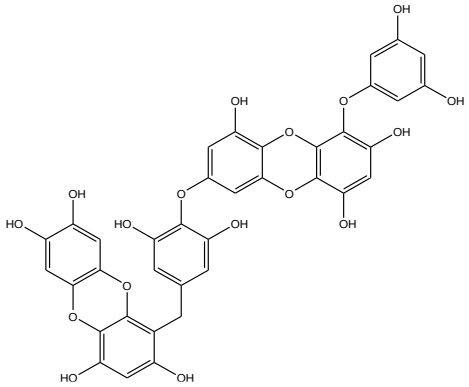
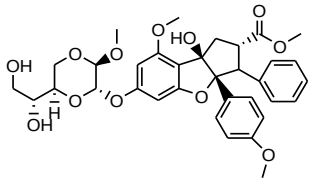
(Table 1) contd…

Chemical Group	Plant Molecule	Source	Coronavirus Targeted	IC_{50}/EC_{50}	Structure
	Cepharanthine	*Stephania tetrandra*	-	IC_{50}= 0.83 µM	
Polyphenol	Tannic acid	Black tea	-	IC_{50}= 3.0 µM	
	3-isotheaflavin-3-3'-gallate	Black tea	-	IC_{50}= 7.0 µM	
	Theaflavin-3 -3'-digallate	Black tea	-	IC_{50}= 9.5 µM	-
	Epigallocatechin gallate	Tea	-	-	
Diterpenoid	Andrographolide	*Andrographis paniculata*	-	-	
	Betulinic acid	*Betula pubescens*	-	IC_{50}= 8.2 µM	

(Table 1) contd…

Chemical Group	Plant Molecule	Source	Coronavirus Targeted	IC_{50}/EC_{50}	Structure
	Savinin	*Pterocarpus santalinus.*	-	IC_{50}= 9.1 µM	
Diarylhep-tanoid	Hirsutenone	*Alnus japonica*	-	IC_{50}= 3.0 µM	
	Curcumin	*Curcuma Longa*	-	EC_{50}= 4.5 µM	
	Rubranoside B	*Alnus glutinosa*	-	IC_{50}= 7.2 µM	
Chalcone	Xanthoangelol E	*Angelica keiskei*	-	IC_{50}= 1.2 µM	
Glucoside	Sinigrin	*Isatis indigotica*	-	EC_{50}= 121 µM	
Phytosterol	beta-Sitosterol	*Isatis indigotica*	-	EC_{50}= 115 µM EC_{50}= 300 µM	
Food Colouring	Indigo	*Isatis indigotica*	-		
Anthraqui-none	Emodin	*Rheum Palmatum*	-	-	

(Table 1) contd…

Chemical Group	Plant Molecule	Source	Coronavirus Targeted	IC_{50}/EC_{50}	Structure
Phloratanin	Diekol	*Ecklonia cava*	-	IC_{50} = 2.7 µM	
Flavagline	Silvestrol	*Aglaia silvestrol*	MERS-CoV, HCoV-22E9	EC_{50}= 1.3 nM EC_{50}= 3 nM	

3.1. Baicalin

Baicalin, a flavone glycoside in various Scutellaria species, including *S. baicalensis* and *S. lateriflora* (Table **1**), exhibits diverse therapeutic effects like antioxidative, anti-inflammatory, and antiapoptotic properties [4, 70]. Following the 2003 SARS outbreak, baicalin demonstrated antiviral properties for SARS CoV (EC_{50} = 12.5 µg/ml) in the fRhK-4 cell line [71]. Additionally, baicalin exhibited ACE2 inhibition (IC_{50} value = 2.24 µM) under *in-vitro* conditions [72]. Molecular docking studies illustrated its robust binding to ACE2, demonstrating an affinity of -8.46 kcal/mol and identifying potential binding sites such as HIS-505, ARG-273, and ASN-149 [73]. In another docking investigation by Laksmiani *et al*. (2020), baicalin displayed binding energies of -8.5, −6.5, −6.4, and −6.9 kcal/mol to key targets of SARS-CoV-2, including PLpro, Spike, 3CLpro, and RdRp, respectively [74]. These combined *in vitro* and *in silico* results propose baicalin's efficacy as a treatment for COVID-19. However, additional research is essential to enhance certainty regarding its efficiency and mode of action.

3.2. Scutellarin

Scutellarin, a flavone derived from *Scutellaria barbata* and *S. lateriflora* (Table **1**), exhibits various pharmacological effects with anticoagulation, vascular relaxation, anti-platelet, antioxidant and anti-inflammatory properties [75]. It exhibited *in vitro* activity for ACE with an IC_{50} of 48.13 ± 4.98 µM, and under *in vivo* conditions, scutellarin treatment decreased the activity and expression of ACE in brain tissue [76]. Molecular docking studies indicated scutellarin's binding to ACE2 at the binding sites ARG-482, UNK-957, and GLU-495, suggesting ACE2 as a potential target for scutellarin [73]. Due to its low toxicity, further investigation is warranted to unravel the efficacy of scutellarin against SARS-CoV-2.

3.3. Hesperetin

Hesperetin, a flavone and a 4′-methoxy derivative of eriodictyol (Table **1**), is notably present in the bitter orange (*Citrus aurantium*) peels and Mandarin orange (*Citrus reticulatae*), extensively employed in traditional Chinese medicine, specifically as "Citri Reticulatae Percarpium or Chen pi," for managing various digestive disorders [77, 78]. Hesperetin blocks the spliting action of the 3C-like protease (3CLpro) of SARS-CoV-2 (IC_{50} = 8.3 µM) [79]. Although its potential against this novel coronavirus is not conclusively established, homology modeling indicates hesperetin's capability to inhibit ACE2 (projected ΔG of -8.3 kcal/mol), primarily interacting with GLU-479, SER-611, ARG-482, and TYR-613 [73]. Subsequent *in silico* studies further reveal hesperetin's potential to block various SARS-CoV-2 target proteins, including ACE2, TMPRSS2, RdRp, PLpro, and 3CLpro with 7.94, -7.00, -5.39, -6.99 and -7.49 kcal/mol binding energies, respectively [74]. Given hesperetin's low toxicity and *in silico* efficacy against SARS-CoV-2 target sites, additional investigations are warranted to assess its potential as a therapeutic candidate.

3.4. Hesperedin

Hesperidin, a flavone glycoside (Table **1**), occurs in fruits like sweet orange (*Citrus sinensis*) and lemon (*Citrus limon*) [80, 81]. It exhibits diverse therapeutic activities, including antiviral, antihypertensive, anti-inflammatory, cardioprotective, venotonic, anti-diabetic, antihyperlipidemic, and anti-atherogenic effects against the influenza virus, reducing virus replication. Molecular docking studies indicate high potential binding affinities of Hesperidin for key sites of SARS-CoV-2-ACE2, RdRp, 3Clpro, Spike, and PLpro-with affinity energies of −8.8, −6.9, −8.0, −6.5, and −7.0 kcal/mol, respectively, suggesting Hesperidin's potential against SARS-CoV-2 [82].

Hesperidin's antiviral action for the influenza virus includes the induction of the mitogen-activated protein kinase (MAPK) pathway, renowned for preventing viral spread and replication, thereby curtailing tissue damage. Given the significance of the interferon-MAPK pathway in boosting the immune response to COVID-19, Hesperidin's activation of host immunity may contribute to patient recovery [83]. Moreover, the potent anti-inflammatory properties of Hesperidin hinder the release of pro-inflammatory cytokines like IL-2and IFN-γ [147]. It prevents the initiation of the NF-κB signaling cascade, thereby blocking the secretion of markers (IL-6 and TNFα) in type 2 diabetic individuals. As an adjuvant therapy, Hesperidin could help control severe inflammatory reactions against COVID-19, emerging as a potential candidate for further investigation in disease treatment [149].

3.5. Glycyrrhizin

Glycyrrhizin, a saponin molecule derived from Liquorice root (*Glycyrrhiza glabra*) (Table **1**), contains active constituents like carvacrol and thymol, known for their significant bactericidal and antiviral effects. Thymol, also identified as a spike protein inhibitor, is found in Thymus vulgaris and extracted from various plant species such as *Ocimum* sp, *Origanum* sp, *Monarda citriodora*, *etc*. [84, 85]. In a study comparing conventional antiviral drugs against two clinical coronavirus isolates, Glycyrrhizin exhibited superior viral inhibitory effects over mycophenolic acid, pyrazofurin, 6-azouridine, and ribavirin. GL effectively blocked SARS-type coronavirus attaching, penetrating, and replication in Vero cells, demonstrating a selectivity index (SI) of 67. While less active during virus adherence, it showed the maximum inhibitory effect when introduced after virus adherence. Chemically modified glycyrrhizin molecules in another study exhibited increased antiviral potency, albeit with a reduced SI compared to glycyrrhizin [86]. In *in-silico* studies, Glycyrrhizin demonstrated potential binding to ACE2 (predicted ΔG of -9.0 kcal/mol), primarily interacting with ASP-30, ARG-393, GLN-388, and ARG-559 [73]. Molecular docking studies also revealed binding energies of glycyrrhizin acid with other SARS-CoV-2 targets-3Clpro, RdRp, Plpro, and Spike -6.9, -7.2, -7.3, -6.5, and kcal/mol, respectively [82]. Given the low toxicity of Glycyrrhizin and its potential interaction with key SARS targets, further investigation into its effectiveness against SARS-CoV-2 is warranted [150].

3.6. Nicotianamine

Nicotianamine, a metal-chelating molecule widely present in higher plants [87], was identified by Takahashi *et al*. (2015) as an efficient inhibitor of ACE2 (IC_{50} = 84 nM). Molecular docking investigations of nicotianamine to the ACE2 enzyme revealed potential affinity (ΔG =-5.1 kcal/mol). The primary binding sites were GLN-442, GLN-522, SER-409, GLU-406, and ARG-518 [73, 88].

3.7. Quercetin

Quercetin, a flavonoid compound abundant in *Ginkgo biloba*, green tea, onions, grapes, berries, and apples (Table **1**) [84], exhibits diverse biological activities, including antiviral properties against various viruses like Hepatitis C Virus (HCV), Enterovirus 71 (EV71), SARS-CoV-2, and Influenza A Virus (IAV) [90, 91]. Studies indicate an inhibition rate of 82% on SARS-CoV 3Clpro [91, 92]. Molecular docking studies by Laksmiani *et al*. (2020) reveal robust quercetin binding to key SARS-CoV-2 targets with promising binding energies, suggesting its potential efficacy against the disease [74]. Considering its potency and wide availability at a relatively low cost, further investigation into quercetin's effectiveness against SARS-CoV-2 is warranted.

3.8. Tea

Tea extracts, rich in polyphenols such as catechin, demonstrate potential coronavirus inhibition *in vitro* (Table **1**). A study from the Centre for Disease Control of Zhejiang Province revealed a significant decrease (more than 100 folds) in SARS-CoV-2 nucleic acid proliferation in Vero cell lines with tea extract pre-treatment (2.5-10 mg/mL). Green tea extracts at 0.25 mg/mL inhibited SARS-CoV-2 infection. Molecular docking experiments identified epigallocatechin gallate as a key molecule, blocking S protein binding to ACE2 (Kd = 121 nM). Considering tea's detoxification, anti-oxidation, and cardio-cerebrovascular benefits, tea's potency against coronaviruses merits further evaluation.

3.9. Saikosaponins A, B2, C, and D

Saikosaponins, triterpene glycosides occurring naturally (Table **1**), derived from herbal medicines like Figwort (*Scrophularia scorodonia*), parsley tree (*Heteromorpha* spp.), and Chinese thorough wax (*Bupleurum* spp.), exhibit antiviral properties for HCoV-22E9. In human fetal lung fibroblasts, SARS-CoV-229E was significantly inhibited by saikosaponin B2, and no cytotoxicity was detected up to 25 μmol/L, making saikosaponins potential candidates for further testing against COVID-19, given their effectiveness against SARS-CoV-229E.

3.10. Resveratrol

Resveratrol, a stilbenoid (Table **1**) identified in plants like *Vaccinium macrocarpon, Vitis vinifera, and Polygonum cuspidatum*, exhibits anti-inflammatory properties and is known to be produced in response to plant injury or pathogen attack. It has demonstrated antiviral properties against MERS-CoV by blocking viral replication and suppressing viral RNA and nucleocapsid expression. Molecular docking studies indicate high binding affinity of resveratrol to key protein targets of coronaviruses (-6.1, -5.3, -6.1, -7.2, and -6.7 kcal/mol on ACE2, 3CLpro, Spike, PLpro, and RdRp, respectively). Given its effectiveness against MERS-CoV and the homology with SARS-CoV-2, further studies on resveratrol's potential in treating COVID-19 are warranted.

Table 2. *In silico* studies of some potent plant derived natural products against key targets of SARS-CoV-2.

Plant Molecule	Target	Binding Energy	References
Saikosaponin V	NSP15	-8.358	[125]
Saikosaponin U	NSP15	-7.272	[125]
Saikosaponin C	NSP15	-6.981	[125]
Saikosaponin K	NSP15	-6.79	[125]
Saikosaponin 1b	NSP15	-6.376	[125]
Saikosaponin U	spike glycoprotein	-8.429	[125]
Saikosaponin V	spike glycoprotein	-8.294	[125]
Saikosaponin C	spike glycoprotein	-7.274	[125]
Saikosaponin K	spike glycoprotein	-6.251	[125]
Saikosaponin R	spike glycoprotein	-6.615	[125]
Pavetannin-C1	spike glycoprotein	-11.1	[130]
Cinnamtannin-B1	spike glycoprotein	-10.2	[130]
6-Glucopyranosyl procyanidin B1	spike glycoprotein	-9.9	[130]
Procyanidin-B7	spike glycoprotein	-9.6	[130]
Proanthocyanidin-A2	spike glycoprotein	-9.4	[130]
Tenuifolin	spike glycoprotein	-8.7	[130]
α-Colubrine	TMPRSS2	-9.2	[126]
2-Hydroxy-3-methoxystrychnine	TMPRSS2	-9.2	[126]
Bicuculine	TMPRSS2	-9.3	[126]
Egenine	TMPRSS2	-9.3	[126]
Ararabinol	cathepsin L.	-8.9	[126]
(+)-Oxoturkiyenine	cathepsin L	-8.3	[126]
3,17-Cinchophylline	cathepsin L.	-8.3	[126]
Rugosanine B	cathepsin L.	-8.2	[126]
Trichotomine	cathepsin L.	-8.2	[126]
Tectol	cathepsin L.	-8.1	[126]
Silymonin	cathepsin L.	-8.1	[126]
Picrasidine M	cathepsin L.	-8.0	[126]
Trisjuglone	cathepsin L.	-8.0	[126]
Piceatannol	S-protein: ACE2 receptor	-8.2	[128]
Pinosylvin	S protein: ACE2 receptor	-7.3	[128]
Pterostilbene	S-protein: ACE2 receptor	-7.0	[128]
Resveratrol	S-protein: ACE2 receptor	-8.0	[128]
Glycyrrhizin	Mpro	-8.1	[131]
Tryptanthrine	Mpro	-8.2	[131]
β-sitosterol	Mpro	-7.2	[131]
Indirubin	Mpro	-7.6	[131]
Indican	Mpro	-7.5	[131]
Hesperetin	Mpro	-7.9	[131]

(Table 2) contd…

Plant Molecule	Target	Binding Energy	References
Indigo	Mpro	-7.5	[131]
Berberine	Mpro	-8.1	[131]
Crysophanic acid	Mpro	-7.3	[131]
Kaempferol	MPro	-8.58	[127]
Quercetin	MPro	-8.47	[127]
Luteolin-7-glucoside	MPro	-8.17	[127]
Demethoxycurcumin	MPro	-7.99	[127]
Naringenin	MPro	-7.89	[127]
Apigenine-7-glucoside	MPro	-7.83	[127]
Oleuropein	MPro	-7.31	[127]
Catechin	MPro	-7.24	[127]
Curcumin	MPro	-7.05	[127]
Epicatechin-gallate	MPro	-6.67	[127]
Crocin	MPro	-8.2	[132]
Digitoxigenine	MPro	-7.2	[132]
β-Eudesmol	MPro	-7.1	[132]

3.11. Andrographolide

Andrographolide, derived from *Andrographis paniculata*, a labdane diterpenoid, exhibits diverse biological activities, including antiviral properties against the Chikungunya virus (CHIKV), Dengue virus (DENV), influenza A virus (IAV), Enterovirus D68 (EV-D68), and human immunodeficiency virus (HIV). In studies for H1N1, it inhibits RLR signaling pathways, reducing virus-induced cell death. Molecular docking studies with key SARS-CoV-2 sites (RdRp, 3CLpro, ACE2, Spike protein, and PLpro) reveal strong binding potentials (-6.0, -6.1, -6.5, -5.7, -6.8 kcal/mol), indicating significant efficacy for SARS-CoV-2. Additional investigations are warranted to validate its effectiveness.

3.12. Silvestrol

Silvestrol, a natural flavagline found in *Aglaia* trees, especially *A. silvestris* and *A. foveolate*, exhibits anticancer activity and potent antiviral properties. It has shown efficacy against the Ebola virus, Poliovirus 1 (PV), and Human Rhinovirus (HRV) A1, HCoV-22E, and MERS-CoV. In studies on CoV-infected cells, silvestrol inhibits cap-dependent viral mRNA translation, demonstrating high effectiveness (EC_{50}=3 nM for HCoV-22E and 1.3 nM for MERS-CoV). Mechanistically, it suppresses the expression of nSPs and SPs and inhibits the establishment of viral transcription/replication complexes. Further investigation of its antiviral properties for SARS-CoV-2 is warranted.

4. NATURAL PRODUCT LIBRARY SCREENING AGAINST SARS-COV-2

Several explorations have delved into the inhibitory potential of naturally occurring compounds for SARS-CoV. In an inclusive screening of 200 Chinese medicinal herbal extracts, Li *et al*. (2005) identified *Lindera aggregatae*, *Pyrrosia lingua*, *Artemisia annua*, and *Lycoris radiata* as potent inhibitors [106]. Isolated from *Lycoris radiata*, Lycorine, demonstrated significant antiviral properties (EC_{50}=15.7 μM). In a separate investigation, Yu *et al*. (2012) explored compounds inhibiting the helicase nsp13 protein 9 (crucial for viral replication) of SARS-CoV, identifying scutellarein and myricetin as potent inhibitors with IC_{50} of 0.86 ± 0.48 μM and 2.71 ± 0.19, respectively [107]. These compounds reduced ATPase activity by over 90% at 10 mM without cytotoxic effects. Furthermore, Wu *et al*. (2004) tested an extensive library of over 10,000 compounds against SARS-CoV [109]. Among the screened substances, escin (EC_{50} = 6.0 μM) and reserpine (EC_{50}=3.4 μM) displayed notable inhibitory effects on SARS-CoV 3CLpro. Reserpine, an alkaloid derivative of *Rauwolfia* species, and escin, a saponin mixture derived from horse chestnut, exhibited promising antiviral activities. These studies collectively underscore the potential of naturally occurring compounds, such as lycorine, myricetin, scutellarein, escin, and reserpine, as candidates for further research in the advancement of drugs for COVID-19.

Yi *et al*. (2004) devised a two-step screening method targeting the SARS-CoV S protein, combining pseudo-typed virus infection assay and frontal affinity chromatography-mass spectrometry (MS/FAC) [110]. Screening 121 small molecules from Chinese herbs with proven activity against hepatitis B virus, RSV, and HIV-1, they identified luteolin and tetra-O-galloyl-β-D-glucose as significant blockers of SARS-CoV infection. These molecules demonstrated dose-dependent inhibition, suggesting their potential as virus entry inhibitors targeting the S2 protein. Similarly, Hoever *et al*. (2005) [86] screened fifteen Glycyrrhizin (GL) deriva-

tives isolated from *Glycyrrhiza radix* against SARS-CoV. Seven GL derivatives were identified to block replication of SARS-CoV *in vitro* at minimal concentrations than the parent molecule. Introducing 2-acetamido-β-D-glucopyranosylamine into the glucoside chain led to a tenfold rise in anti-SARS-CoV properties, surpassing the efficacy of GL Amides. Additionally, conjugates featuring a free 30-COOH function and two amino acid residues demonstrated a remarkable 70-fold increase in action. Additional investigations are required to evaluate these compounds' cytotoxicity, selectivity, and viability as potential lead molecules for SARS-CoV-2.

Assessment of 720 natural compounds for SARS-CoV 3CLpro inhibition revealed two standout inhibitors: 3-isotheaflavin-3-gallate (IC_{50} = 7 μM) and tannic acid (IC_{50} = 3 μM) [111]. These natural polyphenols, found in tea, showed promising inhibitory effects on 3CLpro. Tea extracts from Black and Pu-erh tea exhibited heightened efficacy in blocking 3CLpro compared to Oolong or Green tea. Theaflavin-3-3'-digallate emerged as a potent 3CLpro inhibitor, underscoring the need for additional exploration of these natural products to inhibit SARS-CoV-2 replication.

Assessing *Isatis indigotica* root's aqueous extract on SARS-CoV 3CLpro identified indigo, β-sitosterol, and sinigrin with micromolar IC_{50} values. Hesperetin, among phenolics, exhibited the maximum potency {(IC_{50} values of 8.3 μM (cell-based) and 60.3 μM (cell-free)}. Sinigrin and hesperetin surfaced as promising lead molecules for SARS-CoV [79]. *Torreya nucifera* leaves' ethanol extract significantly restrained SARS-CoV 3CLpro. Amentoflavone, isolated through bioactivity-guided fractionation, exhibited the utmost inhibitory efficacy (IC_{50}= 8.3 μM), suggesting its potential as a lead gainst COVID-19 [90]. Screening of 221 phytocompounds for activity against SARS-CoV led to the identification of specific lignoids and abietane-type diterpenoids, such as savinin and 8-hydroxyabieta-9(11)-13-dien-12-one, as robust blockers of SARS-CoV 3Clpro [114]. Screening *Alnus japonica* for SARS-CoV Plpro inhibitory diarylheptanoid derivatives led to the identification of hirsutenone displaying the lowest IC_{50} value at 3.0 ± 1.1 μM, indicating significant selectivity towards coronaviral proteases [113]. Phlorotannins derived from the ethanol extract of *Ecklonia cava* demonstrated a dose-dependent SARS-CoV 3CLpro inhibition, and Dieckol exhibited the highest inhibitory property [115]. *In silico* studies suggested dieckol's potential as an important molecule for further progress in COVID-19 therapy.

Coumarins and alkylated chalcones derived from *Angelicakeiskei* were tested for their anti-SARS-CoV PLpro and 3CLpro activity. The alkylated chalcones, including xanthoangelol B and E, exhibited competitive dose-dependent inhibition against SARS-CoV 3CLpro, with xanthoangelol E showing the maximum potency. Additionally, xanthoangelol E displayed potent inhibition against SARS-CoV PLpro, making it a prospective remedy against COVID-19 [116]. Polyphenols derived from *Broussonetia papyrifera* were characterized and assessed for their anti-SARS/MERS activity against 3CLpro and PLpro coronavirus cysteine proteases. The polyphenol papyriflavonol A emerged most formidable Plpro inhibitor (IC_{50} =3.7 μM). These results suggest that papyriflavonol A could be a compelling candidate poised for more exploration and advancement as an anti-nCov-2019 agent, although an additional investigation is warranted [92]. The methanol extract from *Strobilanthes cusia* leaves and its chemical constituents were evaluated for antiviral efficacy against HCoV-NL63. Among the main components, including Indigodole B, indigodole A, betulin, tryptanthrin, indirubin, and β-sitosterol, tryptanthrin demonstrated the most potent antiviral efficacy. It hindered viral replication in the initial and final phases, effectively suppressing RdRp and PLpro activities to mitigate HCoV-NL63 [117].

Kim *et al*. (2019) [118] explored the antiviral potential of *Stephania tetrandra* derived bis-benzylisoquinoline alkaloids, namely fangchinoline (FAN), cepharanthine (CEP), and tetrandrine (TET), against human coronavirus (HCoV). CEP, FAN, and TET exhibited noteworthy antiviral effects, displaying IC_{50} of 0.83 ± 0.07, 1.01 ± 0.07, and 0.33 ± 0.03 μM, respectively, and selective indices exceeding 13.63, 11.46, and 40.19. These compounds demonstrated inhibition of virus-induced cell death, suppression of viral replication, and interference with viral N and S protein expression, indicating their antiviral properties for HCoV-OC43. Additionally, these show promise as lead molecules for combating SARS-CoV-2. Cao *et al*. (2015) [119] screened the clinical samples of 720 compounds for anti-coronavirus activity, identifying homoharringtonine as an effective inhibitor for various coronaviruses, including a low IC_{50} of 11 nM against murine coronavirus, without inducing cytotoxicity. Homoharringtonine thus presents itself as a potential anti-coronavirus drug candidate. Evaluating extracts of 7 medicinal plants for HIV/SARS-CoV S pseudovirus led to singling out Caryophylli flos Extract (CFE) and Cinnamomi cortex Extract (CCE) as active. The n-butanol fraction of Cinnamomi cortex (CC/Fraction 2), containing compounds like procyanidin and procyanidin A2, showed average anti-wt SARS-CoV properties with IC_{50}= and 41.3 ± 3.4 and 29.9 ± 3.3 μM, respectively. These compounds hold potential as lead molecules for COVID-19 drug development, warranting further investigation [121]. Ethanol extract of *Psoralea corylifolia* seeds demonstrated robust inhibitory action for SARS-CoV PLpro, boasting an IC_{50} value of 15 mg/ml. Six aromatic compounds from the ethanol extract, including psoralidin and isobavachalcone exhibited a dose-dependent inhibitory effect on Plpro [122]. These compounds show promise for further exploration in the COVID-19 drug development.

5. *IN SILICO* STUDIES OF NATURAL PRODUCT LIBRARIES AGAINST KEY TARGETS OF SARS-COV-2

A comprehensive survey to identify naturally-occurring compounds having established anti-MERS-CoV or SARS-CoV properties led to the exploration of thirteen molecules from 230 Chinese herbs for their potential effectiveness for SARS-CoV-2. The selected compounds, including tanshi-

none, sugiol, quercetin, n-cis-feruloyltyramine, moupinamide, Kaempferol, dihydrotanshinone I, dihomo-c-linolenic acid, desmethoxyreserpine, cryptotanshinone, coumaroyl tyramine, and betulinic acid, exhibited promise against viral entry, viral replication, 3CLpro inhibition, and SARS-CoV PLpro targets, suggesting their potential for COVID-19 therapy [123]. Qamar *et al*. (2020) screened 32,297 potential antiviral phytochemicals from Traditional Chinese Medicine (TCM) against SARS-CoV-2 CLpro, utilizing a 3D homology model. Various compounds derived from plants, such as amaranthin, licoleafol, calceolarioside B, (2S)-eriodictyol 7-O-(6'-O-galloyl)- β-D-glucopyranoside, 3,5,7,3′,4′,5′-hexahydroxy flavanone-3-O-β-D-glucopyranoside, myricetin 3-O-β-D-glucopyranoside, methyl rosmarinate, 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl) isoflavone, and myricitrin, exhibited robust antiviral activity for SARS-CoV-2 [124]. Saikosaponin U and V, derived from herbal sources, demonstrated high affinity to SARS-CoV-2 protein targets NSP15 Endoribonuclease and spike glycoprotein. Computational screening of phytochemicals led to the identification of TMPRSS2 inhibitors, including 2-Hydroxy-3-methoxystrychnine, Pseudo-Alpha-Colubrine, Strychnine N-oxide, alpha-Colubrine, Qingdainone, Adlumidine, and Edgeworoside C, Bicuculline, and Egenine, with potential antiviral activity [125, 126]. Molecular docking helped to identify bioactive compounds such as kaempferol, quercetin, catechin, oleuropein, demethoxycurcumin, curcumin, epigallocatechin, luteolin-7-glucoside, naringenin, and apigenin-7-glucoside, as effective inhibitors of COVID-19 Mpro [78, 127]. Hussain *et al*. (2020) conducted molecular docking studies on stilbenoid analogs, highlighting Piceatannol, Pinosylvin, Pterostilbene, and Resveratrol as compounds with substantial binding affinity, particularly resveratrol, warranting additional *in vitro* and *in vivo* testing [128]. Sevki *et al*. (2020) screened natural compounds against Mpro, identifying apiin, rutin, diosmin, and hesperidin as robust inhibitors, with hesperidin exhibiting the maximum binding energy at the COVID-19 active site [129]. Tenuifolin and Pavetannin C1 from *Cinnamon* are promising compounds with strong affinity against COVID-19 [130]. Narkhede *et al*. (2020) reported Glycyrrhizin, tryptanthrine, rhein, and berberine as compounds with high interaction and favorable drug-like properties in molecular docking studies against the viral protease, signifying their promise for SARS-CoV-2 treatment [131]. Another study docked 67 natural compounds for the key protease of SARS-CoV-2, revealing β-Eudesmol, Digitoxigenin, and Crocin as potential inhibitors based on their binding energies [132]. These findings propose these natural compounds as potential candidates for further investigation against the novel coronavirus (Table **2**) [133-135].

6. RECENT FOLK REMEDIES FOR SARS-COV-2

Specific folk remedies with confirmed effectiveness against COVID-19 have been documented; some of these plant species with antiviral or immune-boosting properties include *Tinospora cordifolia*, *Chamaenerion angustifolium*, *Allium sativum*, *Piper nigrum*, *Curcum alonga*, *Withania somnifera*, *Nigella sativa*, *Ocimum sanctum*, *Azadirachta indica* and *Zingiber officinalis*. These species have been endorsed by the Ministry of AYUSH in India for routine use for COVID-19 due to their phytochemicals and bioactive complexes exhibiting antiviral, antibacterial, antioxidant, and anti-inflammatory properties [136-138] and have been reported to enhance immunity and demonstrate antiviral effects, and alleviate coronavirus symptoms [139]. Emphasizing the need for ongoing research and continually validating these plants' efficacy is crucial. Nevertheless, even at the molecular level, bioactive compounds within these plants have exhibited inhibitory effects on different viral lifecycle stages, like viral attachment, penetration, release, RNA, protein synthesis, and viral proteases [140-143]. Active ingredients like ursodeoxycholic acid, glycyrrhizic acid, and quercetin demonstrate antiviral activity and potentially block the ACE2 protein, hindering SARS-CoV-2 infection [144].

Similarly, olive leaf extract has been reported for its various beneficial activities, including antithrombotic, immunomodulatory, antipyretic, analgesic, and anti-inflammatory effects. These properties are particularly useful in restraining the disseminated intravascular coagulation and associated inflammatory cytokine storm in patients of COVID-19 patients. Olive plant leaves contain triterpenoids like ursolic acid, oleanolic acid, and maslinic acid, as well as phenolic compounds, including hydroxytyrosol, luteolin-7-O-glucoside, verbascoside, apigenin-7-O-glucoside, and oleuropein. Recent *in vitro* and computational studies have identified these compounds as metabolites with reported anti-SARS-CoV-2 activity [145]. Extracts of *Artemisia annua* and its molecules have also demonstrated effectiveness against COVID-19 [146]. Furthermore, herbal medicines, exemplified by Lianhua Qingwen capsules, Xuebijing injection, and *Houttuynia cordata*, exhibit a strong affinity for the critical ACE2 receptor, contributing to COVID-19 prevention and treatment in China. Although these reports indicate pretty encouraging results, it is recommended that folk remedies should be taken under professional guidance. Future research studies are warranted to establish folk medicine's dosages, efficacy, and pharmacological effects in quantifiable matrices specifically.

CONCLUSION AND FUTURE PERSPECTIVES

In conclusion, while FDA-approved antiviral drugs and vaccines have been crucial in managing COVID-19, concerns about waning vaccine-based immunity underscore the need for safe and effective therapeutic bioactives against SARS-CoV-2. This review emphasizes the efficacy of folk remedies and naturally occurring plant molecules with anti-SARS-CoV properties, demonstrating their ability to inhibit vital viral proteins and hinder viral replication. Plant bioactives like homoharringtonine, lycorine, and silvestrol exhibit potent antiviral activity *in vitro*, making them promising lead compounds for further *in vivo* studies on animal models to develop COVID-19 antivirals. The highlighted studies provide essential leads for validation through *in vitro* assays, *in vivo* studies on COVID-19 animal models, and subsequent clinical trials to ensure efficacy and safety before

large-scale administration. Innovative approaches, including high-throughput imaging platforms, sensitive cell-based assays, and *in silico* methods, offer promising avenues for drug discovery. Establishing biosafety infrastructure for screening and validating potential antivirals for SARS-CoV-2 is crucial, enabling the swift identification of plant-based bioactives for COVID-19 treatment. Following *in vitro* and *in vivo* validation, clinical trials may facilitate their use as single or combinational therapies with FDA-approved agents, strengthening preparedness for future viral outbreaks and SARS-CoV-2 evolving variants.

AUTHORS' CONTRIBUTIONS

JK and BAM played a role in conceiving and designing the study and drafting the initial manuscript. SA, SGG, SB, SAM, RKT, LBT, VRR, and NS were involved in writing specific sections and conducting literature surveys. VRR participated in manuscript revision and figure preparation. TM, MH, VRR, and LAP focused on the infection mechanism and manuscript editing. All authors contributed to the manuscript, and their input was acknowledged by reading and approving the final submitted version.

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