



Review Article

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Antiviral Phytocompounds: A Methodical Review of Therapeutic Efficiency Against SARS-Like Human Coronaviruses

Yahyea Baktiar Laskar¹, Udaya Kumar Vandana², Sayani Roy², Pranab Behari Mazumder^{1*}, Anupam Das Talukdar³, Ajaikumar B. Kunnumakkara⁴ and Monjur Ahmed Laskar⁵



¹Natural product and Biomedicine Research Laboratory, Department of Biotechnology, Assam University, Silchar, India

²Microbial Molecular Biology Laboratory, Department of Biotechnology, Assam University, Silchar, India

³Ethnobotany and Medicinal Plant Research Laboratory, Department of Life Science & Bioinformatics, Assam University, Silchar, India

⁴Cancer Biology Laboratory, Department of Biosciences and Bioengineering, Indian Institute of Technology, Guwahati, India

⁵Bioinformatics Centre, Department of Life Science & Bioinformatics, Assam University, Silchar, India

Abstract

Introduction: Coronaviruses are a group of rapidly evolving and single-stranded RNA viruses that cause mild upper respiratory infections. The casualty caused by coronavirus diseases like the Severe Acute Respiratory Syndrome (SARS) in 2004, Middle East respiratory syndrome (MERS) in 2012 and the recently discovered SARS-like disease, Coronavirus disease 2019 (CoVID-19) has been recognized as a threat to public health. Considering all coronaviruses shares similarity in genomic architecture and clinical manifestations, this study is aimed to summarize present knowledge about the therapeutic efficiency of medicinal plant and their compounds against SARS-like human coronaviruses and to report potential preventive drug templates from natural products.

Methods: In this comprehensive review, we have assembled and investigated available published information on natural products with potent anti-viral activity against the pathogenesis of SARS-like coronaviruses from different electronic databases. Systematically we have included plants and their compounds that have been historically active against RNA viruses including SARS-like coronaviruses.

Results: This study observed that promising therapeutic outcome can be anticipated from at least fifteen such traditionally used phytocompounds in the prevention and treatment of coronavirus diseases and its associated health complexities.

Discussion/Conclusions: Because of a variable genome in RNA viruses, it is very difficult to design a drug or vaccine that is effective in the long term. Parallel to contemporary medicines, plant-based natural products with antiviral potential can also be assessed for their efficiency and safety against these diseases.

Keywords

SARS-CoV-2, SARS, MERS, Coronavirus Disease, Phytomedicine, Phytochemical

Introduction

Coronaviruses are a group of rapidly evolving, single-stranded (+) RNA viruses that cause mild to moderate upper respiratory infections generally spread through airborne droplets to the nasal mucosa [1,2]. Previously the two subgroups of coronaviruses and their serotypes - the alpha-coronaviruses (229E, NL63) and the beta-coronaviruses (OC43, HKU1) were known to cause mild respiratory illnesses in human [1,3]. In 2003-2005, a newly discovered beta-coronavirus in China caused SARS with an estimated 8,098 reported cases [4]. Again in 2012, the Middle East respiratory syndrome (MERS) caused by another SARS-like coronavirus belonging to the order *Nidovirales* took 858 lives as reported by the World

Health Organization (WHO) [5]. Recently the emergence of a highly infectious beta-coronavirus, the SARS coronavirus 2 or

***Corresponding author:** Prof. Dr. Pranab Behari Mazumder, Professor & Head, Department of Biotechnology, Assam University, Silchar-788011, Assam, India, Tel: +91-9435075765

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SARS-CoV-2 that causes coronavirus disease 2019 (CoVID-19) which lead to a global public health emergency [6,7]. The first appearance of the disease in China and its subsequent global spread affected more than 12.7 million people worldwide while causing 0.56 million deaths as of July 2020 with a 2% crude case fatality rate [8].

All these viruses mostly originate in mammals other than human and rapidly evolve to become contagious to human [3]. Phylogenetically, all coronaviruses show a typical genomic homology with 14 open reading frames (ORFs) that encode 27 proteins [9]. Typically, the ORF1 and ORF2 encode 15 non-structural proteins (Nsps) essential for replication and other structural proteins like spike protein (S), envelope protein (E), membrane protein (M), nucleocapsid (N) and other accessory proteins [10]. Among them, blocking the envelope projects glycoproteins known as Spike-glycoprotein or S-protein is considered as a vital step in preventing the pathogenesis of coronaviruses as it is crucial for host cell attachment and entry [10]. Further, the established biological function and presence of vital enzyme active site in *Nsps* like chymotrypsin-like main protease (3CL^{pro}), Papain-like proteinase (PL^{pro}), RNA-dependent RNA polymerase (*RdRp*) and *helicase* are considered as excellent therapeutic targets for developing small-molecule inhibitors [11,12]. Especially, the highly conserved 3CL^{pro} is considered a key therapeutic target for its multifunctional role in the production of functional proteins that are essential for viral replication [13]. The 3CL^{pro} along with PL^{pro} processes replicase polyprotein involved in the transcription and replication of viral RNAs [13-15]. The *RdRp* or *nsp12* is the most versatile enzymes of coronaviruses that play a central role in the replication and transcription machinery that leads to the synthesis of viral RNAs [16,17]. Apart from these, double-stranded RNA unwinding *helicase* or *nsp13* is also suggested as a possible target to tackle coronaviruses [18,19]. Besides, *nsp1*, *nsp3c*, and *ORF7a* are the major virulence factors of coronaviruses that impede the host's innate immunity and help the virus escaping the immune response, and hence they are considered as therapeutic targets [12]. Thus, non-covalent inhibitors of these viral proteins could serve as templates for developing therapeutic antivirals [20,21]. As several investigations are underway to design an effective vaccine or drug that can break the viral infection with adequate safety measures, thus far no specific vaccines or drugs are available to treat coronavirus infections. Reportedly encouraging results with rapid symptom improvement was specifically observed with the early combinatory clinical trial of *lopinavir-ritonavir* HIV antivirals, *favipiravir*, *remdesivir* in CoVID-19 patients [22-24]. Besides, antimalarial *chloroquine* and *hydroxychloroquine* gained intense attention for their efficiency against SARS-like coronaviruses [25,26]. Although conventional antivirals and some other drugs are showing promising outcomes, their efficiency and safety in patients of coronaviral diseases are still ambiguous [27].

Consequently, researchers are considering some alternative approaches like herbal therapies using antiviral medicinal plants or their bioactive components to design specific herbal cure of coronavirus diseases [28]. Considering the role of antiviral medicinal plants in both traditional and modern

therapies, their bioactive constituents may help to design an efficient and cost-effective preventive cure against the pathogenesis of rapidly evolving RNA viruses including coronaviruses (CoV) [29]. Historically, several antiviral medicinal plants and their bioactive constituents are used against viral diseases like Influenza, acquired immunodeficiency syndrome (AIDS), hepatitis, and CoV-diseases particularly MERS and SARS [29-32]. Given the identical genomic organization and similar clinical manifestation of all coronaviruses, we have amassed all available information on antiviral plants and their bioactive compounds that were reported previously to exhibit strong inhibitory activity especially against major proteases of SARS-coronaviruses. Previously published information on such plants and their phytocompounds were retrieved from different electronic databases like Elsevier, PubMed, and Google Scholar intending to summarize current knowledge and to report their feasibility in the treatment of coronaviral diseases. This comprehensive data analysis revealed that at least fifteen such phytocompounds could play a significant role in the long-term prevention and treatment of coronaviral pathogenesis that must be validated in a proper clinical setup.

Materials and Methodology

This methodological review was carried out in June 2020 through a literature survey of all the related published articles in the last 20 years. For this, available information was retrieved from specialized electronic databases like Elsevier, PubMed, and Google Scholar using a combination of several keywords: coronavirus, human coronavirus, SARS, MERS, natural product, plant extract, plant product, phytochemicals, herbal product, and antiviral. The inclusion criteria for selecting article were based on the type of study, type of plant extract (pure/crude), isolated bioactive natural compound, the historical effectiveness against RNA viruses, specific effects against human coronaviruses, clinical and preclinical studies, and articles showing keywords in the title, abstract or full text. Articles reporting *in-silico* predictions and other systematic reviews were excluded from the study. The repeated articles were removed and the remaining portion was revised to manually reject the articles that did not satisfy the selection criteria. For pure compounds, data related to their therapeutic target, inhibitory concentrations and plant source were noted. For crude extracts, data related to the part of the plant, type of extract, inhibitory concentrations and mode of bioactivity were recorded.

Results and Discussion

Selection of articles

Preliminary the article retrieval process identified 341 articles in the databases Elsevier, PubMed, and Google Scholar. Among them, 40 articles satisfied the inclusion criteria and necessary data was extracted from them. The general characteristics of the clinical and pharmacological aspects of the plant extracts and their phytocompounds identified by this review are listed in Table 1 and Table 2. The chemical structure of some potential antiviral phytocompounds identified by this study is shown in Figure 1.

Anti-SARS-CoV phytocompounds

Since, SARS-like human coronaviruses resemble high similarity in several aspects like genomic organization, receptor binding, and drug targets, thus previously reported phytocompounds and/or their derivatives that showed potent antiviral activity could be used as a template to design anti-SARS-coronavirus therapeutic [10,33]. Below we've listed fifteen such phytocompounds that are historically known to have astonishing antiviral activities against the pathogenesis of RNA viruses and were proven to be bioactive against SARS-CoV-induced cytopathogenicity in cell-based studies.

Aescin: Aescin is a natural mixture of triterpene saponin isolated from *Aesculus hippocastanum* was found to inhibit viral replication of SARS-CoV (H.K. strain) infected Vero E6 cells at an inhibitory concentration (EC_{50}) of 6.0 μ M [34].

Aescin has clinical significance as a potent anti-inflammatory agent, however, its antiviral mechanism is unknown [34,35]. The anti-inflammatory activity of aescin is primarily attributed to the hypoxia-activated reduced adhesiveness of neutrophils and the associated release of inflammatory mediators [35]. The β -aescin, a structural form of Aescin isolated from the same plant exhibited selective virucidal activity (EC_{50} = 1.5-2.4 μ g/ml) and hindered replication of Herpes Simplex Virus type-1(HSV-1), Vesicular Stomatitis Virus, Adenovirus 5 and Dengue Virus type 2 propagated in human corneal cells and human conjunctival cells [35,36].

Amentoflavone: Amentoflavone is a common biflavonoid compound found in more than 120 plant species [37]. Amentoflavone isolated especially from *Torreya nucifera* is known for its potent antiviral activity against several viral diseases

Table 1: Plant extracts that exhibited bioactivity against the cytopathogenicity of previously discovered human and murine coronaviruses

Plant name	Part used	Extract type	Viral disease	Mechanism of action	EC_{50}/IC_{50} (μ g/ml)
<i>Artemisia annua</i>	Whole plant	Ethanol	SARS [66]	↓CPE	34.5-39.2
<i>Pyrrosia lingua</i>	Leaf	Chloroform	SARS [66]	↓CPE	40.5-43.2
<i>Lindera aggregate</i>	Root	Ethanol	SARS [66]	↓CPE	80.6-88.2
<i>Houttuynia cordata</i>	Whole plant	Water	SARS [95]	CD4 ⁺ ↑, CD8 ⁺ ↑ IL-2↑, IL-10↑, ↓3CL ^{pro}	1000
<i>Rheum palmatum L.</i>	--	Ethanol	SARS [96]	↓3CL ^{pro}	13.76 ± 0.03
<i>Isatis indigotica</i>	Root	Water	SARS [90]	↓3CL ^{pro}	217-1210 μ M
<i>Euphorbia Neriifolia</i>	Leaf	Ethanol	HCoV [100]	Decreased survival	--
<i>Toona sinensis</i>	Leaf	Water	SARS [101]	↓CPE, Inhibit replication	--
<i>Cibotium barometz</i>	--	Methanol	SARS [97]	↓CPE, ↓3CL ^{pro}	39± 3
<i>Gentiana scabra</i>	--	Water	SARS [97]	↓CPE, ↓3CL ^{pro}	>50
<i>Dioscorea batatas</i>	--	Methanol	SARS [97]	↓CPE, ↓3CL ^{pro}	44 ± 2
<i>Cassia tora</i>	--	Water	SARS [97]	↓CPE, ↓3CL ^{pro}	>50
<i>Taxillus chinensis</i>	--	Water	SARS [97]	↓CPE, ↓3CL ^{pro}	>50
<i>Cinnamomi cortex</i>	--	Butanol	SARS [91]	↓CPE	7.8 ± 0.3
<i>Caryophylli flos</i>	--	Butanol	SARS [91]	↓CPE	51.3 ± 4.9
<i>Tribulus terrestris</i>	Fruit	Methanol	SARS [98]	↓PL ^{pro}	15.8-44.4
<i>Paulownia tomentosa</i>	Fruit	Methanol	SARS [98]	↓PL ^{pro}	5.0-14.4 μ M

CPE = Cytopathogenic effect; HCoV = Human Coronaviruses; IL = interleukin; 3CLpro = 3C-like protease; PLpro = Papain-like protease; '↑' = increased/up-regulated; '↓' = decreased/down-regulated; '↓' = inhibition.

Table 2: A summary of anti-SARS-CoV phytocompounds and their possible therapeutic target and efficiency.

Therapeutic target	Compound	IC_{50}/EC_{50}	Plant of origin	Ref.	
Viral attachment & entry	S-protein	Ginsenoside-Rb1	100 μ M	<i>Panax ginseng</i>	[34]
		Glycyrrhizin	> 500 μ M	<i>Glycyrrhiza glabra</i> <i>Glycyrrhiza radix</i>	[60,62]
		Cepharanthine	6-9.5 μ g/ml	<i>Stephania sp.</i>	[48]
	ACE2	Emodin	200 μ M	<i>Rheum rhabarbarum</i> <i>Rheum officinale</i>	[52]
		Cepharanthine	0.98 μ M	<i>Stephania japonica</i>	[49]
	Unclear	Saikosaponin B2	1.7 μ mol/L	<i>Bupleurum chinense</i>	[69]
Lycorine		15.7 μ M	<i>Lycoris radiata</i>	[66]	

Viral replication	3CL ^{pro} PL ^{pro}	Amentoflavone	8.3 μM	<i>Torreya nucifera</i>	[31]
		Baicalin	11 μM	<i>Scutellaria baicalensis</i>	[40]
		Theaflavin-3,3'-digallate	9.5 μM	<i>Camellia sinensis</i>	[85,86]
		Xanthoangelol E	1.2-11.4 μM	<i>Angelica keiskei</i>	[88]
		Igesterin	2.6 μM	<i>Triterygium regelii</i>	[89]
		Tingenone	9.9 μM	<i>Triterygium regelii</i>	[89]
		Pristimererin	5.5 μM	<i>Triterygium regelii</i>	[89]
		Celastrol	10.3 μM	<i>Triterygium regelii</i>	[89]
		Quercetin-3-β-galactoside	42.7 μM	<i>Ginkgo biloba</i>	[92]
		Hirsutenone	4.1 μM	<i>Alnus japonica</i>	[93]
		Tanshinones	0.8-30 μM	<i>Salvia miltiorrhiza</i>	[72]
		3-isotheaflavin-3-gallate	7 μM	<i>Camellia sinensis</i>	[85]
		Tannic acid	3 μM	<i>Camellia sinensis</i>	[85]
	Helicase	Myricetin	2.71 μM	<i>Myrica rubra</i>	[94]
		Scutellarein	0.86 μM	<i>Scutellaria baicalensis</i>	[94]
	RdRp	Theaflavin	--	<i>Camellia sinensis</i>	[86]
Unclear	Reserpine	3.4 μM	<i>Rauwolfia sp.</i>	[34]	
	Aescin	6.0 μM	<i>Aesculus hippocastanum</i>	[34]	
	Tetrandrine	295.6 nM	<i>Stephania tetrandra</i>	[44]	

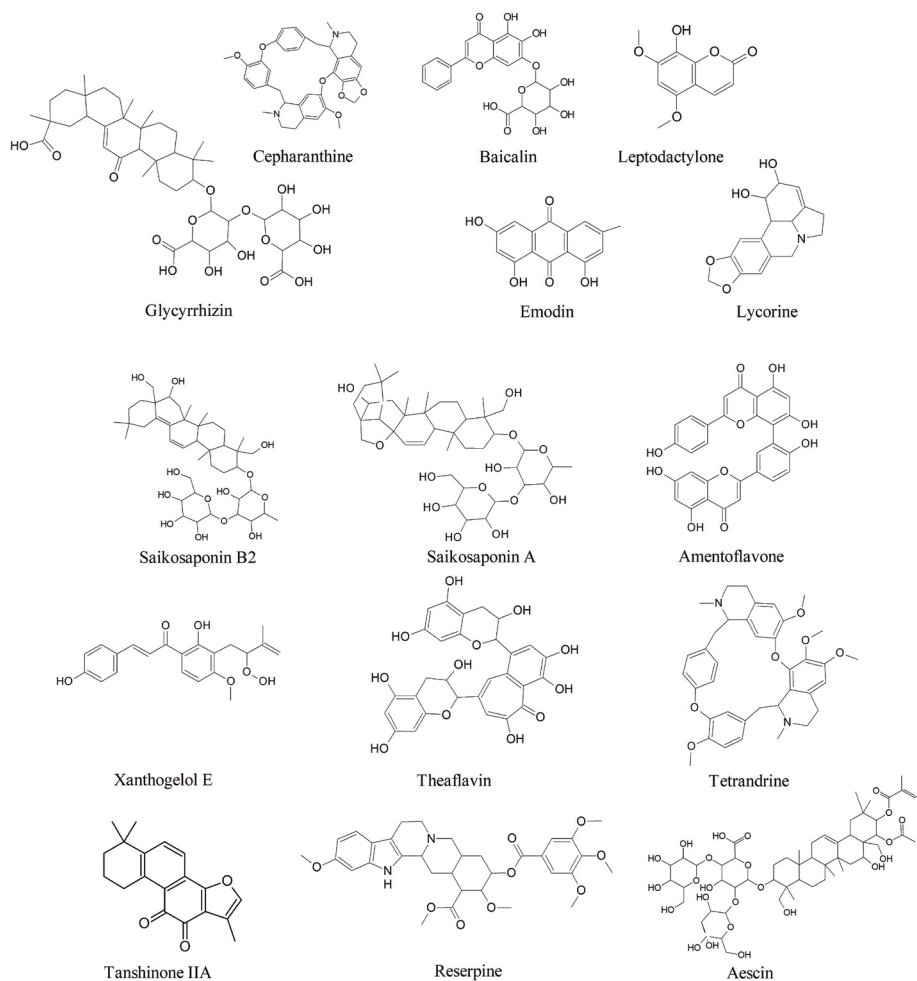


Figure 1: Antiviral Phytochemicals: Some plant-derived compounds that could be a potential therapeutic lead for the prevention and treatment of Human coronaviruses.

including dengue, coxsackie virus B3, human immunodeficiency virus (HIV), and respiratory syncytial virus (RSV) [37]. The biflavonoid showed inhibitory activities against chymotrypsin-like protease (3CL^{pro}) of SARS coronavirus with a low inhibitory concentration of 8.3 μ M [38]. Beside, Apigenin, luteolin, and quercetin from the same plant showed potent activity against 3CL^{pro} in computational studies [38].

Baicalin: Baicalin is a glycosyloxy flavone found in *Scutellaria baicalensis* that shown inhibitory effects against at least 10 different clinical isolates of SARS-CoV [39,40]. Intense inhibitory activity against SARS-CoV was detected in infected Vero cell lines (EC₅₀ = 11 μ g/ml) [40]. In a recent *in-vitro* analysis, baicalin was shown to inhibit highly conserved 3C-like protease (3CL^{pro}) of SARS-CoV-2 [41]. Previously Baicalin was reported to inhibit cellular entry and replication of HIV-1 by conjugating with selected chemokines and inhibiting HIV-1 reverse transcriptase [42]. Besides, baicalin is an anti-inflammatory agent against T lymphocyte activation and gene expression of pro-inflammatory cytokines, which supports its effectiveness against the pathogenesis of respiratory viruses like the RSV [39].

Cepharanthine: Cepharanthine (CEP), a bibenzyl isoquinoline alkaloid found in *Stephania cepharantha* Hayata, *Stephania tetrandra*, and some other allied species of Menispermaceae family [43,44]. It is used widely as conventional medicine in Japan in the treatment of many diseases like leukopenia, snake bites, xerostomia, and alopecia [43]. Beside, CEP has a potent anti-inflammatory, anti-proliferative, apoptotic, and immuno-modulatory effect [43]. The suppressive activity of CEP on the activation of inflammatory cytokine and chemokine reactions is the basis of its antiviral activity against the infection of HIV, Herpes virus, hepatitis B virus, and Coxsackie virus [43,45]. CEP inhibits HIV-1 cell entry by decreasing plasma membrane fluidity and reduces viral replication by inhibition of NF κ B which acts as a strong regulator of HIV-1 gene expressions [43,46,47]. During the SARS-CoV outbreak in 2004, CEP showed inhibitory activity against the SARS-CoV-induced cytopathogenicity in Vero E6 cells infected by F69 strain, with an IC₅₀ value ranging from of 6-9.5 μ g/ml [48]. In a recent study, Cepharanthine alongside two other bis-benzyl isoquinoline alkaloids tetrandrine and fangchinoline were reported to reduce virus-induced cell death of human embryonal lung fibroblast cells (MRC-5), with potent inhibitory effect on viral protein expression (especially, Spike protein and Nucleoprotein) resulted in hindered replication of human coronavirus (HCoV-OC43) [44]. The inhibitory concentration (IC₅₀) of Cepharanthine on HCoV-OC43 was reported to be 729.7 nM [44]. In a recent investigation to repurpose clinically used drugs to treat COVID-19, CEP was found to inhibit both entry (ACE2 inhibitor) and replication of 2019-nCoV-related pangolin coronavirus GX_P2V with an EC₅₀ value of 0.98 μ mol/L [49].

Emodin: Emodin ((1,3,8-trihydroxy-6-methylantraquinone)) is a bioactive anthraquinone commonly found in the genus *Rheum* and *Polygonum* (particularly from *Rheum rhabarbarum*, *Rheum officinale*, and *Polygonum multiflorum*) [50,51]. This plant metabolite is a tyrosine kinase inhibitor, an antineoplastic agent, an anti-inflammatory, and a laxative agent [51]. Emodin isolated from *R. officinale* and *P. multi-*

florum was found to interfere with the binding of S-protein to angiotensin-converting enzyme 2 (ACE2) receptor and reduced infectivity to Vero E6 cells by SARS-CoV with an IC₅₀ value of 200 μ M [52]. An Emodin-derivative named as aloe-emodin (1,8-dihydroxy-3-hydroxyl-methylantraquinone) reportedly inhibited the replication of several viruses including Novel Influenza A (H7N9) virus, Varicella zoster virus, Herpes simplex types 1 and 2 viruses, Pseudorabies virus, Human Cytomegalovirus, and/or Japanese encephalitis virus [53].

Ginsenoside-Rb1: Ginsenoside-Rb1 is pharmacologically active steroid glycosides or triterpene saponins of *Panax ginseng* and *Panax japonicus* used as an anti-inflammatory drug and radical scavenger [54]. Ginsenoside-Rb1 showed promising antiviral activity against SARS-coronaviruses at 100 μ M, however, its mechanism of action is uninvestigated [34,55]. Ginsenoside-Rb1 and its structural analogues have been reported to inhibit host cell entry of influenza A virus [56] reduced cytopathogenicity of coxsackievirus B3, enterovirus 71, human rhinovirus 3 [57] and hepatitis A virus [58].

Glycyrrhizinor Glycyrrhizic acid: Glycyrrhizin or Glycyrrhizic acid, extracted from the root of *Glycyrrhiza glabra* and *Glycyrrhiza radix* was proved to be a potent antiviral agent against hepatitis C virus which cause chronic liver diseases and where contemporary drugs are less effective [59,60]. Additionally, glycyrrhizin is well-known for its anti-inflammatory, antioxidative, anti-allergenic, and antimicrobial properties [61]. Glycyrrhizic acid and its derivatives exhibited a strong inhibitory effect on the *in-vitro* replication of SARS-coronavirus (SARS-CoV). A glycyrrhizin derivative with an added N-acetylglucosamine residues in its carbohydrate part was found to be 10-fold more effective than glycyrrhizin [60]. The N-acetylglucosamine residue binds to the carbohydrates of the viral spike proteins (s-proteins) resulting in blocking of s-protein [60]. In addition to viral adsorption and penetration, glycyrrhizin exhibited an inhibitory effect on SARS-CoV replication and reducing viral cytopathogenicity with a selectivity index of 67 [62]. In a plaque reduction assay supported by neutralization tests, glycyrrhizin suppressed pathogenicity of several clinical isolates of SARS [40].

Leptodactylone: Leptodactylone is a hydroxycoumarin isolated from *Boenninghausenia sessilicarpa* [63]. Leptodactylone has shown an intense protective effect against viral cytopathogenicity in Vero E6 cells infected by SARS-CoV with concentration for 60% inhibition at 100 mg/mL [63]. Although, no significant information is available on its antiviral activity against other viral diseases as it remains a less explored antiviral phytocompound.

Lycorine: Lycorine, an alkaloid with broad antiviral activity found in several members of the Amaryllidaceae plant family [64]. It has potent antiviral activity against HIV-1, poliovirus, flaviviruses, human enterovirus 71, and avian influenza virus H5N1 [64]. The broad-spectrum antiviral activity of lycorine is attributed to its ability to inhibit viral RNA replication and suppress viral protein synthesis [65]. Lycorine especially isolated from the plant *Lycoris radiata* exhibited potent inhibitory activity against SARS-CoV by reducing viral cytopathogenic effects with an inhibitory concentration (EC₅₀) as low as 15.7

± 1.2 nM [66]. Some recent computational studies suggested that lycorine might be a modulator of viral S-protein, however, the exact mechanism of action is still unclear.

Reserpine: Reserpine is an alkaloid, derived from the roots of *Rauwolfia serpentina* and *Rauwolfia vomitoria*, used as a peripheral antihypertensive and as a central depressant drug [67]. Reserpine was found to inhibit viral replication at an inhibitory concentration (EC_{50}) as low as 3.4 μ M when treated in SARS-CoV (H.K. strain) infected Vero E6 cells [34]. However; its adverse health effects limit its clinical use [67].

Saikosaponins: Saikosaponins are a group of oleanane by-products, found in various plant families and well-known for their efficiency against viruses such as HIV, measles, influenza herpes simplex and varicella-zoster virus [68]. Saikosaponin B2 was reported to show selective growth inhibitory effects on the coronavirus strain, HCoV-229E, with an IC_{50} value of 1.7 μ mol/L, cellular cytotoxicity value (CC_{50}) of 383.3 μ mol/L and selectivity index (SI) of 221.9 [69]. The same study also reported the anti-CoV effect of saikosaponin A, C, and D with IC_{50} values of 8.6, 19.9, and 13.2 μ mol/L respectively in 2, 3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) assay [69]. In general, these saikosaponins are predicted to inhibit the early stage of viral attachment, replication, and reducing aberrant pro-inflammatory cytokine production, however, the exact molecular mechanism is uninvestigated [69,70].

Tanshinones: Tanshinones are a class of major bioactive ingredients of *Salvia miltiorrhiza*, known for their intense antioxidant, anti-inflammatory, and antineoplastic activity [71]. Tanshinones isolated from the dried roots of *S. miltiorrhiza* has shown selective inhibitory effects on 3CL^{pro} and PL^{pro}, and other viral cysteine proteases [72]. At least, seven of the tanshinones compounds namely tanshinone IIA, tanshinone IIB, methyl tanshinonate, cryptotanshinone, tanshinone I, dihydrotanshinone I, and rosmariquinone are reported to show inhibitory effects on viral cysteine proteases when expressed in *E. coli* BL21 (DE3) CodonPlus-RIL cells [72]. Except for rosmariquinone, all other compounds act as non-competitive enzyme isomerization inhibitors with concentration for 50% of the maximal effect ranging between 0.8 to 30.0 μ M [72]. Previously, extracts of *S. miltiorrhiza* and tanshinones were found to be active against other RNA viruses like enterovirus 71 [73] and porcine reproductive and respiratory syndrome virus [74].

Tetrandrine: Tetrandrine, a bisbenzyl isoquinoline alkaloid with a wide range of bioactivity, extracted from *Stephania tetrandra* other related species of Menispermaceae [75,76]. It has uses in Chinese traditional medicine as an analgesic and diuretic agent and is efficient against asthma, tuberculosis, malaria, cancer, and fever [75]. This alkaloid compound has been effectively used against the Ebola virus, HIV, and chloroquine-resistant strain of *Plasmodium falciparum* [75,77,78]. Plant-extracted Bis-benzyl isoquinoline alkaloids like cepharanthine and tetrandrine showed encouraging results against human coronavirus HCoV-OC43 in a recent study [44].

Theaflavin: Theaflavin and its derivatives (Theaflavins) are a class of naturally occurring flavonoids primarily found

in black tea or *Camellia sinensis* [79]. These compounds are well-known for their antioxidant, anti-inflammatory, and other disease-curing abilities [79]. Previously, theaflavins and its derivatives were reported for their effectiveness against Influenza [80], HSV-1 [81], hepatitis C virus [82], calicivirus [83] and HIV-1 [84]. Besides preventing inflammatory cytokine expression, theaflavins are effective in thwarting viral attachment/entry and replication [82,84]. During the SARS outbreak in 2004, two theaflavin derivatives namely 3-isotheaflavin-3-gallate, theaflavin-3, 3'-digallate alongside tannic acid have been reported as potential 3CL^{pro} inhibitors with IC_{50} values 7, 9.5 and 3 μ M respectively [85]. Recently, a computerized docking study revealed that theaflavin could be a potential candidate for blocking RdRp protease of coronaviruses [86].

Xanthoangelol E: The leaves of *Angelica keiskei* is a rich source of naturally-occurring chalcones and coumarins like isobavachalcone, 4-hydroxyderricin, xanthoangelol & its derivatives, psoralen, bergapten, xanthotoxin, and isopimpinellin [87,88]. Among these, the alkylated chalcones xanthoangelol E exhibited a strong enzyme inhibitory effect against 3CL^{pro} and PL^{pro} of SARS-CoV when expressed in *E. coli* strain BL21 (DE3) in CodonPlus-RIL cells [88]. The mechanism was roughly estimated as competitive inhibition against 3CL^{pro} (IC_{50} = 11.4 μ M) and noncompetitive enzyme inhibition in the case of PL^{pro} (IC_{50} = 1.2 μ M) [88].

Along with these compounds, four quinone-methide triterpenoid derivatives (iguesterin, tingenone, pristimererin, and celastrol) extracted from the bark of *Tripterygium regelii* and five major phenolic compounds (sinigrin, indigo, aloe-emodin, hesperetin and β -sitosterol) from the root of *Isatis indigotica* were found to inhibit 3CL^{pro} of SARS-Coronavirus [89,90]. Procyanidin A2, procyanidin B1, and cinnam tannin B1 fractionated from *Cinnamomi cortex* exhibited inhibitory effects against wild-type SARS-CoV infection demonstrated in a plaque reduction assay with IC_{50} values 37.35, 15.69 and 5.61 μ M respectively [91]. Quercetin-3- β -galactoside from *Ginkgo biloba* [92], Hirsutenone from *Alnus japonica* [93] inhibited SARS-CoV replication, while Myricetin isolated from *Myrica rubra* and Scutellarein isolated from *Scutellaria baicalensis* were reported as potent inhibitors of SARS-CoV helicase, *nsp13* [94]. However, these compounds need a comprehensive investigation to be used as drug templates.

Among the raw plant tincture, the water extract of a traditional Chinese medicinal plant, *Houttuynia cordata* Thunb. (*Saururaceae*) exhibited a wide range of antiviral activity against SARS-CoV that includes inhibition of 3CL^{pro} and RNA-dependent RNA polymerase (RdRp), increased CD4⁺:CD8⁺ ratio, and elevated levels of cytokines (IL-2 and IL-10) [95]. Also, the extracts of *Rheum palmatum* L., *Isatis indigotica*, *Cibotium barometz*, *Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, and *Taxillus chinensis* showed potent 3CL^{pro}-inhibitory effects with reduced viral cytopathogenic effect [90,96,97]. Further, the methanolic extracts of *Tribulus terrestris* and *Paulownia tomentosa* exhibited strong PL^{pro}-inhibitory effects [98,99]. The alcoholic extracts of *Euphorbia neriifolia*, *Toona sinensis*, *Cinnamomi cortex* and *Caryophylli flos* reportedly linked with reduced viral cytopathogenicity

and survival, with predicted inhibitory effects on viral replication [91,100,101]. These anti-SARS activities suggest the presence of potential therapeutic lead molecule in these plants that need a thorough investigation.

Conclusion

First discovered in the 1960s, these rapidly evolving viruses are emerging as a global public health threat as we are suffering the third major outbreak in the last 15 years. The ongoing Coronavirus Disease 2019 (CoVID-19) caused by SARS-CoV-2 virus, is one of the deadliest infectious disease outbreak since the Asian flu in the 1960s. Given our present understanding of the phylogeny and the pathogenesis of human coronaviruses, they share a typical genomic and clinical features which can be utilized to design a common therapy against them. One major setback of synthetic antivirals is virus developing resistance against them, which is relatively more robust in the case of RNA viruses with a rapid mutation capability. Besides, these diseases affect people from all economic domains hence not everyone can afford a foreseeable costly treatment. Thus exploring antiviral plants and their phytocompounds for treating coronaviral diseases could be a reliable and cost-effective alternative. Reportedly, several plants and their bioactive constituents exhibited strong antiviral activity against the pathogenesis of previous SARS-like diseases. However, as earlier SARS-like diseases disappeared rapidly, no significant progress has been made to link these findings to clinical and therapeutic assessment. Proper clinical investigation of phytocompounds that showed encouraging activity against the pathogenesis of RNA viruses especially against the previous SARS-like viruses may help us to design a cost-effective and efficient preventive remedy.

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Conflict of Interest

All the authors declare that they have no conflict of interest regarding this manuscript.

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