In-vitro Antiviral Activity of Natural Products against Coronavirus Strains: A Systemic Review

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Systematic Review

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Abstract

Coronavirus is a non-segmented, positive-sense RNA genome belonging to the family coronaviridae in the order Nidovirales Corona viral infections have created serious threats in the last couple of decades and recently claiming the death of thousands of human beings. Natural products provide a valuable and powerful resource of chemical compounds alkaloids, tannins, caffeine, biopterin, actinophnine, etc. displaying antiviral properties. The data was reviewed from various databases or search engines: PubMed, Science Direct, MedLine, Google Scholar, and Biomed central for published articles. The data inclusion criteria was natural products and their isolated and different synthetic compounds. Data duplication and titles or contents that do not meet the inclusion criteria and Reports on antiviral activities of natural products or their derivatives against other than CoV strains were excluded. We encountered 49 plants and 19 compound chemically defined natural molecules reported in the literature, which have evaluated for potent antiviral activity against different coronavirus strains. The listed plants and their compounds in this review are highly potent with promising results against coronavirus. These can be further screened for invasive tests and used for making different formulations or may be polyherbal formulations considering its safety profile and toxicity.

1. Introduction

Coronavirus (diameters of approximately 125 nm) is a non-segmented, positive-sense RNA genome belonging to the family coronaviridae in the order Nidovirales [1, 2]. The genome packed inside a helical capsid formed by the nucleocapsid protein (N) and further surrounded by an envelope. The viral envelope consists of four main structural proteins, i.e., spike protein (S) responsible for the formation of structure and attachment to the host receptor. The membrane protein (M) responsible for giving the virion its shape helping to bind to the nucleocapsid, envelope protein (E) responsible for assembly, and release of the virus, which are required for pathogenesis and nucleocapsid protein (N) responsible for replication [3-5].These four proteins are encoded within the 3' end of the viral genome. Some coronavirus also encodes an envelope-associated Hemagglutinin esterase protein that enhances spike protein to mediate cell entry and virus spread through the mucosa. Coronavirus can be classified into four genera, which are alpha, beta, gamma, and delta. Among them, alpha and beta infect mammals, whereas gamma infects avian species, and delta infects mammalian and avians both. The S-protein–receptor collaboration is the essential determinant for a coronavirus to contaminate a host animal category and oversees the infection's tissue tropism. Diverse coronaviruses use peptidases as their cell receptor. It is indistinct why peptidases are utilized, as passage happens even without the enzymatic area of these proteins. Numerous α-coronaviruses use aminopeptidase (APN) as their receptor, SARS-CoV and HCoV-NL63 use angiotensin-changing over enzyme 2 (ACE2) as their receptor, MHV enters through CEACAM1, and as of late recognized MERS-CoV ties to dipeptidyl-peptidase 4 (DPP4) to pick up section into the human cell [6-10].

The first coronavirus was discovered in 1930 when the infectious bronchitis virus caused an acute respiratory tract infection of domesticated chicken. In 1940, two more animal coronavirus, mouse hepatitis virus (MHV) [11, 12], and transmissible gastroenteritis virus isolated. Similarly, the first human coronavirus was identified in 1960 in the form of common cold among human beings. A study carried out in Canada in 2001 showed that more than 500 patients present with flu-like symptoms, on virological analyses, 3.6% of those cases were positive for the HCoV-NL63 strain by polymerase chain reaction [13]. Until 2002, coronavirus was considered a relatively simple, nonfatal virus; however, an outbreak in 2002-2003 in Guangdong province in China, which result in spread to many other countries, caused severe acute respiratory syndrome (SARS-CoV) and high mortality rate in over 1000 patient [14]. Since 2012 middle-east respiratory syndrome coronavirus (MERS-CoV) has infected more than 1700 people with a fatality rate of nearly 36% [15]. Since 2013, the porcine epidemic diarrhoea coronavirus (PEDV) has swept throughout the united states, causing an almost 100% fatality rate in piglets in less than a year [16]. At the end of 2019, in Wuhan province of China, a novel coronavirus, i.e., COVID-19 outbreak, killed more than eighteen hundred and infected over seventy thousand individuals within the first fifty days of the epidemic [17, 18]. In the past, SARS-CoV (2003) infected 8098 individuals with a mortality rate of 9%, across 26 countries in the world whereas novel coronavirus (COVID-19 affected 4218212 individuals with a mortality rate of 3.4% across 116 countries, till the date of this writing which shows transmission rate of SARS-CoV-2 is higher than SARS-CoV. The reason behind it could be genetic recombination event at S protein in the RBD region of SARS-CoV-2, which may have enhanced its transmission ability [19].

The evolution of this virus demonstrates that coronavirus is not a stable virus and can adapt to the new environment through mutation and recombination with relative ease. Hence coronavirus are programmed to alter host range and tissue tropism efficiently to become more virulent, even lethal to human and animal by causing widespread respiratory, GI and CNS diseases in human and another animal. So, mutating this virus's mutating behaviour is becoming a great topic of research among drug developers, researchers, and scientists [20]. After the outbreak of MERS-CoV, SARS-CoV, and other respiratory like diseases bring high mortality and incidence of occurrence, which make it essential public health and economic issue due to which effective prevention is required. There are no specific vaccines or drugs or any formulations that can treat or cure novel coronavirus, and the researcher starts studying the alternative method by comparing the efficacy of the natural product. Resources against the various strains of these viruses with the standard one and emerging viral replication lead to the development and search of a distinct form of solutions from the natural product for drug discovery.

Plants have been the major source of many powerful drugs worldwide, and humans have been using it to heal different illnesses since prehistoric times. Thus, plants are considered the most important source of modern medicines that possess various therapeutic effects [21]. About 25 % of

the medicines used worldwide are derived from plant sources [22]. The phytochemicals or metabolites (primary or secondary) are responsible for various pharmacological activities [23, 24]. Its variation within the plant species confers the specificity in its therapeutic effects [25]. It has always been the challenge and opportunity for researchers to identify the phytochemicals responsible for the particular effects. The emergence of antiviral agents' importance from natural sources requires more research to develop more drugs to treat viral infection. Thus, we need to apply antiviral phyto-constitutes within medication therapy to achieve an increased pharmacological response. Herbal medicine is a promoting subject in medicine, and of course, we have to increase our knowledge about them. Therefore, in this review, an effort has been made to provide information about the medicinal plant that possesses antiviral activity against different coronavirus strains.

2. Results And Discussion

In common use today, many phytochemicals are associated with health benefits. Natural products have been the primary source of commercial medicines and drug leads until now. A recent survey revealed that 61% of the 877 drugs introduced worldwide could be traced to or inspired by natural products, out of roughly 350000 species of plants believed to exist, one-third of those yet to be discovered [26]. The search for antiviral materials from plants is inadequate compared to the investigation of the antimicrobial properties. Preliminary studies have shown that plants have an optimistic antiviral activity in vitro and in vivo [27]. However, the same plants can have different antiviral activities against RNA or DNA viruses, regardless of whether they are coated or not, and even against different types or strains of viruses [28, 29]. Many viral infectious diseases still cause high mortality. Although antiviral chemotherapy has made great strides, antivirals are still mandatory. The appearance of drug-resistant viruses during treatment poses a potential difficulty for effective therapy. New viral pathogens can also be discovered. Biologically active substances of plant origin have long been recognized as viral inhibitors. These antiviral compounds can be extracted from sources such as higher plants, which, for many reasons, have been discovered much less than the traditional ones [30].

There is a great need for readily available antiviral drugs at a reasonable cost with the least side effects. From now on, traditional drugs need to be investigated as new antivirals because many of these old drugs, which contain various plant metabolites, have strong antiviral activities [31]. Research into the antiviral potential of plants began in 1952, and 12 of the 288 plants are effective against influenza. Various screening studies have been conducted in recent years to determine the antiviral efficacy of natural products using in vitro and in vivo tests [32]. The fall of the SARS CoV and MERS CoV highlight the inadequacy of available treatment for life-threatening zoonotic CoV infection in humans. Still, there is no specific drug or vaccine that has been available for its treatment. The FDA (Food Drug Administration) has approved various drugs that inhibit entry and replication of MERS-CoV, SARS-CoV, or another human coronavirus in multiple cell lines; still, various plants and their compounds are on investigation for the search of the antiviral agent against coronavirus strain in this pandemic condition [33].

Table 1: Plants showing antiviral activity against different coronavirus strains

S.N	Plant source	Families	Parts used	Culture cells	Virus/ strain	Method applied	Compounds responsible	Results		Conclusion	Ref.
								Test Samples	Standard		
1	*Allium porrum*	Alliacease	ND	Vero cell ATCC line	SARS-CoV Frankfurt 1strain	CPE based Antiviral assay	Mannose specific lectin	Most potent against the SARS-CoV induced CPE with EC50 (0.45µg/ml) CC50(>100) and SI (222)	ND	Probably interfering with the glycons on the spike protein during virus entry and virus release	[34]
2	*Urtica dioica*	Urticaceae	ND	Vero cell ATCC line	SARS-CoV frankfurt 1strain	CPE based Antiviral assay	N-acetyl glucosamine -specific lectin	Markely active against the SARS-CoV with EC_{50}(1.3±0.1µg/ml), CC_{50}(>100) and SI (>77)	ND	Probably interfering with the glycons on the spike protein during virus entry and virus release	[34]
3	*Hippeastrum hybrid*	Amaryllis	ND	Vero cell ATCC line	SARS-CoV frankfurt 1strain	CPE based Antiviral assay ,Virus entry assay	Mannose -specific lectin	Shows marked inhibition against SARS-CoV with EC_{50}(3.2±2.8 µg/ml) CC_{50}(>100) and SI (>31.3) Showed active at 4 degree C having 2 time more active (EC_{50}=2.5µg/ml) in compare to attachement and penetration at 37degree Celsius EC_{50}(5.2µg/ml)	ND	Probably interfering with the glycons on the spike protein during virus entry and virus release	[34]
4	*Nicotiana tobacum*	Solanacea	ND	Vero cell ATCC line	SARS-CoV frankfurt 1strain	CPE based Antiviral assay	N-acetyl glucosamine -specific lectin	Markely active against the SARS-CoV with EC_{50}(1.7±0.3µg/ml) and CC_{50}(>100), SI (>59)	ND	Probably interfering with the glycons on the spike protein during virus entry and virus release	[34]
5	*Laurus nobilis*	Lauraceae	Berry	Vero cell	SARS-CoV	Cytotoxicity assay Antiviral assay	ND	Strong antiviral activity against SARS-CoV with IC_{50}=120±1.2µg/ml And SI value (4.2) ,TC_{50}(500±1.02) when compare with positive control	Where positive control glycyrrhizin shown IC_{50} 641µg/ml with SI value (1.2)	ND	[35]
6	*Thuja orientalis*	Cupressaceae	Fruit	Vero cell	SARS-CoV	Cytotoxicity Antiviral assay	ND	Certain activitiy against SARS-CoV with IC_{50} 130µg/ml and SI value (3.8) ,TC_{50}(>1000)	Where positive control glycyrrhizin shown IC_{50} 641µg/ml with SI value (1.2)	ND	[35]
7	*Calophyllum blancoi*	Guttiferae	Roots	MRC-5	HCoV 229E	CPE based Antiviral assay	Blanco xanthone	Potential candidate for the treatment of Corona virus infection with EC_{50} 3µg/ml	Actinomycin D (IC_{50} 0.02µg/ml)	ND	[36]
8	*Broussonetia papyrifera*	Moraceae	Roots	*E. coli*BL21 HIT competent cells	MERS-CoV 3Cl Pro MERS CoV Pl pro SARS CoV 3CL pro SARS-CoV PL pro	Antiviral assay by Protease inhibition method	Broussochalcone B(against MERS-cov 3Cl pro) Biphenyl propanoid (against MERS-CoV PL pro) Flavan 5(against SARS-CoV 3Cl pro) Prenylated flavone (against SARS-CoV PL pro)	Showed effective IC_{50}27.9µm against MERS-CoV 3Cl pro Showed most potent IC_{50} 39.5µm against MERS-CoV PL pro Showed most potent IC_{50} 30.2±6.8 against SARS-CoV 3CL pro Showed highest inhibitory activity against SARS-CoV PL pro with IC_{50} 3.7µm	Quercetin shows IC_{50} (52.7µm) against SARS-CoV 3CL pro	May be prenyl group form strong hydrophobic interaction with enzyme	[37]
9	*Paulownia tomentosa*	Paulowniaceae	Fruits	*E. coli*	SARS-CoV Pl pro	Protease inhibitiom assay(flurogenic assay)	Compound(1-12) flavonoids	Showed inhibition of Pl pro in a dose dependent manner with IC_{50} range between 5.0 and 14.4µm	ND	Compound having dihydro-2H-pyran group shows better inhibition and may be all this compound bind allosteric site	[38]

										of the protease enzyme for inhibition of their activity	
10	*Psoralea corylifolia*	Fabaceae	Seeds	BL21(DE3) *E. coli*	SARS-CoV PLpro	Protease inhibition assay	Compound (1-6)	All this compound showed inhibitory action against protease enzyme with IC_{50}value of Bavachinin (38.4±2.4) , neobavaisoflavone(18.3±1.1), isobavachalcone(7.3±0.8) ,methyl bavachalcone(101±1.2) , psoralidin(4.2±1.0) , corylifol A(32.3±3.2) when compared with control	The IC_{50} value for psoralen as control >150 against SARS-CoV Pl pro enzyme.	Compound Isobavachalcole and psoraladin showed reversible mixed type of mechanism for inhibition of enzyme and coumestrol (compound 5) group of compound show most potent inhibitor against enzyme.	[39]
11	*Juniperus oxycedrus*	Cupressaceae	Berry	Vero cell	SARS-CoV	Cytotoxicity assay, Antiviral assay		Certain activitiy against SARS-CoV with IC_{50} 270µg/ml and SI value (3.7),TC_{50} (1000±1.7)	Where positive control glycyrrhizin shown IC_{50} 641µg/ml with SI value (1.2)		[35]
12	*Sambus formosana*	Adoxaceae	Stem	LLC-MK2 cells	HCoV-NL63	Virucidal assay Attachement assay Plaque assay	Caffeic acid (most prominet result)	Extract show antiviral activity with IC_{50} (1.75µg/ml) for virus yield , IC_{50} (4.67µg/ml) for plaque formation, IC_{50} (15.75µg/ml) for virus attachment Compound show antiviral activity with IC_{50} (3.54µg) for virus yield , IC_{50} (3.40µm) for plaque formation and IC_{50}(8.10µm) for virus attachment assay	ND	Caffeic acid may interfere the binding interation of HCOV-NL63 with heparan sulfate proteogylcans and ACE2 receptor on the cell surface	[40]
13	*Lycoris radiate*	Amaryllidaceae	Stem cortex	Vero E6 / HEPG2 line	BJOO1 BJOO6	CPE/MTS assay	Lycorine	SI(370) for BJ001 strain and SI(422) for BJ006 strain by extract Lycorine showed SI value >900 (this data is sufficient to show this compound have antiviral activity against SARS-CoV	Interferon a showed SI value (>151) for BJ001 and SI value (>170) for BJ006	May be by interacting with expressed viral protein / antigen	[41]
14	*Artemisia annua*	Asteraceae	Whole plant	Vero E6 / HEPG2 line	BJOO1 BJOO6	CPE/MTS assay	ND	SI= 31 (against BJ001) SI=27(against BJ006) That shows it have certain amount of antiviral activity against SARS-CoV strain in vero cells	Interferon a showed SI value (>151) for BJ001 and SI value (>170) for BJ006	Can be moderate antiviral activities against this strain of virus	[41]
15	*Pyrrosia lingua*	Polypodiaceae	Leaf	Vero E6 / HEPG2 line	BJOO1 BJOO6	CPE/MTS assay	ND	SI= 55 (against BJ001) SI=59 (against BJ006) That shows it have certain amount of antiviral activity against SARS-CoV strain in vero cells	Interferon a showed SI value (>151) for BJ001 and SI value (>170) for BJ006	ND	[41]
16	*Lindera aggregata*	Lauraceae	Root	Vero E6 / HEPG2 line	BJOO1 BJOO6	CPE/MTS assay	ND	SI= 16 (against BJ001) SI=17(against BJ006) That shows it Have certain amount of antiviral activity against SARS-CoV strain in vero cells.	Interferon a showed SI value (>151) for BJ001 and SI value (>170) for BJ006		[41]
17	*Isatis indigotica*	Brassicaceae	Root	Vero cells	SARS-CoV 3CL pro	Cell based cleavage assay	Sinigrin	With IC_{50} = 217µg/ml was more efficient in blocking the cleavage processing of the	ND	Sinigrin block the cleavage process of the	[42]

								3CL pro then other compound present on extract		3Cl pro in cell based assay where aloe emodin and hesperetin inhibit cleavage activity of 3Cl pro in dose dependent manner	
18	*Torreya nucifera*	Taxaceae	leaves		SARS-CoV 3CL pro	FRET analysis Dockling analysis	Biflavone amentoflavone Apigenin	Inhibitory effect of extract on enzyme about 62% at 100µg/ml. Active compound showed potent 3CL pro inhibitory effect at IC_{50}=8.3µg/ml Apigenin IC_{50}=280.8µg/ml show 3Cl pro inhibitory effect respectable.	Abietic acid showed 58.0±4.8% inhibition with IC_{50} = 189.1± 15.5 µm	May be due to presence of Apigenin moiety at position C-3' position of flavone as biflavone has an effect of 3CL pro inhibitory activity	[43]
19	*Cimicifuga rhizoma*	Ranuculacease	ND	DBT cells/ vero cells	MHV-A59/ PEDV	Cell viability assay, Plaque assay,	ND	EC_{50} value 19.4+/_7um/ml, SI(12.3) for MHV-A59 replication and also decreases PEDV production in dose dependent manner	ND	ND	[44]
20	*Meliae cortex*	Meliaceae	ND	DBT cells/ vero cells	MHV-A59/PEDV	Cell viability assay, Plaque assay	ND	EC_{50} value 13.0+/_1.4µg/m , SI(25.6) for MHV-A59 and decreases PEDV production in dose dependent manner	ND	May be due to the inhibition of RNA dependent RNA polymerase	[44]
21	*Coptidis rhizoma*	Cibotiaceae	ND	DBT cells/ vero cells	MHV-A59/PEDV	Cell viability assay, Plaque assay	ND	EC_{50} value 2.0+/_0.5µg/m. SI-(34.9) for MHV -A59 strain and also decreases PEDV production in dose dependent manner	ND	May be due to the inhibition of RNA dependent RNA polymerase	[44]
22	*Phellodendron cortex*	Rutaceae	ND	DBT cells/ vero cells	MHV-A59/PEDV	Cell viability assay, Plaque assay	ND	EC_{50} value 10.4±2.2µg/ml, SI(13.4) for MHV A59 and also decreases PEDV production in dose dependent manner	ND	May be due to the inhibition of RNA dependent RNA polymerase	[44]
23	*Sophora subprostrata radix*	Fabaceae	ND	DBT cells/ vero cells	MHV-A59/PEDV	Cell viability assay, Plaque assay	ND	EC_{50} value 27.5±1.1µg/ml SI(11.1) ,for MHV -A59 and also decreased PEDV production in dose dependent manner	ND	May be due to the inhibition of RNA dependent RNA polymerase	[44]
24	*Torilis fructus*	Apiaceae	ND	DBT cells/ vero cell line	MHV-A59/PEDV	Plaque assay, viability assay	ND	Extract reduced intracellular viral MRNA7(93%) , protein (100%)and production and replication of virus with EC_{50}=0.8±0.0 and SI value 195.6	Ribavirin showed inhibitory action against MHV-A59 strain with EC_{50} 17.5±2.9 µg/ml and SI value 61.5	Antiviral activity may be due to inducing COX2 expression through the activation of ERK and P38 or ERK alone	[45]
25	*Acanthopanacis cortex*	Araliaceae	ND	DBT cells/ vero cell line	MHV-A59/PEDV	Plaque assay, ,cell viability assay	ND	Extract reduced intracellular viral MRNA7(90%) , protein (98%)and production and replication of virus with EC_{50} =0.9±0.1µg/ml and SI value 188.9	Ribavirin showed inhibitory action against MHV-A59 strain with EC_{50} 17.5±2.9 µg/ml and SI value 61.5	Antiviral activity may be due to inducing COX2 expression through the activation of ERK and P38 or ERK alone	[45]
26	*Sophorae radix*	Fabaceae	ND	DBT cells/ vero cell line	MHV-A59/PEDV	Plaque assay, viability assay	ND	Extract reduced intracellular viral MRNA7(78%) , protein (62%)and	Ribavirin showed inhibitory	ND	[45]

								production and replication of virus with EC_{50}=0.8± 0.2µg/ml and SI value 696.0	action against MHV-A59 strain with EC_{50}17.5±2.9 µg/ml and SI value 61.5		
27	*Sanguisorbae radix*	Rosaceae	ND	DBT cells/ vero cell line	MHV-A59/PEDV	Plaque assay, cell viability assay	ND	Extract reduced intracellular viral protein (45%) and production and replication of virus with EC_{50} =0.9 ±0.1 µg/ml and SI value 105.0	Ribavirin showed inhibitory action against MHV-A59 strain with EC_{50} 17.5±2.9 µg/ml and SI value 61.5	Reduce CoV production partly as a result of decreased in protein synthesis	[45]
28	*Gentiana scabra*	Gentianaceae	Rhizome	Vero E6 cells	SARS-COV 3CL pro	CPE assay, cell proliferation assay,viral replication assay, MTT assay(cell based assay),protease inhibition assay	ND	In GSH fraction, Inhibitory cytopathogenic effect at 25 to 200µg/ml Inhibition of viral replication EC_{50}= 8.70 µg/ml at concentration 0.1-10µg/ml with SI (>57.5) Inhibition of 3CL protease enzyme at IC_{50} (>50µg/ml) ,with biological safe for host cell in concentration 10 to 500µg/ml	SARS-CoV replication inhibition shown by Valinomycin with SI value (41.4) Inhibitory activity against SARS-CoV 3Cl protease with IC_{50} =13±0.7 µg/ml	ND	[46]
29	*Dioscorea batatas*	Dioscoreae	Tuber	Vero E6 cells	SARS-CoV 3CL pro	CPE assay, cell proliferation assay,viral replication assay, MTT assay(cell based assay protease inhibition assay)	ND	In DBM fraction, Inhibitory cytopathogenic effect at 25 to 200µg/ml Inhibition of Viral replication EC_{50}= 8.706 g/ml at con 0.1-10µg/ml with SI (>62) Considerable inhibitory of SARS-CoV protease activity at IC_{50} value 44±2µg/ml, with biological safe for host cell in concentration 10 to 500µg/ml	SARS-CoV replication inhibition shown by Valinomycin with SI value (41.4) Inhibitory activity against SARS-CoV 3Cl protease with IC_{50} =13±0.7 µg/ml	ND	[46]
30	*Cassia tora*	Fabaceae	Seed	Vero E6 cells	SARS-CoV 3CL pro	CPE assay, cell proliferation assay,viral replication assay, MTT assay(cell based assay), protease inhibition assay	ND	In CTH fraction, Inhibitory cytopathogenic effect at 25 to 200µg/ml Inhibition of Viral replication EC_{50}= 8.70µg/ml at con 0.1-µwith SI value (>59.3) Inhibitory effect on 3Cl protease enzyme with IC_{50}(>50 µg/ml) with biological safe for host cell in concentration 10 to 500µg/ml	SARS-CoV replication inhibition shown by Valinomycin with SI value (41.4) Inhibitory activity against SARS-CoV 3Cl protease with IC_{50} =13±0.7 µg/ml	ND	[46]
31	*Taxillus chinesis*	Loranthaceae	Stem with leaves	Vero E6 cells	SARS-CoV 3CL pro	CPE assay, cell proliferation assay, viral replication assay, MTT assay(cell based assay) protease inhibition assay	ND	In TCH fraction, Inhibitory cytopathogenic effect at 25 to 200µg/ml Inhibition of Viral replication EC_{50}= 5.3 µg/ml at con 0.1-10µg/ml with SI (>92.8) Inhibitory effect on 3CL protease enzyme with IC_{50}(>50µg/ml), with biological safe for host cell in concentration 10 to 500µg/ml	SARS-CoV replication inhibition shown by Valinomycin with SI value (41.4) Inhibitory activity against SARS-CoV 3Cl protease with IC_{50} =13±0.7 µg/ml	ND	[46]

32	*Cibotium barometz*	Cibotiaceae	Rhizome	Vero E6 cells	SARS-CoV 3CL pro	CPE assay, cell proliferation assay,viral replication assay, MTT assay(cell based assay) protease inhibition assay	ND	In CBE /CBM fraction, Inhibitory of cytopathogenic effect at 25 to 200µg/ml SI (>59.4) for CBE shows anti-SARS-CoV activity IC_{50} (39µg/ml) for CBM shows inhibitory effect SARS-CoV 3CL Protease activity, with biological safe for host cell in concentration 10 to 500µg/ml	SARS-CoV replication inhibition shown by Valinomycin with SI value (41.4) Inhibitory activity against SARS-CoV 3Cl protease with IC_{50} =13±0.7 µg/ml	ND	[46]
33	*Toona sinesis*	Meliaceae	Leaf	Vero cell line	HCoV 229E	Antiviral assay (CPE ,MTT)	ND	TSL -1 show the evident effect against SARS-CoV strain with SI value (15)	Actinomycin D is used as positive control	Tender leaf extract of Toona sinesis roem can inhibit SARS-CoV in vitro	[47]
34	*Camellia japonica*	Theaceae	Flower	Vero cell	PEDV	Cytotoxicity assay, CPE assay,	Oleane triterpene (R'=H ,R^2=CH2OH)ketone group at C-16 and hydroxymethyl group at C-17 position	SI(44.54±8.34) showed potent inhibitory effect on PEDV replication	Inhibitory effect of Azauridine on PEDV replication with SI value (14.30±1.24)	May be by reducing the RNA level associated with GP6 nucleocapsid ,GP2 spike and GPS protein responsible for PEDV replication	[48]
35	*Saposhnikovia divaricata*	Apiaceae	Radix	Vero cell	PEDV	Cytotoxicity assay, CPE assay,	Cis-3-isovaleryl -4'-acetylkhellactone	SI (>23.90±4.11) showed inhibition effect on PEDV induced CPE.	Inhibitory effect of Azauridine on PEDV induced CPE with SI value 9.94 ±0.82)	Inhibitory effect on gene encoding PEDV GP6 nucleocapsid GP2 spike ,GPs membrane protein	[49]
36	*Dryoteris crassirhizoma*	Dryoptridaceae	Rhizomes	Vero cells	PEDV	Cytotoxicity assay, CPE assay,	Methylene -bis-methyl phlorobutyropheone	SI(39.21±0.27) showed potent antiviral effect on PEDV .	With SI value for 6-azauridine 10.28±0.54	Inhibitory effect on gene encoding PEDV GP6 nucleocapsid GP2 spike ,GPs membrane protein	[49]
37	*Rheum palmatum*	Polygonaceae	Leaves	*E. coli*expression	SARS-CoV 3CL pro	inhibition assay through determination of enzyme velocity represented by absorption assay	ND	Inhibiting the interaction of SARS-CoV S protein and ACE2 in dose dependent manner an maximum result is 96% inhibition with IC_{50} =13.76±0.003 at 100µg/ml	CHEN-312-5 showed inhibitory effect IC_{50} at 2.25± 0.24 at conc 20µg/ml with % inhibition was 88.3±2.60.	ND	[50]
38	*Houttuynia corda*	Saururaceae	Whole parts	Mouse splenic lymphocyte	SARS-CoV 3CL pro	protein based fluorescence assay,ELISA	ND	Extract shows inhibiting effect in decrease in fluorescein ratio of the substrate implying that it could inactivate the SARS-CoV 3CL protease enzyme at con. 200µg/ml and increased CD4+ cell after 48hr and CD8+ cell after 24hr and IL -2 after 72hr in dose dependent manner	ND	By activating cell mediating immunity before the invasion of SARS-CoV Or by slowing the viral replication process by inhibiting pivotal enzyme and trigger negative feedback control in	[51]

										immune system	
39	*Euphoria nerifolia*	Euphorbiaceae	Leaves	MRC-5 cells	HCoV-229E	XTT assay to determine cell viability	3-friedelanol Epitaraxrol Friedelin	This three compound showed 132.4% , 111.0%, 109% cell survival through inhibition of virus respectively	Actinomycin shows 69.5% cell survival against HCoV-229E strain	Friedlone skeleton can be used as potential scaffold for development of new anti - HCoV-229E virus	[52]
40	*Black tea/puer tea*	Theaceae	Leaves	vero cell	SARS –CoV 3Cl pro	Protease inhibition assay	TF2B , TF3 containing gallate group	50% inhibition of 3Cl protease enzyme activity encoded by SARS-CoV at concentration <10 µm	N-ethylmaleimide showed inhibition of protease activity against SARS-CoV 3CL	Gallate group attached to the 3'position to TF2B and TF3 might be playing role for interacting with the 3CL Protease active site	[53]
41	*Prunus serrulata*	Rosaceae	Cherry	Vero ATCC CCL-81	PEDV	CPE assay	ND	Extract showed highest anti-PEDV with 50% CPE inhibition at 1.95µm/ml conc.	Ribavirin, interferon a inhibit 50% PEDV replication at conc.; 4.1µg/ml and 9µg/ml respectively	ND	[54]
42	*Nigella sativa*	Ranuculaceae	Seeds	Murine fibroblast LR7	MHV-A59	MTT assay, Time of addition assay, ELISA, Calcium conc. assay Viral load assay	ND	Have concentration dependent cytotoxicity, activity for inhibiting the replication before to infection, with increased IL-8 at 24 hr., and calcium concentration with decrease in TRP gene expression	ND	ND	[55]
43	*Galanthus nivalis*	Amaryllidaceae		FCWF-4	F-CoV	MTT assay, CPE assay	ND	With CC_{50} (>1.92nm) , CPE inhibition occur in conc. dependent manner	Nelfinavir with CC_{50} (11.45nm) , blocked the induction of CPE foci only at the high conc.	Two agent extract and standard show synergistic effect where nelfinavir affect post entry and extract affect pre entry steps leading to completely blockage of viral replication, that is useful for prophylaxis treatment	[56]
44	*Rosa nutkana*	Rosaceae	Whole part	MDBK	IBV	Antiviral assay	ND	Extract showed antiviral effect against enteric coronavirus	ND		[57]
45	*Alstonias scholaris*	Apocynaceae	ND	Vero	IBV	Plague assay, ,antiviral assay	Alstotides	Pretreatment with AS1 could inhibit plaque formation in dose -dependent manner with EC_{50}(35µm) ,at 50µm retain the inhibition activity(38% inhibition) .	ND	As1 bind to IBV fusion glycoprotein, S protein which is important for entry and attachment of virus to host cells, inhibit α–amylase too at early stage of infection .	[58]
46	*Sambucus nigra*	Adoxaceae	Fruit	Vero	IBV	Plague assay, cytotoxicity assay,	ND	No cytotoxicity , pretreatment with extract inhibit viral replication dramatically by reducing viral titers by 4 to 6 orders of	ND	It could bind viral protein and inhibit replication	[59]

								magnitude in dose dependent manner			
47	*Chamaecyparis obtusarar*	Cupressaeae	Heart wood	Vero E6	SARS-CoV 3CL	CPE assay, Inhibition of viral replication assay(ELISA), protease inhibition assay	8-β hydroxyabieta 9(11),13-diene-12one (5) Pinusolidic acid (9) Savinin (16)	Compound 5 ,9 showed high inhibition against SARS-CoV induced CPE with SI value >510 ,89.8 against SARS-CoV replication and compound 16 showed potent inhibition activity against SARS-CoV 3 CLpro with IC_{50} (25um)	Positive control niclosamide showed high inhibition against CPE induced by virus with SI value >221 against virus replication and IC_{50} (40) against protease activity encoded by SARS-CoV	ND	[60]
48	*Juniperus formosana*	Cupressaeae	Heart wood	Vero E6	SARS-CoV 3CL	CPE assay, Inhibition of viral replication assay(ELISA), protease inhibition assay	3-β ,12 , diacetoxyabieta-6,8,11,13 tetra(8) Butulonic acid(14)	Compound 8, 14 showed high inhibition against SARS-CoV induced CPE with SI value 193, 180 respectively against SARS-CoV replication.	Positive control niclosamide showed high inhibition against CPE induced by virus with SI value >221 against virus replication and IC_{50} (40) against protease activity encoded by SARS-CoV	ND	[60]
49	*Cryptomerica japonica*	Cupressaeae	Heart wood	Vero E6	SARS-CoV 3CL	CPE assay, Inhibition of viral replication assay(ELISA), protease inhibition assay	7β-hydroxydeoxycryptojaponol(6)	Compound 4 showed high inhibition against SARS-CoV induced CPE with SI value 111 against SARS-CoV replication	Positive control niclosamide showed high inhibition against CPE induced by virus with SI value >221 against virus replication and IC_{50}(40) against protease activity encoded by SARS-CoV Another positive control bitulinic acid showed IC_{50}(10um) against protease activity	ND	[60]

$IC_{50:}$ concentration required to inhibit 50% of virus growth, TC_{50}: drug concentration that reduces the cell growth by 50% (cellular toxicity), CC_{50}: concentration required for the reduction of cell viability by 50%, SI: Selectivity Index, ND: Not Defined

Table 2: Compounds showing antiviral property against different coronavirus strains

SN	Compound	Source	Culture cell	Virus(strain)	Method	Result	Conclusion	Reference
1	Saikosaponin B2	Sigma Chemical (St Louis, MO, USA)	MRC-5 cell	HCoV-229E	XTT assay, Attachment assay/penetration assay	At concentration 0.25-25µmol/l showed strongest activity with EC_{50} =1.7±0.1µmol/l and SI =221.9	May be due to interference in the early stage of viral replication , absorption, and penetration of the virus	[61]
2	Glycyrrhizin	ND	Vero cells	FFM-1 FFM-2	Viral replication assay, cytopathogenicity assay, cytotoxicity assay	Most effective when given at early steps of viral replication and during and after adsorption with SI =>67, show potent inhibition of viral replication	May be by affecting cellular signaling pathway or by inducing production of nitrous oxide which inhibit viral replication	[62]
3	Tannic acid	MicroSource Discovery Systems, Inc., Gaylordsville, CT	E-coli	SARS-CoV 3Cl pro	Protease inhibition assay, flurogenic substrate peptide assay	Found to have inhibitory activity against 3Cl pro encoded by SARS-CoV with IC_{50} =3µm	Gallate group may be responsible for inhibitory activity against target strain	[53]
4	3-isotheaflavin-3-gallate(TF2B)	MicroSource Discovery Systems, Inc., Gaylordsville, CT	E-coli	SARS-CoV 3Cl pro	Protease inhibition assay, flurogenic substrate peptide assay	Found to have inhibitory *activity* against 3Cl pro encoded by SARS-CoV with IC_{50}=7µm	Gallate group may be responsible for inhibitory activity against target strain	[53]
5	Theaflavin -3',3'-digallate (TF3)	MicroSource Discovery Systems, Inc., Gaylordsville, CT	E-coli	SARS-CoV 3Cl pro	Protease inhibition assay, flurogenic substrate peptide assay	Found to have inhibitory activity against 3CL pro encoded by SARS-CoV with IC_{50}=9.5µm	Gallate group may be responsible for inhibitory activity against target strain	[53]
6	Myricetin	Chromadex	MCF10A	SARS helicase ,nsp13	FRET DS ,DNA unwinding assay ATP hydrolysis assay	Inhibit the ATP ase activity of nsp13 by more the 90% at concentration 10µm	By interfering with ATP/ADP binding pocket of the SARS- CoV helicase protein	[63]
7	Scutellarein	Scutettaria baicalensis	MCF10A	SARS helicase ,nsp13	FRET DS ,DNA unwinding assay ATP hydrolysis assay	Inhibit SARS CoV helicase with IC_{50}=0.8±0.19µm	By interfering with ATPase activity of the SARS CoV helicase protein	[63]
8	Tetrandrine	Wuhan ChemFaces Biochemical Co., Ltd. (Wuhan, China)	MRC-5 human lung cells	HCoV-OC43	CPE/MTS assay Time addition assay Replication inhibition assay	Anti HCoV-OC43 in dose and time dependent manner with SI>40 with IC_{50} = 0.33±0.03	Inhibit virus induced cell death at the early stage of virus infection an suppressed the replication of virus and inhibited viral S and N protein expression	[64]
9	Fangchinoline	Wuhan ChemFaces Biochemical Co., Ltd. (Wuhan, China)	MRC-5 human lung cells	HCoV-OC43	CPE/MTS assay Time addition assay Replication inhibition assay	Anti HCoV-OC43 in dose and time dependent manner with SI>11 with IC_{50} =1.01±0.07µm	Inhibit virus induced cell death at the early stage of virus infection an suppressed the replication of virus and inhibited viral S and N protein expression	[64]
10	Cepharanthine	Wuhan Chem Faces Biochemical Co., Ltd. (Wuhan, China)	MRC-5 human lung cells	HCoV-OC43	CPE/MTS assay Time addition assay Replication inhibition assay	Anti HCoV -OC43 in dose and time dependent manner with SI >13 with IC_{50} =0.83±0.07µm	Inhibit virus induced cell death at the early stage of virus infection an suppressed the replication of virus and inhibited viral S and N protein expression	[64]
11	Quercetin	Sigma–Aldrich	Picia pastoris GS 11	3CL pro SARS-CoV	FRET inhibition assay Docking analysis	82% inhibition of SARS-CoV 3CL pro activity with IC_{50} =73±$_{4µm}$	numerous hydrophobic and H-bonds interaction with amino acid residues in the active site pocket of 3CL pro and inhibiting the activity.	[65]
12	Epigallocatechin gallate	Sigma–Aldrich	Picia pastoris GS 11	3CL pro SARS-CoV	FRET inhibition assay Docking analysis	85% inhibition of SARS-CoV 3Cl pro activity with IC_{50}=73±2µm	Numerous hydrophobic and H-bonds interaction with amino acid residues in the active site pocket of 3CL pro and inhibiting the activity.	[65]
13	Gallocatechin gallate	Sigma–Aldrich	Picia pastoris GS 11	3CL pro SARS-CoV	FRET inhibition assay Docking analysis	91% inhibition of SARS 3CL pro activity with IC_{50} =47±0.9	Numerous hydrophobic and H-bonds interaction with amino acid residues in the active site pocket of 3CL pro and inhibiting the activity	[65]
14	Herbacetin	ND	ND	3CL Pro MERS-CoV	Antiviral assay, tryptophan based FRET assay, Docking analysis	Block enzymatic activity of MERS -CoV 3Cl pro with IC_{50} 40.59µm	inhibition of main viral proteases and thus nullify a process of virus peptides	[66]
15	Isobavachalcole	ND	ND	3Cl Pro MERS-CoV	Antiviral assay, tryptophan based FRET assay, Docking analysis	Block enzymatic activity of MERS -CoV 3Cl pro with IC_{50} 35.85µm	inhibition of main viral proteases and thus nullify a process of virus peptides	[66]
16	Quercetin -3-B-d glucoside	ND	ND	3Cl Pro MERS-CoV	Antiviral assay, tryptophan based FRET assay, Docking analysis	Block enzymatic activity of MERS -CoV 3Cl pro with IC_{50} 37.03µm	inhibition of main viral proteases and thus nullify a process of virus peptides	[66]
17	Helichrysetin	ND	ND	3Cl Pro MERS-CoV	Antiviral assay, tryptophan based	Block enzymatic activity of MERS -CoV 3Cl pro with IC_{50} 67.0sµm	inhibition of main viral proteases and thus nullify a process of virus peptides	[66]

					FRET assay, Docking analysis			
18	Kaemferol derivatives (Juglanin glycoside)	Viola odorata L	Xenopus oocyte	3a protein of SARS-CoV	Voltage clamp experiment	At 20µm , 10µm it show complete inhibition of ion flow through 3a protein with IC_{50} 2.3µm and at -100mv the current was inhibited to 0.77±0.08 of control current in the absence of the drug	May be by blocking 3a channel , counteracting virus production and interfering with other steps of viral cycle	[67]
19	Emodin	ND	Xenopus oocyte, Rhabdomyosarcoma cells	HCOV-a43/ SARS-Cov 3a	Volatge clamp experiment	Inhibit of 3a channel with k1/2 value of about 20um and also inhibit HCoV-OC43 release from infected RD cells	By inhibition of ion flow through 3a protein channel in a sense that viral ion channel may be involved in MOA of viral release from infected cells	[68]

In this review, as per the data available on the various parts of the plants and compounds from different articles published, they showed that they possess antiviral activity against coronavirus strains (human coronavirus and non-human coronavirus)in the mild, moderate and strong condition. Through in-vitro tests on various parts of the plant (leaves, flower, aerial parts, rhizomes, and fruit) and different compound bought from the market/pharmaceutical/chemical company. Among various techniques used for the detection of viral inhibition, cytopathic reduction assay was the most common technique for in-vitro analyzation in the antiviral study. We know that medicinal plants are the good sources of various phytochemical compounds that provide the basis for the development of new antiviral agents against different virus strains. The WHO (world health organization) has an estimated 80% of the world population fulfil their healthcare needs from phytomedicinal sources. The mechanism of the antiviral potential of plant extract or various compounds varies among the different strains of the virus. Some phytochemical compounds target viral envelope, some membrane protein, some of them focus ion channel, some inhibit the virus's attachment to the host cell, and some inhibit CPE (cytopathogenic effect) on host cells/plagues formation or ion concentration intracellularly.

The present review showed that the above mention plant and compound (Table 1 and Table 2) containing bioactive substances have some amount of promising antiviral activity. Among the listed plants, the most prominent and potent effect shown by *Allium porum, Urtica dioica, Lycoris radiata, Juniperus formosa* and *Cryptomerica japonica* against SARS-CoV with SI value 222, >77, >900,>180 and >111 respectively as compared with standard mentioned by [69]. Similarly, *Sophorae radix was* found to have the highest inhibition activity against MHV -A59 coronavirus with SI value 696 compared with other compounds. Plant and for SARS-CoV 3 CL proenzyme Dioscorea batatas showed the most effective reasult*Cibotium barometz, Cassia tora* with SI value >62,> 59.4, >59.3 respectively.

Calophyllum blancoi , Torilis fructus , Acanthopanacis cortex,,Sophorae Radix , Allium purum , Urtica dioica and *Nicotiana tobaccum* were found to have 50% maximum potent activity against coronavirus species. At low concentration 3µg/ml, 0.8µg/ml, 0.9±0.1 µg/ml, 0.8±0.2µg/ml, 0.45µg/ml, 1.3±0.1µg/ml and 1.7±0.3µg/ml respectively which have a comparable result to the standard drug used for the coronavirus strain according to [69]. *Taxillus chinesis* showed a similar effect with the standard one to inhibit replicating the virus with EC50 5.3µg/ml. Similarly, plants showing the highest IC50 activity at lower concentrations are *Brousnoeti papyrifera* (IC50=3.7µm), *Paulownia tomentosa* (IC50=5-14.4µm), *Torreya nucifera* (IC50=8.3µg/ml) against SARS-CoV enzyme. *Sambus formosana* showed the most potent IC50 value activity against plaque formation (IC50=1.75) and for virus attachment (4.67µg/ml) in host cells infected with HCoV-NL63 strain of the virus. *Torilis fructus, Acanthopancis cortex* showed the highest value for reducing intracellular viral mRNA by 93% and 90%, respectively. *Euphoria nerifolia* was showed >100% cell survival through inhibition of virus activity against coronavirus when compared with standard.

A compound like Saikosaponin B2 was found to have maximum effective against Human coronavirus in a dose-dependent and time-dependent manner with SI (221.9) and EC50 =1.7±0.1µmol/l, Isobavachalcole against 3CL pro-MERS CoV with IC50 (35.8µm) and Gallocatechin gallate against 3CL pro-SARS CoV with IC50 (47±0.9um).

We encountered 49 plants and 19 compound chemically defined natural molecules reported in the literature, which have evaluated for potent antiviral activity against different coronavirus strains. The active compounds, which have been isolated and identified, belong to the classes of alkaloids, terpenoids, xanthones,), flavonoids, steroid, lipids, oxygen benzenoids, carbohydrates, lignans, proteins, coumarins, phenylpropanoids, polyphenols,resins, glycosides, etc. These natural metabolites act as a key for antiviral activity.

3. Methodology

A search was conducted in the following databases or search engines: PubMed, Science Direct, MedLine, Google Scholar, and Biomed central for published articles. The keyword 'coronavirus' was paired with 'natural products', 'medicinal plants', 'phytochemicals', 'alkaloids', 'glycosides', 'flavonoids', 'saponins', 'terpenes', 'monoterpenes', 'diterpenes', 'sesquiterpenes', 'triterpenes', 'terpenoids', 'tannins', 'saponins', 'phenols', 'polyphenols', 'herbal drugs', 'crude extracts', or 'synthetic derivatives of natural products' to obtain published records till May 2020. No language restriction was imposed. Obtained records in this study were included and excluded based on the following criteria. The inclusion data criteria included

1. Studies involving crude extract, fraction, or their preparation of plants acting against CoV strains.

2. Studies related to derivatives of natural products (e.g., isolated compounds) and chemicals or biochemicals acting against CoV strains.
3. Studies with natural product inspired synthetic derivatives acting against CoV strains.

The exclusion data criteria included: (a) Data duplication and titles or contents that do not meet the inclusion criteria, (b) Reports on antiviral activities of natural products or their derivatives against other than CoV strains.

4. Conclusion

Natural products provide a valuable and authoritative resource of chemical compounds displaying antiviral properties. Structure modification of these compounds may help in improving and increasing their potency. The development of antiviral drugs is a challenge, and some antiviral medications can only prevent virus replication or inhibit further infection. In this review, different methods and its possible mechanism showing antiviral property have been highlighted. In the present situation, there is no proper development of antiviral drugs due to which the world is searching for its remedies in nature. All the listed plants and their compounds in this review are highly potent with promising results against coronavirus. These can be further screened for invasive tests and used for making different formulations or may be polyherbal formulations considering its safety profile and toxicity.

5. Declarations

Author contribution: conceptualization, writing, , referencing, Sindhu KC, Conceptualization, referencing, writing, supervision, Draft preparation, Manoj Pandit, writing, reviewing, editing, Amit Kumar Shrivastava

Conflict of interest: the author declares no conflict of interest

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