Pharmacogn Rev. 2021;15(30):96-106
A multifaceted peer reviewed journal in the field of Pharmacognosy and Natural Products
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Review Article

Plant Phenolics with Antiviral Activities against Human Corona Virus and Structure-Activity Relationships – A Review

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ABSTRACT
The ability of human coronaviruses to infect respiratory tracts and transmit through respiratory droplets makes them highly contagious and potential to become pandemic. The current pandemic situation developed due to COVID-19 infection warrants the rapid development of effective and safe antivirals for disease management. Natural products are considered as a reliable and valuable source for rapid drug discovery. Phenolics, a major class of plant secondary metabolites, have been screened on a large scale for their antiviral efficacy to combat emergent mutants of coronavirus. Phenolics have a lower risk for the development of toxicity comparing to synthetic compounds as we are naturally adapted to most of the plant Phenolics as part of our vegetarian diet. The available literature has shown that Phenolics could interfere with the various key enzymes associated with virus-host cell interactions and thus alleviate the severity of the disease. The review of structure-activity relationships indicated the roles of hydrophobic aliphatic side chains, catechol groups, pyran ring, glycosylation, flexible linkages between aromatic rings, etc in modulating the interactions of Phenolics with human coronavirus proteins. The summary of the current literature available in this review might be useful for the selection of Phenolics with diverse structural properties and to design semi-synthetic products with better drug properties against coronaviruses.
Key words: Coronavirus, SARS, MERS, PL^{pro}, $3CL^{pro}$, RdRp, N-protein, Polyphenols.

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History
- Submission Date: 24-04-2021;
- Review completed: 08-06-2021;
- Accepted Date: 14-07-2021

DOI : 10.5530/phrev.2021.15.12

Article Available online
http://www.phcogrev.com/v15/i30

INTRODUCTION

Coronavirus (CoV) (Family: Coronaviridae) is a crown-like enveloped virus containing non-segmented, positive-stranded genomic RNA. CoVs can cause several diseases, including bronchitis, gastroenteritis, and hepatitis in birds, humans, and other animals. Human coronaviruses (HCoVs) represent a major group of CoVs associated with various respiratory diseases from the common cold to serious pneumonia and bronchiolitis.[1] HCoVs were found to be the causative agents of contagious and fatal respiratory illnesses such as Middle East Respiratory Syndrome (MERS).[2] Severe Acute Respiratory Syndrome (SARS),[3] and COVID-19.[4] SARS, first reported in China in November 2002 quickly spread to other Asian countries, North America, and Europe, infecting more than 8000 individuals and causing approximately 800 deaths. The Middle East Respiratory Syndrome coronavirus (MERS-CoV), a deadly HCoV that emerged in 2012 killed approximately 36% of infected patients in Saudi Arabia and South Korea. COVID-19 first reported at Wuhan city in China at the end of the year 2019, rapidly developed as a global pandemic causing more than 1 million deaths to date. Among the CoVs, porcine epidemic diarrhea virus (PEDV) and murine hepatitis virus (MHV) have been reported as pathogenic to swine[5] and mice[6] respectively. SARS, MERS, and MHV belong to the Group 2 CoVs and are classified under the genus Betacoronavirus. HCoVs are recognized as one of the fastest-evolving viruses derived from their characteristic high genomic nucleotide replacement rates and recombination.[7] HCoV's ability to infect respiratory tracts and transmit thorough respiratory droplets makes them highly contagious and potential to become pandemic. Most of the CoVs are zoonotic and found as resrved in animals like bats, raccoon, dogs, palm civets, camels, etc., thus posing a potential risk for epidemics. Therefore, continuous development of therapeutic and prophylactic counter measures against potentially deadly CoVs is warranted.

Molecular Mechanism of CoV Infection

The process of infection of the enveloped virus to the host cell usually involves the following steps: attachment and receptor binding, virus-cell fusion, RNA replication, and encapsulation and emission of viroids to the extracellular area. Attachment, receptor binding, and virus-cell fusion of CoV to the host cell are mainly mediated by its spike (S) protein in the viral envelope. SARS and HCoV-NL63 spike with the angiotensin-converting enzyme 2 (ACE2) receptor of the host cell.[8-10] MERS-CoV enters the host cell through the CEA cell adhesion molecule 1 (CEACAM1) and dipeptidyl-peptidase 4 (DPP-4).[11] Then an acid-dependent proteolytic cleavage of S protein leads to the fusion of viral body with

Cite this article: Arimboor R. Plant Phenolics with Antiviral Activities against Human Corona Virus and Structure-Activity Relationships – A Review. Pharmacog Rev. 2021;15(30):96-106.

endosomes or plasma membrane in the host cell followed by the releases of the viral genome into the cytosol.[12,13] The replicase genes of CoV encode two overlapping polyproteins; pp1a and pp1ab that are required for viral replication and transcription. Two cysteine proteases, main protease (M^{pro}) also called 3C-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro}) of HCoV mediate the proteolytic processing of replicase pp1a and pp1ab into functional proteins.[14,15] The functional proteins including RNA-dependent RNA polymerase (RdRp) and helicase for RNA replication, nucleocapsid (N) protein involved in the processing of virus particles by enveloping the RNA, SNE-3a protein designed for the formation of ion channels for the release of viral particles from the host cells, etc have also been associated with the virus replication and release. Interfering the functions of viral proteins that have a major role in their interactions with host cells and are specific to CoV genera is an effective antiviral strategy in suppressing viral genome replication to cure CoV infection.

Plant Phenolics

Phenolics are one of the major classes of plant secondary metabolites, mostly evolved as a chemical defense system against the detrimental effects of ultraviolet radiations, pathogen aggression, and oxidative stress. Structurally, the term polyphenol refers to the presence of one or more phenolic rings with hydroxyl groups. Phenolics based on the chemical structure are generally classified as flavonoids, lignans, stilbenes, phenolic alcohols, phenolic acids, etc. Flavonoids, based on the chemical structure are further classified as flavonols, flavanols, flavones, chalcones, and anthocyanins. Flavans, flavones, flavanones, isoflavones, flavonols, and flavanols contain a chromone ring with a phenyl group at C-2 or C-3 positions with variations in substitution and unsaturation. Phenolics constitute major class active compounds in herbal-based complimentary medicinal systems. A wide spectrum of medicinal properties including antibacterial and antiviral potentials has been attributed to plant phenolics. Antiviral potential of plant phenolics against HSV,[16] influenza,[17] Epstein-Barr virus[18] has also been reported. This paper mainly aimed at the review of current literature on the antiviral potential of plant polyphenols against HCoV and their structure-activity relationships. Reports on the antiviral properties of compounds with identified structures are only considered for the review. The structures of polyphenols with anti-HCoV activities are given in Figure 1 and Figure 2 and are referred to as superscript with the compound names in the text.

Viral Entry Inhibition by Phenolics

The interaction of the spike protein of CoV with the receptor of the host cell is an important step in the viral infection. Luteolin*B1* and tetra-O-galloyl-β-D-glucose*p5* have shown a strong affinity towards SARS S2 protein. It has also been shown that luteolin (EC_{50} =9 μM and 4 μM) and tetra-O-galloyl-β-D-glucose (EC_{50} = 3 μM and 4 μM) have inhibited the entry of HIV-luc/SARS pseudotyped virus and wild-typed SARS-CoV into Vero E6 cells without substantial cytotoxicity to Vero E6 cells as well as mice toxicity.[19] Emodin, an anthraquinone compound derived from genus *Rheum* and *Polygonum*, has inhibited the interaction between of SARS-CoV S protein and ACE2 receptor in a dose-dependent manner with an IC_{50} value of 200 μM. It has also inhibited 94% infectivity of S protein- pseudotyped retrovirus to Vero E6 cells at 50 μM.[20]

Phenolics as RNA Replicase Inhibitors
Inhibition of protease Enzymes

The protease enzymes of HCoV namely; PL^{pro} and $3CL^{pro}$ (M^{pro}) cleave the polyprotein into individual polypeptides that are required for the replication and transcription of the virus.[14] Following the translation of the messenger RNA to yield the polyproteins, the $3CL^{pro}$ is first

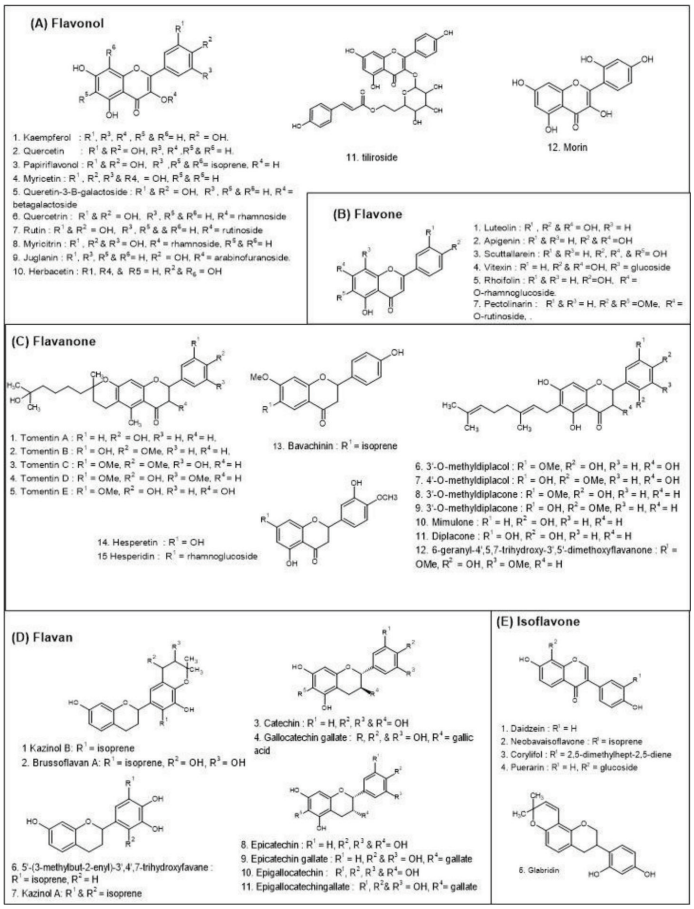

Figure 1: Structures of polyphenols with anti-HCoV activities.

auto-cleaved from the polyproteins to become a mature enzyme. The nsp^5 protein, $3CL^{pro}$ further cleaves all the 11 remaining downstream non-structural proteins. Hence, $3CL^{pro}$ is an essential viral protein for the viral replication cycle and is considered as an attractive target for anti-SARS drug development.[15] The PL^{pro}, an essential component of HCoV replication machinery is the nsp3 protein which is a part of the synthesized ORF1a polyprotein during replication, which processes the replicase polyprotein at three conserved cleavage sites.[21,22] In addition to its protease activity, PL^{pro} has been shown to have deubiquitination and DelSGylation Activities.[22,23] Since its homologs are found in all CoVs, it has also been proposed to be a good target for drug discovery for HCoV.

Inhibition of HCoV PL^{pro}

The inhibition of CoV PL^{pro} activity has been considered as an effective strategy to prevent and manage the CoV infection. The HCoV PL^{pro} inhibitory potentials of polyphenols are summarized in Table 1. An activity order of papyriflavonol A^{A3}> quercetin^{A2}> kaempferol^{A1} has been reported for the inhibition of SARS-CoV PL^{pro} (IC_{50}< 16 μM) and its deubiquitination (IC_{50}< 61 μM) and DelSGylaton (IC_{50}< 72 μM) activities.[24] Apart from kaempferol, both quercetin and papyriflavonol A have a catechol group as their C ring, which is presumed to have a role in the inhibition. The inhibition of SARS-CoV PL^{pro} and its deubiquitination, and DelSGylaton activities by papyriflavonol A was better than quercetin, indicating the increase in hydrophobicity due to the presence of isoprene units favored its attachment with the protein. Significantly lower inhibitory potential of quercetin-β-galactoside^{A5} than flavonol aglycones might be an indication of the

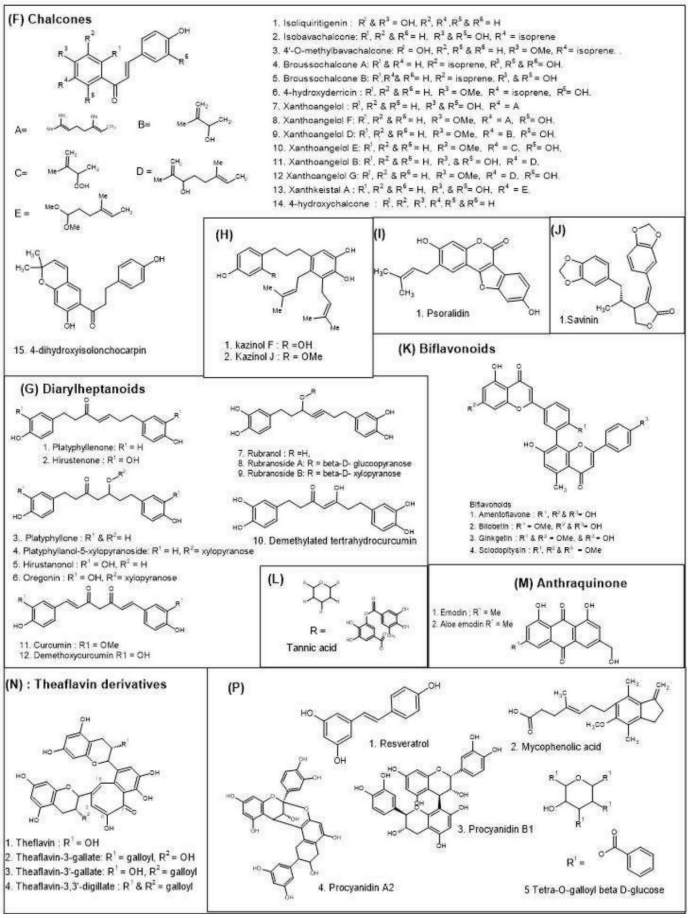

Figure 2: Structures of polyphenols with anti-HCoV activities.

role of the C-3 hydroxyl group in the interaction with protein. The decreasein hydrophobicity in glycosides might also be a reason while considering the activity of papyriflavonol A. These flavonols have also inhibited MERS-CoV PL^{pro} activity with IC_{50} values > 100 μM.[24]

Flavansisolated from *Broussonetia papyrifera* namely 5'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavane*D6* (5-Iso-THFn), Kazinol A*D7*, kazinol B*D1* and broussoflavan A*D2* have been reported to inhibit SARS CoV PL^{pro} (IC_{50} = 30 - 66 μM) and its deubiquitination (IC_{50} = 21 - 75 μM) and DelSGylation activities (IC_{50} = 21 - 71 μM) in a dose-dependent manner.[24] It has been shown that the increase in the number of isopryl groups from one (5-Iso-THFn) to two (kazinol A) in the C ring has reduced the PL^{pro} inhibitory potential. Kazinol B and broussoflavan A with a dimethylated dihydropyran ring formed by the cyclization of isoprene moiety with a phenolic group have better SARS- CoV PL^{pro} inhibitory potential than kazinol A. These flavans also inhibited MERS-CoV PL^{pro} in an order of 5-Iso- THFn = broussoflavan A > kazinol A = kazinol B indicating the role of both isoprene moieties and hydrophobicity in the interaction with protein. The better MERS-CoV PL^{pro} inhibitory potential of broussoflavan A, than kazinol B indicated the role of hydroxyl groups at pyran ring. Isoflavones from *Psoralea corylifolia;* neobavaisoflavone*E2* (IC_{50} = 18 μM) and corylifol A*E3* (IC_{50} = 32 μM) have inhibitedSARS-CoV PL^{pro} with mixed kinetics.[25] The structural activity evaluation of these isoflavones showed that substitution of bulky alkenyl groups in ortho to the phenolic –OH group in the C ring resulted in a reduction in their inhibitory potential. In the same report flavanone, bavachinin*C13*(IC_{50} = 38 μM) has also been shown to inhibit SARS-CoV PL^{pro} with mixed kinetics.[25]

Flavanones isolated from *Paulownia tomentosa* have inhibited SARS-CoV PL^{pro} activity with IC_{50} values ranging from 5 to 15 μM through mixed inhibition kinetics.[26] Five of these compounds, tomentin A*C1*, tomentin B*C2*, tomentin C*C3*, tomentin D*C4* and tomentin E*C5* are geranyl derivatives formed by the cyclization of 3,7-dimethyl-2,6-octadienyl moiety of corresponding diplacols. The better inhibitory potentials of geranyl flavanones than their parent compounds have indicated the role of the dihydro-2H-pyran group in interaction with the enzyme. The decrease in the length of side chain on cyclization might also improve the activity. The presence of more than one methoxy group in the 3',4' or 5' position also seemed to decrease the inhibitory potential.

Isobavachalcone*F2*and 4'-O-methylbavachalcon*F3* isolated from *P. corylifolia* have inhibitedSARS-CoV PL^{pro} without significant difference in their IC_{50} values (< 10 μM).[25] The comparable SARS-CoV PL^{pro} inhibitory potentials of broussochalcone A*F4* and broussochalcone B*F5* has indicated that the number of hydroxyl substitutions in B ring was insignificant in deciding the activity. However in the case of MERS-CoV PL^{pro} inhibition, the presence ofa meta hydroxyl group in B ring is reported to significantly increase the inhibitory potential of broussochalcone B. Isobavachalcone, broussochalcone A and broussochalcone B have almost double SARS-CoV PL^{pro} inhibitory potential than isoliquiritigenin*F1*, which might indicate the role of isoprene unit in chalcones in the interaction with the protein and hydrophobicity. SARS-CoV PL^{pro} inhibitory effect of alkylated chalcones isolated from *Angelica keiskei* has ranged from 1 to 46 μM of IC_{50} values.[27] Xanthoangelol E*F10* and F*F8* have been found as good inhibitors of SARS-CoV PL^{pro} and its deubiquitination and DelSGylation activities with IC_{50} values < 6 μM. The role of perhydroxyl group in the alkyl side chain in forming the hydrogen bonds has been presumed to be the reason for its higher activity. The methylation of the hydroxyl group at C-4' in isobavachalcone*F2* and xanthogelol B*F11* has resulted in the lowering of the inhibitory potential of 4-hydroxy-derricin*F6* and xanthoangelol G*F12*. The PL^{pro} inhibition values for isobavachalcone, xanthoangelol, and xanthoangelol B*F11* indicated that the variations in their side-chain did not have a significant effect on the inhibitory potential. On the other hand the presence of methoxyl groups at C-4' position, due to its bulkiness, has affected the spatial orientation of alkenyl chain at C-3' to result in significant changes in the inhibitory potential of 4-hydroxyderricin, xanthoangelol F and xanthoangelol G with the variations in the sidechain.

SARS-CoV PL^{pro} inhibitory potentials of diarylheptanoids isolated from *Alnus japonica* and curcumin have been studied in detail by Park *et al.* 2012. It has been shown that hirsutenone*G2* (IC_{50} = 4 μM) containing an α,β- unsaturated carbonyl group with a catechol moiety in the backbone, was the most effective inhibitor among these diarylheptanoids. The reduced inhibitory potentials of diarylheptanoids with monohydroxy substitution (platyphyllenone*G1*, platyphyllone*G3*, and platyphyllanol-5-xylopyranoside*G4*) in the aryl rings than the corresponding structures with a dihydroxy substitution (hirsutenone*G2*, hirsutanonol*G5*, and oregonin^{G6}) indicated the significant role of the catechol group in the interaction with the viral protein. Diarylheptanoids with catechol moieties have shown mild variation in the activity with changes in the functional groups in the aliphatic linkage between catechols in the order of α,β-unsaturated carbonyl (hirsutenone, IC_{50} = 4 μM) > β-hydroxyl carbonyl (hirsutanonol 5, IC_{50} = 8 μM) > hydroxyl at C-9 (rubranol*G7*, IC_{50} = 12 μM). The formation of a covalent bond between the carbonyl group in diarylheptanoids and the cysteine residue in the active site of cysteine protease has been proposed as the mechanism of inhibition by the authors. The increase in activity with the increase in electronegativity at carbonyl moiety in presence of α,β-unsaturation has been reported as evidence for this mechanism.[28] But in my opinion, the

Table 1: HCoV PL^{pro} inhibitory potentials of polyphenols.

Compounds (Structure No.)	SARS CoV PL^{pro} (IC_{50} in µM)			MERS CoV PL^{pro} activity	Reference
	Total activity	Deubiquitination Activity	DelSGylation Activity		
Kaempherol (A1)	16 (NC)	62	72	207	[24]
Quercetin (A2)	9 (NC)	21	34	-	[24]
Papyriflavonol (A3)	4 (NC)	8	8	113	[24]
Quercetin-β-galactoside (A5)	52 (NC)	137	68	129	[24]
Neobavaisoflavone (E2)	18 (M)	-	-	-	[25]
Corylifol (E3)	32 (M)	-	-	-	[25]
3'-(3-methylbut-2-enyl)-3',4',7- trihydroxyflavane (D6)	36 (NC)	41	34	48	[24]
Kazinol A(D7)	66 (NC)	75	71	88	[24]
Kazinol B(D1)	31(NC)	21	21	95	[24]
Broussoflavn A (D2)	30 (NC)	60	52	49	[24]
Bavachinin (C13)	38 (M)	-	-	-	[25]
Tormentin A, B, E (C)	< 6 (M)	-	-	-	[26]
Tormentin C, D (C)	12 (M)	-	-	-	[26]
3'-O-methyldiplacol, 4'-O- methyldiplacol, 3'-O- methyldiplacone, 4'-O-methyldiplacol, Mimulone, Diplacone, 6-Geranyl-4',5,7- trihydroxy-3',5'-dimethoxyflavanone (C)	9 -14 (M)	-	-	-	[26]
4-O-methylbavachalcone (F-3)	10 (M)	-	-	-	[25]
Isobavachalcone (F2)	7 (M)	-	-	-	[25]
	13 (M)	16	11		[27]
Broussochalcone B (F5)	12 (NC)	9	10	113	[24]
Broussochalcone A (F4)	9 (NC)	22	13	42	[24]
Isoliquiritigenin (F1)	25 (NC)	17	13	82	[24]
4-hydroxyisolonchocarpin (F14)	35 (NC)	31	29	172	[24]
Kazinol F (H1)	28 (NC)	45	32	40	[24]
Kazinol J (H2)	15 (NC)	33	30	55	[24]
4-hydroxyderricin	26 (NC)	15	9	-	[27]
Xanthoangelol (F7)	12 (NC)	10	6	-	[27]
Xanthoangelol F (F8)	6 (NC)	5	1	-	[27]
Xanthoangelol D (F9)	19 (NC)	13	8	-	[27]
Xanthoangelol E (F10)	1 (NC)	3	5	-	[27]
Xanthoangelol B (F11)	12 (NC)	17	8	-	[27]
Xanthoangelo G (F12)	46 (NC)	44	10	-	[27]
Xanthokeistal A (F13)	21 (NC)	30	11	-	[27]
Hirsutenone (G2)	4 (NC)	3	-	-	[28]
Hirsutanonol (G5)	8 (M)	24	-		[28]
Oregonin (G6)	20 (NC)	44	-	-	[28]
Rubranol (G7)	12 (UC)	7	-	-	[28]
Rubranoside B (G9)	8 (NC)	7	-	-	[28]
Rubranoside A (G8)	9 (NC)	14	-	-	[28]
Curcumin (N1)	5.7	-	-	-	[28]
Psoralidin (I1)	4.2	-	-	-	[25]

NC: non-competitive kinetics, M: mixed kinetics, C: competitive kinetics

catechol group is having more roles in the inhibition activity because the effect of change in substitution in the aryl rings from monohydroxy to dihydroxy seemed to be more significant than that due to the changes in the aliphatic linkage. Curcumin*G11* and demethylated curcumin*G12*, which have two α,β-unsaturated carbonyls in aliphatic linkage have exhibited inhibitory potencies (IC_{50} < 6 μM) comparable to that of hirsutenone.[28] However, the incorporation of a keto-enol group into tetrahydrocurcumin*G10* has afforded a less potent derivative with (IC_{50} = 60 μM). These resultshave been indicated as proof of the role of α,β-unsaturated carbonyl group in the inhibition mechanism. Thus, the above finding altogether suggested that both the α,β-unsaturated carbonyl and catechol groups have pivotal roles in SARS-CoV PL^{pro} inhibition. Diarylheptanoid glycosides have been reported to show lesser activity than their aglycons.[28] In my opinion, the effect of glycoside substitution in C-7 position has a lesser effect than changes in the numberof hydroxyl groups in aryl rings.

Inhibition of CoV 3CL ^{Pro}

The functional importance of $3CL^{pro}$ in the viral life cycle, as well as the absence of closely related homologs in humans, makes $3CL^{pro}$ an attractive target for the design of antiviral drugs against HCoV. The results of studies on CoV $3CL^{pro}$ inhibitory potentials of polyphenols are summarized in Table 2. Park *et al*. (2017) have reported orders of inhibitory potential of quercetin *A2*> kaempferol *A1* = papyriflavonol A*A3* = quercetin-β-galactoside*A4* and quercetin = kaempferol > papyriflavonol A= quercetin-β-galactoside against SARS-CoV $3CL^{pro}$ and MERS-CoV $3CL^{pro}$ respectively. Isoprene substitution in A ring seemed to decrease the CoV $3CL^{pro}$ inhibitory potential of papyriflavonol

A. It has also been reported that quercetin has insignificant SARS-CoV $3CL^{pro}$ activity in both cell-free and cell-based cleavage assays up to 100 μg/mL.[29] Through the computational docking studies, it has been shown that free phenolic hydroxyls at C-7 in myricitrin*A8*, quercetrin*A2* and rutin*A7* formed H-bonds with catalytic amino acid residues of M^{pro}. Phenolic hydroxyls at C-3' and C-4' and some of the hydroxyls in glycoside moiety have also involved in the interaction with the enzyme through hydrogen bonding. Quercetin-β-galactoside has formed six hydrogen bonds using hydroxyls at C-7, C-3' and C-4' and oxygen in glycoside moiety with the catalytic residues of amino acids in SARS- CoV $3CL^{pro}$.[30] Phenyl moiety of kaempferol, morin^{A12}, and herbacetin^{A10} has been shown to occupy in S1 site, whereas their chromen-4-one scaffold occupies in S2 site of SARS-CoV $3CL^{pro}$.[31] Phenyl moiety of kaempferol and morin has placed in S1 site of SARS-CoV $3CL^{pro}$ through the hydrogen bond between C-4' hydroxyl and Glu 166, whereas their chromen-4-one scaffold located in S2 site with the interaction with hydroxyls at C-3 and C-7. In thecase of herbacetin, the presence of hydroxyl group at C-8 has been shown to increase the binding with catalytic residues in the S2 pocket of the protein.

5-IsoTHFn^{D6} has the highest inhibitory potential among the flavanes isolated from *B. papyrifera* against SARS-CoV $3CL^{pro}$ (IC_{50} = 30 μM) and MERS-CoV $3CL^{pro}$ (IC_{50} = 35 μM) activities.[24] Similar to the inhibition to PL^{pro}, the increase in the number of isopryl units from one to two has reduced the $3CL^{pro}$ inhibition potential of the flavanes. It has also been shown that the cyclization of the isoprene moiety of flavanes has significantly reduced their SARS-CoV $3CL^{pro}$ and MERS-CoV $3CL^{pro}$ inhibitory potentials. Isoprene being a bulky hydrophobic group could have a major role in modulating the interactions with the catalytic sites of $3CL^{pro}$. The presence of hydroxyl groups on the pyran ring seemed to increase the MERS-CoV PL^{pro} inhibitory potential of broussoflavan A^{D2} than kazinol B^{D1}. An IC_{50} value of 47 μM has been reported for gallocatechingallate^{D4} (GCG) against SARS-CoV $3CL^{pro}$.[32] The galloyl moiety of GCG has been proposed to form four hydrogen bond interactions with catalytic amino acid residues in $3CL^{pro}$. In another molecular docking study, it has been shown that epigallocatechingallate*D11* (EGCG), epicatechingallate*D9* (ECG), and GCG have interacted with one or more catalytic residues (His41 and Cys145) of M^{pro} by hydrogen bonding along with other non-covalent interactions resulting in stabilized complexes. Meta hydroxyl groups in galloyl moiety and trihydroxy benzene ring and hydroxyls at C-5 and C-7 of EGCG and ECG have been found as involved in hydrogen bonding with amino acids in docking sites of M^{Pro}. In the case of GCG, only hydroxyls in gallic and trihydroxy benzene have involved in hydrogen bonding with the amino acid residues.[33] In another docking study with M^{pro}, the meta-hydroxyl group in trihydroxy benzene ring and hydroxyls at C-3 and C-5 in EGChave been reported to form hydrogen bonds with catalytic amino acid residues. Meta-hydroxyl and carbonyl groups in gallic acid and meta hydroxyl group in the trihydroxy benzene ring of EGCG and ECG have been found as involved in hydrogen bonding with amino acids in docking sites of M^{Pro}.[34]

Luteolin*B1* has been shown to be 10 times better in inhibiting SARS-CoV $3CL^{pro}$ activity than apigenin*B2*, which indicated the role of the catechol group in flavones in the protein interaction [35]. Hesperetin^{C14} has inhibited the cleavage activity of SARS-CoV $3CL^{pro}$ both in cell-free (IC_{50} = 60 μM) and cell-based (IC_{50} = 8 μM, SI = 328) assays. The lesser inhibitory effect of hesperetin in cell-free assay than in cell-based assay has been attributed to its lesser water solubility.[29] Computational docking study with hesperidin^{C15} (hesperetin-7-O-rhamnoside) has shown that phenolic hydroxyl at C-7 and some of the hydroxyls at glycoside moiety are involved in the interaction with amino acid residues in M^{pro} through hydrogen bonds. A docking study on the binding probabilities of 8-C-glucoside (vitexin^{B4}) and 7-O-rhamnoglucoside (rhoifolin^{B5}) of apigenin with M^{pro} has shown that hydroxyl groups at C-7 of vitexin and C-4' of rhoifolin have formed hydrogen bonds with catalytic residues. Hydroxyl groups in glycoside moieties of both compounds have also involved in binding with the enzyme.[34] Jo *et al*. 2020 have predicted the spacing of flavones glycosides rhoifolin and pectolinarin*B7* in the catalytic pockets of SARS-CoV $3CL^{pro}$ through molecular docking studies. The main scaffold of the flavones has been shown to be located in S2 and S3' pockets of the protein. The carbohydrate group at C-7 position of the chromen-4-one scaffold has occupied the S1 and S2 sites. The better affinity of rhoifolin might be due to orchestrated binding through S1, S2, and S3' sites. The isoflavone, daidzein has moderate activity against SARS-CoV $3CL^{pro}$[29] C-7 hydroxyl and C-3 carbonyl groups in puerarin*E4* (daidzein-8-C-glucoside) and C-7 hydroxyl group in glabridin*E5* formed H-bonds with M^{pro}.[34]

Biflavonoids isolated from *Torreya nucifera* have been reported to inhibit SARS-CoV $3CL^{pro}$ in a decreasing order of amentoflavone*K1* (IC_{50} = 8 μM), ginkgetin*K3* (IC_{50} = 32 μM), sciadopitysin*K4* (IC_{50} = 38 μM) and bilobetin^{K2} (IC_{50} = 72 μM). Docking study has revealed that amentoflavone fit into a binding pocket of $3CL^{pro}$, by forming hydrogen bonds using phenolic hydroxyl group at C-5. Bilobetin with C-4' methoxy group has been shown to have lesser inhibitory potential than amentoflavone. In my opinion, the decrease in the potential of bilobetin might be due to the change in spatial orientation of the molecule due to the presence of a bulky methyl group at C-4' position. The other two biflavonoids ginkgetin and sciadopitysin with methoxy groups respectively at C-4' and C-7 and C-4', C-7 and C-4" are better in inhibiting $3CL^{pro}$ than bilobetin. The presence of the methoxy group at C-7 might be increasing the C-5 H-bonding ability of ginkgetin and sciadopitysin. The 200 folds inhibitory potential of amentoflavone than apigenin indicated the importance of spatial arrangement of biflavonoid to fit into the binding site of $3CL^{pro}$.[35]

Table 2: HCoV 3CL^{pro} inhibitory potentials of polyphenols (IC_{50} in μM).

Compounds (Structure No.)	SARS-CoV 3CL^{pro}	MERS-CoV 3CL^{pro}	Reference
Quercetin (A-2)	24, 53	35	[35], [24]
Kaemferol (A-1)	116	35	[35]
Papyriflavonol (A-3)	104	64	[30]
Quercetin-β-galactoside (A-5)	43, 129	68	[35], [24]
3'-(3-methylbut-2-enyl)-3',4',7-trihydroxyflavane (D-6)	30	35	[24]
Kazinol A (D-7)	85	88	[24]
Kazinol B ((D-1)	233	95	[24]
Broussoflavn A (D-2)	92	49	[24]
Apigenin (B-2)	281	-	[35]
Luteolin (B-1)	20	-	[35]
Hesperetin (C-14)	60	-	[29]
Catechin, EGC, EGCG, EC, ECG (D)	100	-	[37]
Daidzein (E-1)	105	-	[29]
Amentoflavone (K-1)	8	-	[35]
Ginketin (K-3), Sciadopitysin (K-4)	< 38	-	[35]
Bilobetin (K-2)	72	-	[35]
Broussochalcone B (F-4)	58	28	[24]
Broussochalcone A (F-3)	88	36	[24]
4-hydroxyisolonchocarpin (F-14)	203	194	[24]
Isoliquitrigenin (F-1)	62	34	[24]
Isobavachalcone (F-2), xanthogelol (F-7),	31-44 (C)	-	[27]
xanthogelol A (F-13), F (F-8) 4-hydroxyderricin (F-6)	81 (C)	-	[27]
Xanthoangelol B (F-11) and D (F-9)	22- 27 (C)	-	[27]
Xanthoangelol E (F-10)	11 (C)	-	[27]
Hirsutenone (G-2)	36	-	[28]
Hirsutanonol (G-5), oregonin (G-6), rubranol	102 – 130	-	[28]
(G-7), rubranoside A (G-8), B (G-9) 3-isotheaflavin-3-gallate	7	-	[37]
Tannic acid (L-1)	3	-	[37]
Theaflavin	56	-	[37]
Theaflavin-3-gallate and Theaflavin-3'-gallate	43	-	[37]
mixture Theaflavin-3,3'-digillate	9	-	[37]
Kazinol F (H-1)	43	-	[24]
Kazinol J (H-2)	64	-	[24]
Savinin (J-1)	9		[36]
Aloeemodin (anthraquinone) (M-2)	132	-	[28]

C: competitive kinetics

Chalcones isolated from *B. papyriera* have shown a similar trend of inhibitory potential against SARS-CoV 3CL^{pro} and MERS-CoV 3CL^{pro} viz. broussochalcone B*F5*> broussochalcone A*F4*> 4-hydroxyisolonchocarpin*F15*.[24] The cyclization of the isoprene unit in broussochalcone B seemed to hamper its 3CL^{pro} inhibitory potential resulting in more than 4 times increase in IC_{50} values for 4-hydroxyisolonchocarpin. Xanthoangelol E*F10* has been reported as the most potent inhibitor of SARS-CoV 3CL^{pro} among the alkylated chalcones isolated from *A. keiskei*. Interestingly these chalcones were competitive inhibitors of 3CL^{pro} activity, which is very rare in phenolics. The role of perhydroxyl group in the alkyl side chain in forming hydrogen bonding has been presumed to be the reason for its higher activity. This has been further confirmed by docking simulation studies in which xanthoangelol E has been shown to fit perfectly into the active site of 3CL^{pro}. The chalcones with hydroxyl group at C-4' (isobavachalcone*F2* and xanthoangelol B*F11*) has higher activity than those with the methoxy

Table 3: Cell culture-based anti-HCoV potentials of polyphenols.

Compound (Structure No.)	Activity	IC_{50} (μM)	Ref
Quercetin (A-2)	HIV-luc/SARS pseudotyped virus infection on VeroE-6 cells	83	[19]
Luteolin (B-1)	HIV-luc/SARS pseudotyped virus infection on VeroE-6 cells	9 (SI = 17)	[19]
	SARS- Cov(wild type) infection on VeroE-6 cells	11(SI = 14) 4 (SI = 34)	[19]
Hesperetin (C-14)	Vero cells with plasmid containing $3CL^{pro}$ –substrate-luciferase-in frame gene	8 (SI= 328)	[29]
Procyanidin A2 (P-4)	HIV/SARS CoV pseudovirus infection on HepG2 cells	121 (SI = 7)	[50]
Procyanidin B1(P-3)		161 (SI = 4)	[50]
Procyanidin A2(P-4)	SARS- Cov(wild type) infection on VeroE-6 cells	30 (SI = 37)	[50]
Procyanidin B1(P-3)		41(SI = 16)	[50]
4-hydroxychalcone (F-14)	HCoV-OC43 infection on BHK 21 cell.	1 (SI > 13)	[51]
	HCoV NL63 infection on LLC-MK2 cells	7 (SI > 3)	[51]
	MERS Cov infection on VeroE-6 cells	10 (SI > 2)	[51]
Isobavachalcone (F- 2)	Vero cells with plasmid containing $3CL^{pro}$ –substrate-luciferase-in frame gene	12 (SI = 1)	[27]
4-hydroxyderricin (F-6)		51 (SI < 1)	[27]
Xanthoangelol (F-7)		6 (SI = 3)	[27]
Xanthogelol B(F-11), D (F-9), E (F-10), xanthokeistal A (F- 13)		< 10 (SI >3)	[27]
Xanthoangelol F (F- 8)		33 (SI < 1)	[27]
Aloe emodin (M-2)		366 (SI =32)	[29]
Tetra-O-galloyl-β-D- glucose (P-5)	HIV-luc/SARS pseudotyped virus infection on VeroE-6 cells	3 (SI = 377)	[19]
Mycophenolic acid (P-2)	SARS- Cov(wild type) infection on VeroE-6 cells	4 (SI = 240)	[19]
	HCoV-OC43 infection on BHK 21 cell.	2 (SI = 2)	[51]
	HCoV NL63 infection on LLC-MK2 cells	0.2 (SI = 19)	[51]
	MERS Cov infection on VeroE-6 cells	2 (SI = 2)	[51]
	MHV-A59 infection on 17Cl-1 cells	0.2 (SI = 24)	[51]

SI: Selection Index

group (4-hydroxyderricin*F6* and xanthoangelol G*F12*). The chalcones except for xanthoangelol F*F8* and xanthoangelol G have shown lower IC_{50} values for $3CL^{pro}$ in cell-based system than cell-free assay. Xanthoangelol, xanthoangelol D*F9*, xanthoangelol E, xanthoangelol B and xanthokeistal A*F13* have shown IC_{50} values lesser than 10 μM against $3CL^{pro}$.

Diarylheptanoids isolated from *A. japonica* have inhibited SARS-CoV $3CL^{pro}$ with IC_{50} values ranged from36 to 145 μM. Hirsutenone has shown the highest inhibitory potential among these diarylheptanoids.[28] The significantly higher inhibitory potential of hirsutenone among the diarylheptanoids indicated the role of α,β-unsturated keton with catechols as aryl rings in the interaction with the viral protein. Hirsutenone*G2* and rubranoside B*G9* have anti- deubiquitination activity with IC_{50} values < 7 μM respectively. In a recent study using computational docking technique, both the keto-enol moiety and para hydroxyl groups in aryl rings of curcumin*G11* and demthoxycurcumin*G12* have been shown to be involved in hydrogen bond formation with amino acid residues in SARS-CoV-2 M^{pro}.[34] A lignin, savinin*J1* has inhibited SARS-CoV $3CL^{pro}$ activity.[36] Tannic acid^{L1} (IC_{50}= 3 μM), theaflavin-3-gallate^{N2} (IC_{50}= 7 μM) theaflavin-3,3'-digillate^{N4} (IC_{50}= 3 μM) and theaflavin^{N1} (IC_{50}= 56 μM) in tea leaves have been reported to inhibit SARS-CoV $3CL^{pro}$ in a dose-dependent manner. Gallates of theaflavin were found to be better inhibitors than theaflavin, indicating the role of the gallic acid moiety in the inhibition.[37] Aloe emodin^{M2} and hesperetin in *Isatis indigotica* root extract have inhibited cleavage activity of the $3CL^{pro}$, with IC_{50} values 366 and 8.3 μM respectively in the cell-based assay.[29]

HCoV RdRp inhibition

RdRp, a key enzyme for the replication of the virus has been considered as a potential drug target against SARS-CoV.[38] The resemblance in RdRp in various CoVs, as well as the lack of similar human polymerase counterparts, minimize the risk of crosstalk with human polymerases with RdRp inhibitors.[39,40] Recently, Yin *et al.* reported the crystal structure of RdRp of SARS-CoV-2 complexed with an antiviral drug, remdesivir.[41] In a recent study, theaflavin has been shown to have a promising docking score in the catalytic pocket of RdRp of SARS-CoV-2 (−9.11

kcal/mol), SARS-CoV (−8.03 kcal/mol), and MERS-CoV (−8.26 kcal/mol). Hydrophobic interactions were reported as the major contributor of the binding energy and additional hydrogen bonds were found between theaflavin and RdRp.[42] EGCG, theaflavin^{N1}, theaflavin-3'-gallate^{N2}, theaflavin-3'-gallate^{N3}, theaflavin 3,3'-digallate^{N4}, hesperidin, quercetagetin, and myricetin were reported to strongly bind to the active site of RdRp.[43] Meta-hydroxyl group ingallic acid moiety, para hydroxyl group in the trihydroxy benzene ring, hydroxyls at C-5 and C-7 of EGCG have been shown to involve in hydrogen bonding with amino acids in docking sites. Hydroxyl groups at C-4, C-5, C-5" and C- 7" and hydroxyl groups in gallic acid have been reported to form hydrogen bonds with RdRp.

CoV N-protein inhibition

The nucleocapsid (N) protein has a major role in assembling and enveloping RNA during the replication of CoV in host cells and is regarded as a drug target against SARS-CoV infection. Roh 2012 reported that (-)-catechin gallate and (-)-gallocatechin gallate at a concentration of 0.05 μg mL^{-1}, inhibited 40% of N protein activity of SARS-CoV in a nanoparticle-based RNA oligonucleotide biochip system.[44] In another report, it has been shown that resveratrol*p1* has decreased the expression of N protein in MERS-CoV replication, inhibited MERS-CoV infection to Vero E6 cells, and prolonged cellular survival after virus infection at a concentration range of 125-250 μM.[45]

Inhibition of Viral Release Mechanisms

Several viruses encode for ion-selective channels that become incorporated into the membrane of the infected cell. Activation of such channels seems to be involved in the process of virus production and release. SNE-3a protein of SARS-CoV is presumed to form an ion channel for virus release from the infected cell.[46,47] Emodin^{M1} has been shown to block ion channels in virus-infected cells by inhibiting SARS-CoV SNE-3a protein and thus reduce the presence of extracellular viral RNA copies. The antiviral potential exhibited by emodin has been assumed as the result of combined inhibitory effects on the interaction between spike protein and ACE2 receptor and SNE-3a protein activity.[48] Kaempferol and its glycosides have also been shown to inhibit the CoV 3a protein channel. At 20 μM concentration kaempferol resulted in 18% reduction in 3a mediated current, whereas glycosides of kaempferol, Juglanin^{A9}, and tiliroside^{A11} respectively resulted in 100 and 50% inhibition of 3a protein channel, indicating the importance of sugar residues in the activity. Quercetin, naringenin, and genistein have been shown to be not effectivein inhibiting 3a protein channel.[49]

Other Antiviral Assays

The cell culture based anti-viral properties of polyphenols are summarized in Table 3. Quercetin*A2* (EC_{50} = 83 μM) has been shown to have potent antiviral activity against HIV-luc/SARS pseudotyped virus.[19] Procyanidin A2*P4* and procyanidin B1*P5* isolated from *Cinnamomi cortex* have shown moderate inhibition on infection of HIV/SARS pseudovirus on HEPG2 cells (IC_{50}< 161 μM) and *wt*SARS CoV on Vero E6 cells (IC_{50}< 41 μM).[50] In another study 4- hydroxychalcone*F14* has been shown to inhibit HCoV-OC43, HCoV-NL63, MERS- CoV, and MHV-A59 with EC_{50} values varying from 1 to 10 μM and CC_{50} values > 20 μM. Mycophenolic acid^{R2} has been reported to inhibit HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59 with EC50 values < 2 μM.[51] Myricetin and scutellarein in micromolar concentrations have been reported to inhibit the SARS-CoV helicase protein *in vitro* by affecting the ATPase activity.[52]

DISCUSSION

A review of literature on the antiviral potential of natural products against HCoV, in general, showed that polyphenols contributed a major fraction of antiviral compounds. The interactions of phenolic groups with catalytic amino acid residues in viral proteins through hydrogen bonding and other covalent interactions could be the major reason for their increased activities. Hydroxyl groups at C-3, C-7, C-3', C-4', C-8, etc of flavonoids have been assumed to be involved in the interactions with the viral proteins. Though the phenolic hydroxyl group favors the hydrogen bonding with proteins, the increased presence of hydroxyl groups decreases the hydrophobicity of the molecule. The approach and insertion of the molecule into the protein pockets are largely controlled by its hydrophobic interactions with the protein. The presence of nonpolar hydrocarbon chains in the molecules seemed to have a major role in modulating its interactions with viral proteins. Papyriflavonol A, an isopryl derivative of quercetin was significantly better in inhibiting CoV PL^{pro} than quercetin, whereas its $3CL^{pro}$ inhibitory potential was lesser than quercetin. The increase in the number of isopryl groups from one to two in the C ring of flavans has reduced the HCoV cysteine protease inhibitory potentials.[24] Isobavachalcone, broussochalcone A and broussochalcone B have significantly higher SARS-CoV PL^{pro} and SARS-CoV $3CL^{pro}$ inhibitory potentials than isoliquiritigenin, which also indicated the role of isoprene units in chalcones in the interaction with the protein. The hydrophobic nature and bulkiness of isoprene moieties might be the reason for its ability to alter the interactions with proteins. Cyclization of isoprene or other aliphatic side-chains with a phenolic hydroxyl group to form dihydropyran rings in flavans[24] and flavanones[26] reported to increase PL^{pro} and decrease $3CL^{pro}$ inhibitory potentials. The presence of hydroxyl or peroxyl groups in alkenyl side chains has also been shown to improve PL^{pro} and $3CL^{pro}$ inhibitory potentials of chalcones.[27] The inhibitory potentials of phenolics substituted with different side chains could be explored for developing the understanding of the role of side chains in anti HCoV molecules. Based on the literature review and structure-activity relationships of phenolics, it is suggested to assess the molecules like embelin, with benzoquinone ring and long alkyl side chain,[53] and its derivatives for the anti- HCoV potential. Glycosylation of phenolics not only decreases their hydrophobicity but also hides the nearby active groups from the interactions with proteins. On the other hand, glycosides offer more hydroxyls for interaction with proteins. Glycosylation at C-3 position has significantly decreased both PL^{pro} and $3CL^{pro}$ inhibitory potential of quercetin. In the case of rhoifolin, the glycoside moiety has been reported to rearrange the spatial configuration of the molecule in a more interactive manner with $3CL^{pro}$.[31]

Though flavonoid glycosides may be absorbed in the small intestine, biodegradation limits their therapeutical application.

Apart from kaempferol, both quercetin and payriflavonol have a catechol group as their C ring, which is presumed to have a role in the inhibition. The role of catechols and gallic acids in improving the interactions with viral proteins is also warranted in detailed studies. The probability of non-specific protein precipitating nature of gallotannins and other gallic acid derivatives to mislead the viral protein inhibition results has also to be addressed in these studies. Chalcones contain two aryl groups linked with α-β unsaturated ketone linkage and are more flexible than the other flavonoids with chromane scaffold. The role of α-β unsaturated ketone in viral protein inhibition has also been evidenced in the study of diarylheptanoids. A flexible structure with varying numbers of phenolic groups might make chalcones a class of compounds with special attention for synthetic modifications for anti-CoV drugs. The docking studies indicated that the spatial orientation of biflavonoids has an important

role in the interactions with viral protease enzymes. Compounds like tetrahydroamentoflavone, which has already been proved to have xanthine oxidase inhibitory potential,[54] could be a possible candidate for the inhibition of the viral enzymes as it has more flexible molecular structure than amentoflavones due to the presence of saturated chromone rings.

The high selective index values reported for hesperetin and tetra-O-galloyl-β-D-glucose warrants special attention for further studies. Though the *in silico* experiments help to predict the chemophores and their interactions with proteins, the findings have to be supported by further laboratory experiments. The IC_{50}/EC_{50} value of enzyme inhibition is directly proportional to the quantity of enzymes used for the experiment. Hence comparing the IC_{50}/EC_{50} values reported in different experiments might not be adequate for assessing the relative activities of compounds. A system of reporting IC_{50}/EC_{50} values after normalizing the obtained values in the experiment to a fixed quantity of enzyme (say 100 nM) might be helpful to get a better understanding of the relative activities of compounds.

CONCLUSION

The pandemic nature of the current COVID-19 infection warrants the identification and application of anti-virals for disease management on a war foot basis. The development of synthetic antiviral molecules is a time-consuming process, hence natural products are considered as a reliable and valuable source for the rapid drug discovery of antivirals against HCoV. Among the natural products, the current literature has identified plant polyphenols as a major source of anti HCoV molecules. We are naturally adapted to most of the plant phenolics as, they are part of our vegetarian diet though in minute quantities, hence phenolics have a lower risk for the development of toxicity comparing to synthetic products. Polyphenols, due to the presence of phenolic hydroxyls have increased affinity towards the proteins, hence ensuring the required concentrations of phenolics at the sites of infection will be a real challenge. In the current literature, apart from the *in-vitro*, cell culture and *in silico* studies, pre-clinical and clinical studies to assess the antiviral potential of phenolics against HCoV are rather limited. The possibility to use polyphenols with potential antiviral properties as pre and post-exposure prophylaxis of SARS CoV-2 to decrease the viral load and reduce the serious complications associated with the disease might be explored. The present review on the anti-HCoV potential of natural phenolics and their structure-activity relationships is expected to help researchers to explore the potential of plant phenolics and their semi-synthetic derivatives for the battle against HCoV.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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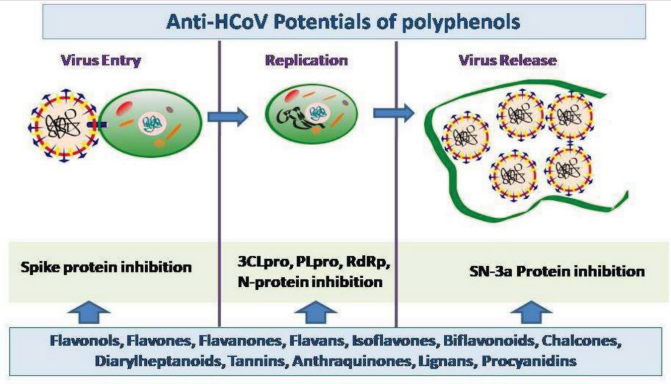
GRAPHICAL ABSTRACT



SUMMARY

Coronaviruses are a large family of RNA viruses, naturally present in tropical animals. The pathogens like coronaviruses with increased ability to transmit from animals to humans and develop highly contagious diseases are considered as an emerging threat to the human health management system. The ability of human coronaviruses to infect respiratory tracts and transmit through respiratory droplets makes them highly contagious and potential to become pandemic, which warrants the rapid development of effective and safe antivirals against coronaviruses. Phenolics being a class of natural compounds with lesser toxicity comparing to synthetic compounds are considered as a valuable source of anti-viral agents. This review on the current literature on anti-human coronavirus potentials of plant phenolics is expected to be useful for the selection of phenolics with diverse structural properties and to design semi-synthetic products with better drug properties against coronaviruses.

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Cite this article: Arimboor R. Plant Phenolics with Antiviral Activities against Human Corona Virus and Structure-Activity Relationships – A Review. Pharmacog Rev. 2021;15(30):96-106.