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Anthraquinone and coumarin as potential natural products against human coronavirus strain

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ABSTRACT

The COVID-19 pandemic has prompted researchers to look for novel compounds with SARS-CoV-2 antiviral potential. Numerous studies have demonstrated that natural compounds have potent antiviral properties. This review suggests potential natural products and their isolates for treating human coronaviruses based on effective herbal treatments for coronavirus infections. Given the effects of human coronavirus strains, finding alternative isolated compounds from plants (like anthraquinones and coumarin) that could prevent viral infection will aid in hastening the medication discovery process. It is known that anthraquinone derivatives have immune-stimulating, anti-inflammatory, and antiviral properties. Coumarin, a naturally occurring compound, is also a promising therapeutic candidate because of its solubility, stability, and low toxicity. These natural substances may interfere with target-specific proteins to stop viral replication in the host. Natural remedies not only stop viruses from attaching to the host body but also stop them from reproducing and strengthen the host's immune system.

Keywords: antiviral, human coronavirus, COVID-19, natural products, protease

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INTRODUCTION

Coronaviruses (CoVs) are a family of viruses that can cause illness in humans and animals. They belong to the subfamily Coronavirinae in the family Coronaviridae, and they derive their name from their crown-like appearance when viewed under a microscope. The four coronavirus genera are α-, β-, γ-, and -δ, each contain a positive-sense single-stranded RNA genome[1]. Due to CoVs' tendency for mutation and recombination during replication, coronaviruses are more diverse than they otherwise could be. Human Coronaviruses (HCoVs) are recognized respiratory infections linked to a variety of respiratory outcomes. The emergence of Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 and severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003 highlighted the significance of human coronaviruses and their potential for high pathogenicity. These outbreaks prompted increased attention and research focused on understanding and mitigating the impact of HCoVs[2,3].

The primary pharmacologically active targets of severe acute respiratory syndrome coronavirus (SARS-CoV-2) are 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), RNA-dependent RNA polymerase, and spike (S) proteins. There are currently no proven antiviral treatments or preventative coronavirus vaccinations available[4]. However, several synthetic drugs have shown promise, such as hydroxychloroquine and chloroquine phosphate, which function by various mechanisms, including the alkalization of the phagolysosomes of the host cell[5]. Several more recent antiviral drugs are also promising, including lopinavir, remdesivir, and arbidol. Along with these, lopinavir/ritonavir, nucleoside analogs, neuraminidase inhibitors, and the peptide EK1 are also recommended as possible treatments[6].

To prevent coronavirus disease (COVID-19) infection, natural products, and herbal remedies are employed since they potentially impact medication discovery[7]. Drug development for several illnesses is already based on plant, fungal, and marine sources of natural compounds. These exhibit antiviral activity against human CoV-2, contributing to the creation of a high-quality medication for the treatment of COVID-19. These herbal remedies operate by preventing the S protein from interacting with the angiotensin-converting enzyme-2 (ACE-2) receptors of host cells[8]. Many of these boost the immune system's ability to fight the virus, inflammation, oxidative stress, and fibrosis caused by COVID-19[9].

To prioritize the screening of compounds against SARS-CoV-2 in the quest for innovative therapeutic candidates to treat or prevent COVID-19, a compre-

hensive assessment of the antiviral activity attributed to well-known natural products is a helpful place to start[10]. The present study claims that the natural products anthraquinone and coumarin have strong anti-SARS-CoV-2 efficacy.

METHODOLOGY

SARS-CoV and natural products

The SARS-CoV-2 family of enveloped RNA viruses infects people and causes severe pneumonia and life-threatening respiratory illnesses. The spike protein binds to ACE-2 receptors and facilitates the fusion of the virus and the host membrane, which allows the coronavirus (CoV) to enter host cells (pulmonary and bronchial epithelial cells)[11,12,13,14]. Viral variety and SARS-CoV capacity for fast mutation, even during an epidemic, have impeded the creation of potent antiviral medicines with a broad range of action. Therefore, it is crucial to create antiviral medications that may either greatly lessen the signs and symptoms of SARS-CoV infection or safely and effectively prevent the transmission of SARS-CoV. It would be crucial to focus on creating straightforward, tiny molecules that are affordable to create and administer. Recently, numerous promising treatments against SARS-CoV-2 virus, including remdesivir, infliximab, and imatinib, have been discovered. Remdesivir has been approved for use in urgent situations and exhibits strong antiviral activity[15,16]. To stop the illness from spreading, finding new medication leads that are more generally effective against coronavirus is crucial.

Natural products may be used to treat COVID-19 by preventing some stages of the virus' life cycle, such as C3en the virion binds to the appropriate receptor on the cell surface. Transmembrane protease serine 2 is a 3CLpro that is important for cleaving viral peptides into virulence-enhancing functional units. It can activate spike proteins and is involved in the infection of host cells by SARS-CoV-2. Because excessive soluble versions of the ACE-2 are implicated at this stage, utilizing ACE-2 inhibitors as a therapy option is a possibility[3]. Coronavirus replication-transcription complex enzymes involved in transcription, translation, virion assembly, budding, and release include reverse transcriptase and RNA-dependent RNA polymerase (RdRP). Many of the aforementioned mechanisms have been observed for the action of natural coumarin compounds[17]. Therefore, it is expected that blocking the SARS CoV-2's main protease, non-structural proteins (NSP10/NSP16) methyltransferase, phosphatase, and endoribonuclease by a possible inhibitor molecule may significantly increase the coronavirus's ability to develop and infect its host as shown in Figure 1.

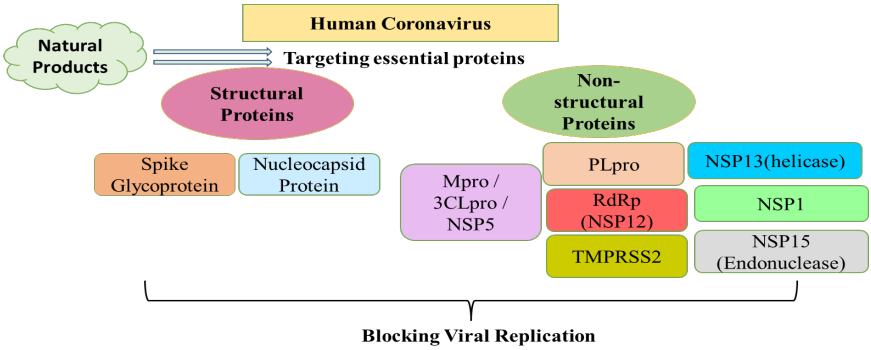


Figure 1. Overview of inhibition of human coronavirus protein

RESULTS and DISCUSSION

Anthraquinone against human coronavirus

Anthraquinone

Anthraquinones (AQs) are a class of chemicals derived from a variety of herbal remedies (Figure 2), including Senna species, that are used in both traditional Chinese medicine and the Ayurvedic medical system to treat a variety of infectious and non-infectious disorders[18]. Additionally, anthraquinone derivatives have been linked to antiviral[19], anti-inflammatory[20], and immunological boosting properties[21]. Therefore, it may be advantageous in the COVID-19 infection if the bioactive is shown to have anti-viral, anti-inflammatory, and immune-stimulating characteristics. This may be proven using the idea of network pharmacology or a polypharmacological approach.

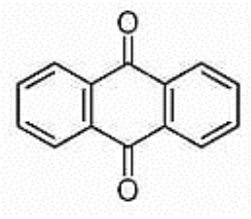


Figure 2. Structure of anthraquinone

Bioactives of anthraquinone

About 700 compounds associated with AQs have been identified. 200 of these were extracted from plants, while the remaining were found in diverse marine and terrestrial sources like lichens, bacteria, fungi, marine invertebrates, and

sponges[22]. For instance, the most well-known and well-studied AQs, emodin, chrysophanol, and physcion, were found in marine fungi such as *Aspergillus*, *Penicillium*, and *Microsporum sp*., as well as in terrestrial sources (plant endophytic fungi). Amrubicin, daunorubicin, diacerein, doxorubicin, epirubicin, idarubicin, mitoxantrone, and valrubicin are examples of commercially available medications that contain anthraquinone scaffold[23].

Bioactive compounds of anthraquinone against human coronaviruses and their antiviral mechanism

Numerous investigations revealed that anthraquinones might be used to prevent the entrance, replication, and release of numerous viruses, including coronaviruses as shown in Table 1. Aloe-emodin, anthrarufin, alizarine, dantron, and emodin are some of the anthraquinones of *R. emodi* that have been shown to bind to SARS-CoV-2 in the active sites of the RNA binding domain of nucleocapsid phosphoprotein using *in silico* studies. The compounds might be completely evaluated and released as possible therapeutic candidates to treat COVID-19 due to their ability to bind to all three active sites with binding energies ranging from -25.45 kcal/mol to -45.48 kcal/mol[24].

Various research indicates that emodin exhibits significant antiviral activities against coxsackie B virus, herpes simplex viruses, hepatitis B virus, human cytomegalovirus, Japanese encephalitis virus, Cypridine herpesvirus 3 virus, influenza A virus, Zika virus, poliovirus, and several viral diseases. Therefore, it has been stated that emodin has antiviral properties that help to prevent or lessen SARS-CoV infection[25]. According to Hsiang and colleagues, emodin can prevent spike protein-pseudotyped retrovirus infectivity and SARS-CoV spike protein interactions with ACE-2 in Vero E6 cells[26]. Researchers also demonstrated that emodin can prevent the release of SARS-CoV from infected cells as well as the 3A ion channel of the coronavirus[27]. Blind molecular docking experiments revealed that certain naturally occurring antiviral anthraquinones could work well as COVID-19 main protease (Mpro) inhibitors because they bind close to the active site that contains the catalytic dyad HIS41 and CYS145 through non-covalent forces[28].

Hepatitis B virus replication was suppressed by Rhein from *Rheum palmatum* ethanol extract[29]. Rhein is a promising therapeutic drug for the treatment of SARS-CoV-2 because it inhibits the interaction between the S protein and ACE-2[30]. The S protein-ACE-2 interaction was reduced by pre-incubating rhein with biotinylated S protein. The influence of rhein on the activity of the human liver enzyme cathepsin B within endosomes is a crucial stage in SARS-CoV-2

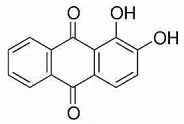
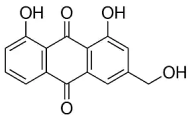
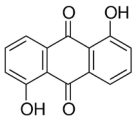
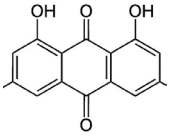
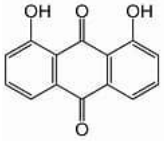
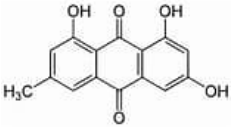
infections, as described by Savarino et al. in 2007[31]. It has been demonstrated that rhein is also capable of docking the spike proteins including PLpro, Mpro, and RdRP active sites. Rhein is favorable as a SARS-CoV-2 inhibitor as a result of all these discoveries. Furthermore, the scientists demonstrated that rhein from Polygonaceae had a minor suppression of the interaction of enzymes with S proteins[30]. Rhein has demonstrated its capacity to prevent several human coronaviruses (HCoV-229E, HCoV-OC43, and SARS-CoV-2) from infecting and replicating in research[32].

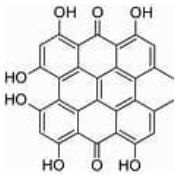
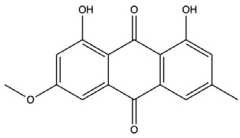
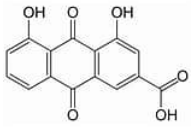
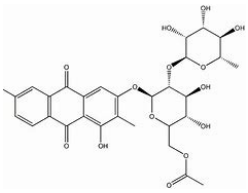
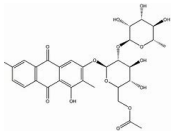
A powerful inhibitor of SARS-CoV-2 Mpro is the antitumoral valrubicin[33]. Our research revealed that valrubicin has a strong affinity for Mpro, PLpro, and RdRp, as well as for spike proteins, allowing us to hypothesize that valrubicin may be a viable inhibitor of SARS-CoV-2. It has been demonstrated that idarubicin has a multi-target anti-SARS-CoV-2 impact due to its ability to bind to spike proteins as well as Mpro, PLpro, and RdRp. Idarubicin showed a significant affinity for endoribonuclease[34]. According to Jin et al., daunorubicin was claimed to be a possible SARS-CoV-2 Mpro inhibitor[35]. According to the current study, daunorubicin shows a strong affinity for PLpro, RdRp, and spike proteins. Doxorubicin, an anticancer medication with previous antiviral efficacy, might be employed to beat SARS-CoV-2 by elevating cellular methylglyoxal content to virucidal levels[36]. Patients with COVID-19 may benefit from very brief therapy with doxorubicin that increases cellular MG. Human cytomegalovirus inhibition by emodin, rhein, and hypericin was reported[17], and the antiviral activity of emodin, aloe-emodin, chrysophanol, physcion, and rhein, against the Japanese encephalitis virus, was also reported[37]. Aloe-emodin, emodin, and chrysophanol were also shown to inhibit the SARS-CoV 3CLpro[38].

With an IC_{50} value of 366 μM, aloe-emodin has been shown to have anti-viral properties against SARS-CoV-2 by reducing the cleavage activity of 3CLpro in a dose-dependent manner[38]. The results of docking research demonstrated that several anthraquinones and their derivatives like emodin 8-glucoside, and chrysophanol 8-O-D-glucoside may bind to SARS-CoV-2 proteins, including the spike protein, papain-like protease, and 3CLpro. 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-O-(6′-O-acetyl)—d-xylopyranosyl-(1->2)-d-glucopyranoside and Torososide B were identified as the top hits[39]. The viral polypeptides are incorporated into the ubiquitin system by 3CLpro, which also interferes with the homeostatic action of functional proteins[40], and was primarily targeted by torososide B. Additionally, PLpro modifies the role of protein phosphatases 1A and 1B as replicase proteins to modify the viral life cycle, which is mostly blocked by torososide B[41].

Similar to how ACE-2 serves as a receptor for spike proteins to enter the host cell, this process is primarily controlled by 1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-O-(6′-O-acetyl)—D-xylopyranosyl-(1->2)—D-glucopyranoside[42]. These findings suggest the likelihood that COVID-19 will be resistant to the antiviral effects of anthraquinone derivatives.

Table 1. Anthraquinones involved in the inhibition of target proteins of coronavirus

Bioactive compounds	Structure	Source(s)	Target Inhibitor	References
Alizarine		*Rheum emodi*	binds to SARS-CoV-2 in the RNA binding domain of the nucleocapsid phosphoprotein active sites	[24]
Aloe-emodin		*Aloe vera, Rheum emodi, Rheum officinale, Rheum palmatum*	inhibits the SARS-CoV 3CLpro	[38]
Anthrarufin		*Rheum emodi*	binds to SARS-CoV-2 in the RNA binding domain of the nucleocapsid phosphoprotein active sites.	[24]
Chrysophanol		*Aloe vera, Rheum emodi, Rheum officinale, Dianella longifolia*	binds to SARS-CoV-2 proteins, including 3CLpro, PLpro and spike protein	[39]
Dantron		*Rheum emodi*	binds to SARS-CoV-2 in the RNA binding domain of the nucleocapsid phosphoprotein active sites	[24]
Emodin		*Aloe vera, Cassia occidentalis, Cassia obtusifolia, Rheum palmatum, Polygonum multiflorum, Rumex chalepensis, Scutellaria baicalensis*	prevents SARS-CoV spike protein interactions with ACE-2	[26]

Hypericin		*Hypericum perforatum*	binds to the membrane envelope of SARS-CoV-2 with a strong affinity	[43]
Physcion		*Rheum officinale, Rheum palmatum*	binds to SARS-CoV-2 proteins	[37]
Rhein		*Rheum officinale, Rheum palmatum*	reduces S protein-ACE-2 interaction	[30]
Torososide B		*Cassia torosa*	inhibits 3CLpro and PLpro	[39]
1,3,6-trihydroxy-2-methyl-9,10-anthraquinone-3-O-(6'-O-acetyl)—D-xylopyranosyl-(1 2)—D-glucopyranoside		*Morinda citrifolia*	prevents SARS-CoV spike protein interactions with spike protein and ACE-2	[39]

Coumarin against human coronavirus

Coumarin

The naturally occurring heterocyclic compounds known as coumarins (2H-1-benzopyran-2-ones) are made up of fused benzene and pyrone rings (Figure 3). They are O-hydroxycinnamic acid lactone derivatives. The term "coumarou", which is the French name for the tonka bean (*Dipteryx odorata*, Fabaceae), from which coumarin was initially isolated in 1820, served as the basis for the name coumarin[44]. A group of naturally occurring or artificially altered chemicals of natural origin known as coumarin derivatives demonstrate a wide range of biological properties, including antibacterial, anticancer, antioxidant, anti-HIV, and antiviral activities[45,46,47,48]. Given that coumarin derivatives and pharmaceuticals share a similar structural makeup, it is reasonable to assume that this class of chemicals may also be active against SARS-CoV-2.

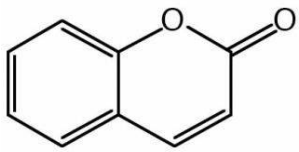


Figure 3. Structure of coumarin

Bioactives of coumarin

More than 1300 coumarins have been identified from a variety of natural sources, including fungi, bacteria, and plants. About 150 distinct plant species from over 30 different families, including Asteraceae, Apiaceae, Caprifoliaceae, Calophyllaceae, Fabaceae, Guttiferae, Moraceae, Nyctaginaceae, Oleaceae, Rutaceae, and Thymelaeaceae, have been documented to contain coumarins[49]. The numerous plants contain coumarin and its derivatives, which are referred to as "natural coumarins". Examples include floroselin, frutinone A, and rutamarin, which were derived from the respective plants *Ruta graveolens*, *Polygal fruticose*, and *Seseli sessiliflorum*[50]. Simple coumarins, furanocoumarins, pyranocoumarins, phenylcoumarins, and diocoumarins are the different types of natural coumarins.

Bioactive compounds of coumarin against human coronaviruses and their antiviral mechanism

The most highly recommended plant-derived drugs that may have considerable inhibitory effects on COVID-19's primary protease were bergapten, heraclenin, heraclenol, imperatorin, oxypeucedanin, psoralen, and saxalin[51]. Numerous studies have looked into how different classes of naturally occurring coumarin phytochemicals affect the activity of viral proteins like protease, integrase, reverse transcriptase, and DNA polymerase, as well as how they affect the blocking of viral entry against a variety of human viruses like the influenza virus, human immunodeficiency virus, herpes simplex virus, and hepatitis B and C[52]. Researchers have demonstrated the *in silico* screening of coumarin derivatives against methyltransferase NSP10/NSP16, protease, ADP-ribose of phosphatase NSP3, and NSP15 endonuclease of SARS-CoV-2[53].

The findings demonstrated the identification of eight compounds from coumarin phytochemicals (licopyranocoumarin, glycycoumarin, inophyllum, oxypeucedanin hydrate, mesuol, and wedelolactone) with a significant inhibitory potential against the SARS coronavirus. All of these drugs docked at the active site and interacted with 3CLpro proteins catalytic dyad (Cys-His) in a manner reminiscent of ritonavir and lopinavir[54].

Bavacoumestan A (C-97) and 6-O-D-Glucopyranosyl-5-hydroxyangelicin (C-88) were two of the substances with the highest docking scores in the main protease active site. Daphnorin (C-49) and glycycoumarin (AV-29), which were tested against methyl transferase, produced the best results. In comparison to other studied compounds, daphnorin has good effects when docked in the active site of RBD-COV-2-S proteins. Finally, the most effective coumarin was inophyllum G2 (AV-35) against human ACE-2[55].

To compare the binding scores of 17 coumarin derivatives with those of the model inhibitors like favipiravir, warfarin, hydroxychloroquine, and remdesivir, molecular docking studies were performed against MPro, Spike with ACE-2, NSP12 with RNA, NSP15, and NSP16. All receptors were found to be sensitive to the coumarin series; however, NSP12 or NSP12/RNA received the highest ratings[56].

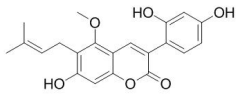
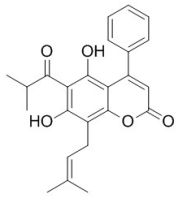
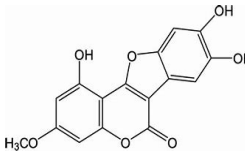
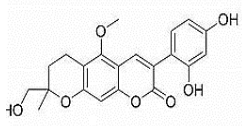
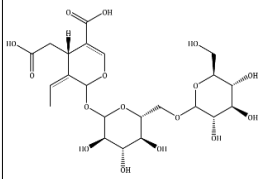
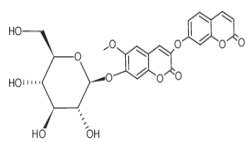
All three of the developed derivatives of hymecromone, psoralen, and phenprocoumon showed strong interactions and high binding affinities with the drug target. The high binding attractions were caused by the compound's -OH groups, His41, a catalytic dyad in Mpro, and the quantity and distance of hydrogen bond interactions with the SARS-CoV-2 targets[57]. Aerial portions of *Artemisia glauca* were used to extract a novel dicoumarin, jusan coumarin. Jusan coumarin and X77, the co-crystallized ligand of Mpro, showed a lot of similarities. Four ligand-based computational, molecular similarity, fingerprinting, Density Functional Theory (DFT,) studies, and pharmacophore studies were used to confirm the similarities. The molecular docking tests of jusan coumarin against Mpro demonstrated that it binds perfectly, with a binding energy of about -18.45 kcal/mol[58].

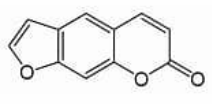
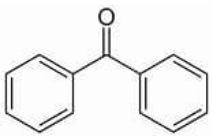
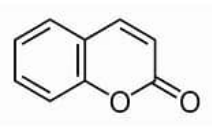
The primary viral protein 3-CLpro, was the target of *in silico* research that demonstrated the antiviral potential of coumarin and benzophenone derivatives with favourable docking scores[59]. In a recent study, Singh and co-workers suggested benzophenone-coumarin derivatives (BCDs) as effective inhibitors of the SARS-CoV-2 virus's major target RdRp, which is important in the replication of the viral genome[60,61].

According to the findings of the molecular docking investigation, the binding affinities of the complexes L1 ((3-(1-((3-chlorophenyl)amino)ethylidene)-chroman-2,4-dione), L2 ((3-(1-((4-chlorophenyl)amino) ethylidene)-chroman-2,4-dione), and L3 ((3-(1-(phenylamino)ethylidene)-chroman-2,4-dione)) and their corresponding palladium complexes were higher than those of chloroquine and cinanserin. All of the compounds were attached to the protein's active site near the His41-Cys145 catalytic dyad[62].

According to the molecular dynamics simulation results, coumarin-triazole-thiophene hybrid4-(((4-ethyl-5-(thiophene-2-yl)-4H-1,2,4-triazol-3-yl)thio) methyl)-6,7-dimethyl-2H-chromen-2-one forms stable complexes with PLpro, Mpro, and NSP3 (range 207-379-AMP and 207-379-MES)[63].

Table 2. Coumarins involved in the inhibition of target proteins of coronavirus

Bioactive compounds	Structure	Source(s)	Target Inhibitors	References
Glycycoumarin		Vegetable roots	interacted catalytically with His41, and inhibited 3CLpro via hydrogen bonding with Cys44 and Asp48	[54]
Mesuol		Stem Bark of *Mesua borneensis* L.	inhibit the SARS-CoV CLPro	[54]
Wedelolactone		*Eclipta alba* (false daisy) and in *Wedelia calendulacea*	inhibit the SARS-CoV CLPro	[54]
Licopyrano coumarin		*Glycyrrhiza uralensis*	inhibit the SARS-CoV CLPro	[54]
6-O-D-Glucopyranosyl-5-hydroxyangelicin (C-88)		*Ficus ruficaulis*	inhibit the SARS-CoV MPro	[55]
Daphnorin (C-49)		-	inhibit the SARS-CoV methyltransferase	[55]

Psoralen		*Psoralea corylifolia* seeds, celery, common fig, parsley, West Indian satinwood, and in all citrus fruits	inhibit the SARS-CoV MPro	[57]
Benzophenone-coumarin derivatives (BCDs)		-	inhibit the SARS-CoV RdRp	[60]
Jusan coumarin		*Artemisia glauca*	inhibit the SARS-CoV MPro	[58]

The current study discusses the possibilities for treating COVID-19 and the role of natural compounds like anthraquinone and coumarin that have shown promise as anti-CoV medicines. To fully understand the underlying cellular and molecular mechanisms, however, extensive *in vivo* investigations on relevant animal models are required because various research regarding the antiviral effects of these drugs is still in the preliminary stages. There aren't many pharmacokinetic studies on these compounds, but they ought to be done to develop a pharmacokinetic profile. Clinical trials are necessary to examine the effectiveness and security of their anti-CoV medications on human beings. More significantly, research should be done to examine any possible interactions between available natural antivirals and anti-CoV effects.

STATEMENT OF ETHICS

This article does not contain any studies with human participants or animals performed by any of the authors.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest relevant to this article.

AUTHOR CONTRIBUTIONS

All authors contribute the work equally throughout.

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