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A Critical Review on the Potency of Phytoconstituents in the Management of COVID-19

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Abstract

Natural products and their derivatives have traditionally been used as a source of therapeutic agents. Their beneficial properties are due to large varieties in their chemical structures and biochemical actions. The discovery of natural products such as phytoconstituents have crucial role in the development of less toxic and more effective drugs. Phytoconstituents have shown to be beneficial in treating viral diseases such as the previous chikungunya virus, hepatitis C virus, SARS, and MERS viral diseases. Flavonoids, alkaloids, terpenoids, and other group of compounds combat against COVID-19 in several ways like by protease inhibition, spike protein inhibition, Nrf2 inhibition. The accumulation of NRF2 inhibits the development of the SARS-CoV-2 virus and stimulates anti-inflammatory action. The present review highlights the therapeutic importance of compounds isolated from medicinal plants and/or herbs, such as crude extracts of Curcumin I-III, Leptodactylone, Ginsenoside-Rb1, Lycorine, Reserpine, Saikosaponin B2, Cepharanthine, Withanoside V, Gingerol, Piperanine, chromans, flavonoids, Amentoflavone etc. against SARS-CoV-2. Natural products are typically safe, stable, and dependable source for finding drugs to control the current pandemic. Antiviral secondary metabolites many medicinal plants have given ingredients that were isolated. The selected plants based phytoconstituents may potentially be used against viruses' development on anti-SARS-CoV-2 to offer a reference point in this field.

Keywords: COVID-19, SARS-CoV-2, Natural Products, Alkaloids, Flavonoids, Target Proteins, Pharmacological Activity

INTRODUCTION

The novel coronavirus (SARS-CoV-2 virus) is the main issue of 2nd decade of 21st century in due to its rapid spread across the globe and attacking features. The disease COVID-19 dispatched by contact with infectious, inhalation and incubation duration vary from 2 to 14 days.[1-3] SARS-CoV-2 virus is like previous SARS-CoV and MERS (not pandemic) virus with genome modification and WHO declared the COVID-19 as a pandemic on 11 March 2020.[4,5] It is noted that viral diseases such as Hepatitis B virus, hepatitis C virus, Zika virus, Ebola virus, malaria, HIV, SARS, and MERS virus have often survived and addressed serious public health challenges in previous days. Although, SARS-CoV-2 virus damages the respiratory system[6] but increased rate is with pediatric and adult with cardiovascular diseases[7] and diabetes.[8] The novel virus represents a global warming and poses a new provocation where vaccine is required for primary treatment and synthetic compound to treat infected patients.[9,10] Vaccine (biological preparation) and immunotherapy which boost the body immune system against pathogens and treat various diseases. It has been the most efficient medical method in immunology to minimize death and morbidity of the previous century.[11] According to the researchers, synthetic antigens are susceptible to evoke anti-protein immune feedback.[12] Macromolecules may contain a massive and variety of antigenic sites but just a specific number of possible antigenic sites are significant.[13] The coronavirus family contain huge number of spike proteins which are used as mediator to entry into the epithelial cell in host whereas, the ACE2 enzyme in the human body is the recognition site for spike protein; authorized for entry by this virus into the circulation system of the human being. On the other hand, RNA virus (coronavirus is an RNA virus) manifest RNA polymerase in epithelial cell of human body and approaches new genome sequences or daughter genome sequence using viral RNA template.[14] The current study shows phytoconstituents are capable to treat viral diseases [15] such as previous chikungunya virus, hepatitis C virus, SARS and MERS viral diseases and showed effective positive result.[16-19] and various guidelines were issued to treat and prevent COVID-19 using herbal medicine in different stages.[20] There are around 4000 phytochemicals where more than 150 phytochemicals are studied in detail. From these phytochemicals flavonoids, alkaloids, terpenoids, and miscellaneous compounds are found in most of the plants/herbs which prevent the microbial, fungal and viral infection.[21-28] Flavonoids have been depicted to plummet various coronavirus diseases by blocking function of protease and helicase enzyme or interacting with spike protein and suppressing the function of ACE2.[29,30] In addition, NRF2 is a transcription factors which conjugate with antioxidant response elements to facilitate factor of transcription in target gene to repair the macromolecular damage and maintain redox homeostasis[31,32] as well as decrease the inflammation[33] which present in the cytoplasm. Accumulation of NRF2 can inhibit the SARS-CoV-2 virus replication and stimulate the anti-inflammatory activity.[34-36] There are available synthetic drugs have been using such as chloroquine, favipiravir, arbidol, remdesivir,[37] interferon-alpha 1b, monoclonal antibodies, novaferon and azithromycin as combine therapy although these are not introduced into the international community by FDA.[38]

The aim of the study is to overview the current strategy and role of phytoconstituents to treat and manage COVID-19 dealing with *in silico*, *in vitro* and *in vivo* experiments.

Effect of phytoconstituents against SARS-CoV-2 (*in silico* approaches)

Phytocompounds have long been thought to be a source of medicinal substances. With a vast range of options in their chemical compositions and biochemical specificity they have proven to be beneficial properties. The development of natural product drugs is crucial in the pharmaceutical development of less toxic and more effective drugs and having potential. These natural resources have scientific evidence (Table 1).[39,40]

In principle, COVID-19, pedunculagin, tercatain, and punicalin were used to avoid outbreaks. The structural relationship functioning of the plant of hydrolysable tannins as potential antiviral agents & top 3 hit records inhibit COVID-19's initial protease and hence viral replication.[41] Polyphenols, including two anti-HIV medicines (darunavir and lopinavir) which are

exposed to subatomic drugs, (brousochalcone A (C2), papyriflavonol A (C4), 30-(3-methylbut-2-enyl)-30, 40,7-trihydroxyflavane (C5), kazineol A (C6), broussoflavane A (C8), kazinol F (C9) and kazineol J (C10). AutoDock Vina's energy estimates for both these polyphenols were higher than darunavir. Six of them were related to large accumulations of Mpro-reactants (C2, C4, C5, C8, C9 and C10) (His41 The RMSD and RMSF profiles clearly indicate that the buildings of these six Mpro polyphenols are highly stable and conformable. Research from SASA found that all Mpro-polyphenol buildings are slightly smaller and probably larger. The existence of intermolecular hydrogen connections with B in households. The polyphenols of papyrifera (C2, C4, C5, C8, C9 and C10) indicate the security of these polyphenols in the pocket connections of Mpro more strikingly than in the complex of Mpro-darunavir/lopinavir. Both the structures of Mpro-polyphenol were much more stable than the complexes of Mpro-darunavir and Mprolopinavir. The more potent inhibitors of Mpro than previously indicated were T-brousochalcone A 30-(3-methylbut-2, enyl) -30, 40, 7-treihydroxyflavane, and kazinol J. (darunavir and lopinavir).[42]

In addition, following reputable protein structures, three-dimensional compliance was balanced by the phytocompounds amentoflavone unambiguously connected to the objective proteins. *In silico* drug likeness and ADMET profiling of the combinations also indicated potential therapeutic activity. In SARS-CoV-2 3CL M-master, compared to COVID-19 remdesivir, oleanolic corrosive has a higher limiting potential. They should be used in conjunction with the official ACE2 to CASP-3 flagging pathway, which needs further research and is meant to offer logical direction, to have an impact on apoptosis. COVID-19 is treated via a variety of organic cycles and routes have been the fundamental goal proteins CASP-3, CASP-9, and XIAP that aid in the management of COVID-19 have been combined into the synthetic blends.[43]

The different *Cryptolepis sanguinolenta* alkaloids have shown highly restrictive partiality and thus anticipated inhibitory action against two of the major SARS-CoV-2 prions, the primary protease, and the RNA dependent polymerase. The different *Cryptolepis sanguinolenta* alkaloids have shown extremely restrictive partiality and thus anticipated inhibitory action against two of the major SARS-CoV-2 prisons, the primary protease, and the polymerase-dependent RNA.[44] Eucalyptol has high tilt limits and minimum power constraints. Therefore, it has been recommended that Eucalyptol may be linked to possible treatment options and may be present in therapeutic plants, as predicted by COVID-19 Mpro inhibitors.[45]

It was predicted that the operation of SARS-CoV-2 (Mpro) was Restorative plants, likely acting as a constraint, and SARS-CoV-2, with high affinity (Mpro), the deterring additional understanding of the viral protein that helps to harm the vital host organs. Certain phytochemicals against COVID-19 may be repurposed. An innocuous ADMET profile has the most effective docked mixtures having drug-like characteristics that can be used to develop more sophisticated, efficient COVID-19 inhibitors. The directions investigating the contemplated buildings showed clear protection during MD runs.[46]

Glycyrrhizin, tryptanthrin, bicylogermecrene, beta-sitosterol, indirubin, indican, indigo, hesperetin, crysophanic corrosives, rhein, berberin and beta-caryophyllene, which can be considered to be a possible natural competitor hostile to SARS-CoV-2 viral activity. Promising mooring outcomes were carried out that validated the useful essence of these preferred alternatives to combat COVID-19 disease for potential medicine advancement.[47]

Ginger phytoconstituents such as 10 Gingerol, 8-Gingerol and Piperanine, Piperdardiine is substantially dynamic against COVID-19 with a significant Glide score compared to the second-hand medication Hydroxychloroquine at present (-5.47). Docking results in a similar mode of interaction between its compounds to COVID-19. HIE41, GLN189, SER46, ARG189, MET165, ASP187, THR24, LEU27, THR25, GLY143 and ASN142 Critical function residues attach to ligands. Pepper phytoconstituents such as Piperazine, Piperdardiine and Ginger, such as 10-Gingerol, 8-Gingerol, are significantly opposed to COVID-19.[48]

The phytoconstituents of turmeric like Cyclocurcumin, Curcumin and similar to andrographolide from *Andrographis paniculata*, When compared to currently approved COVID-19

medications such hydroxychloroquine (-5.47) nelfinavir, dihydroxy dimethoxy flavone are substantially bound to the active site of the primary SARS-CoV-2 protease (-5.93). Cyclocurcumin from turmeric is significantly more active when compared to common Remdesivir (-6.38). According to the docking results, the drugs interacted with SARS in a similar manner. SARS is brought on by the CoV-2 virus. Important ligand binding residues include THR24, THR25, THR26, LEU27, SER46, MET49, HIE41, GLN189, ARG188, ASP187, MET165, HIE164, PHE181, and THR54.[48]

From an *in silico* study, Glu288, Asp289, Glu290, Lys5 are found as the key sites. In addition, Ala285 and Leu286 are found as regulatory sites of interaction. C23 indole-chalcone interacted at Glu288, Asp289 residues with the docking score -10.4 kcal/mol. Quercetin has been found to block the interaction sites of viral spike as well as the main protease's Glu290 with -9.2 kcal/mol docking score.[49] Glycosylated flavonoids: quercetin 3-rhamnoside (-9.7 kcal/mol), myricetin 3-rutinoside (-9.3 kcal/mol) and rutin (-9.2kcal/mol) exhibit higher docking score than the other flavonoids *in silico*. Compounds result from the substitution at C-3 position of flavonoids with sugar moieties especially have more affinities with main protease active site.[50] Kaempferol acts as an inhibitor of 3CLpro and PLpro.[51] Based on a study ,[52] other flavonoids including luteolin-7-O-glucoside, naringenin, desmethoxycurcumin, curcumin, apigenin-7-O-glucoside, oleuropein, catechin and epicatechin-gallate could potentially inhibit SARS-CoV-2 3CLpro. Taifolin, the other flavonoid has strong inhibitory potentials against SARS-CoV-2 according to a molecular docking study.[53] While antiproteases' key purpose is to inhibit or deactivate proteases, newer research is revealing that they also play a role in regulating excessive inflammation and microbial infection.[54] Finding multifunctional plant protease inhibitors may thus provide multistep defense against coronavirus infection. Among all the tropane alkaloids from Schizanthus porrigens schizanthine Z, schizanthine Y expressed binding affinity values -7.5 kcal/mol & 7.1 kcal/mol, respectively. Molecular dynamic simulation, ADME analysis study confirmed that schizanthine Z could be the best drug candidate that blocks papain like protease.[55]

Phytoconstituents against COVID-19 (*in vitro* and *in vivo*)

Natural phytoconstituents have been shown to be beneficial in treating viral diseases such as the previous chikungunya virus, hepatitis C virus, SARS, and MERS viral diseases. Among them, flavonoids and alkaloids have been investigated *in vitro* and *in vivo* to combat COVID-19 in many ways like protease inhibition, spike protein inhibition, Nrf2 inhibition. Role of phytoconstituents in the treatment of COVID-19 are given in Table 2.

Alkaloids

The Nrf2 signaling system regulates anti-inflammatory gene expression and prevents inflammation from progressing.[63] Upregulation of Nrf2 signaling, in particular, prevents the overproduction of IL-6, pro-inflammatory cytokines, and chemokines while also limiting NFB activation. Endothelial dysfunction results from a failure to guard against oxidative stress-induced neuronal disruption in cardiovascular disorders and other metabolic syndrome-related pathologies. In cellular redox homeostasis, many antioxidant pathways are involved, with the Nrf2 signaling pathway being one of the most important.[64] Against oxidative pulmonary disease, pathological inflammatory and immune reactions, and apoptosis, Nrf2 activates cellular rescue pathways (Figure). The Nrf2 pathway has been shown to defend against acute lung damage and acute respiratory distress syndrome.[65] Basically, COVID-19 patients with critical situations present the signs of oxidative stress & systemic inflammation, the main cause of lethality.[66,67] Nrf2 controls the antioxidant response participating genes, redox homeostasis genes expressions. It also activates these genes leading to the protection of cells from inflammation [63]. In an *in vivo* test depicted that Nrf2 knockout mice suffered from uncontrolled inflammatory reaction contribute to tissue damage.[68] Nrf2 activation also causes the suppression of inflammation through its transcriptional repressor activity- in macrophages it inhibits the expressions of cytokine (IL-1ג, IL-6, TNFⅼ) production, the most pertinent cause of critical illness due to COVID-19.[69] The protective role of Nrf2 was shown in numerous animal inflammatory models that Nrf2 inducers

decreased the pro-inflammatory cytokines in the bloodstream.[70-72] Often, obesity is a significant factor in COVID-19 severity.[73] Obesity, diet, and COVID-19 can interact, and this could be attributed to Nrf2.[74]

Alkaloids are one of the most diverse groups of natural goods, with members of the Ranunculaceae, Solanaceae, Papaveraceae, Rubiaceae, Fabaceae, and Amaryllidaceae families being the most abundant. The inclusion of the nitrogen atom in their arrangement is the group's most distinguishing characteristic.[75] These are natural compounds with diversified actions against various diseases including COVID-19. Homoharringtonine and emetine with notable anti-herpes activity were reported inhibiting replication of SARS-CoV-2.[76] Sinomenine is an isoquinoline alkaloid isolated from *Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson's stem and rhizome (Menispermaceae). It decreases lung damage caused by lipopolysaccharides (LPS) and E. coli by regulating the inflammatory signaling cascade, which included downregulation of IL-1, IL-6, NF-B, TNF-α, iNOS, and COX-2, as well as upregulation of the anti-inflammatory adenosine A2A receptor. Sinomenine also blocked oxidative stress indicators, such as superoxide dismutase (SOD) production and malondialdehyde (MDA) production.[77,78] Furthermore, 1 hour after causing lung damage in mice with LPS (8 mg/kg), sinomenine [100 mg/kg, i.p.] upregulated the expression of Nrf2 and autophagy-related molecules (Atg5, LC-3II, and Beclin1), as essential mediators in increasing cell tolerance to inflammation and oxidative stress. Furthermore, sinomenine reduced the pulmonary edema, protein leakage, and lung wet/dry (W/D) ratio into bronchoalveolar lavage fluid (BALF), both of which are pathological indicators of lung damage.[79] In addition, total alkaloid extraction and six isosteroid alkaloids (verticinone, imperialine, imperialine-3—D-glucoside, verticine, peimisine, and delavine) isolated from bulbs of Fritillaria cirrhosa D.Don (Liliaceae) showed protective effects on lung injury induced by LPS and cigarette smoke, increased the expression of Nrf2 and heme oxygenase (HO-1), and reduced.[80,81] Thalimonine and sophaline D showed to be potential drug candidate targeting Mpro of SARS-CoV-2 after performing molecular dynamic simulation and other *in silico* approaches.[82] Toll-like receptor

4 (TLR4) is an inflammatory signalling system whose expression is elevated in patients with acute lung injury.[83] Sophocarpine (50 and 25 mg/kg, i.p.), a quinolizidine alkaloid isolated from the seeds of *Sophora alopecuroides* L. (Fabaceae), inhibited TLR4 expression and thus decreased LPS-induced lung damage in mice.[84] *In vitro* (mouse bone marrow-derived macrophages, 10 M) and *in vivo* (20 mg/kg, i.p.) and studies found that tabersonine, a monoterpenoid indole alkaloid extracted from the root of *Catharanthus roseus* (L.) G.Don (Apocynaceae), protected against lung damage caused by LPS. Tabersonine inhibited the activities of p38MAPK-activated protein kinase 2 (MAPK/MK2) and NF-κB by decreasing the expression of TNF receptor-associated factor 6 (TRAF6). The improvement of the above signaling pathways/mediators results in the suppression of proinflammatory mediators and a decrease of pathological indices of lung damage, such as total protein concentrations in BALF.[85] Berberine, an isoquinoline alkaloid extracted from *Berberis vulgaris* L. (Berberidaceae) and *Coptis chinensis* Franch. (Ranunculaceae), has been shown to shield C57BL/6 mice from LPS-induced lung damage at 10 mg/kg (i.p., 24 and 2 h before injection of LPS, 2.5 mg/kg), as well as *in vitro* on the hu Berberine was also beneficial to mice suffering from pulmonary edema and protein deficiency in their BALF.[86] Matrine (tetracycloquinolizindine),[87] antidesmone (tetrahydroquinoline),[88] epharanthine (bisbenzylisoquinoline),[89] epigoitrin (pyrrolidine),[90] isotetrandrine (bisbenzyltetrahydroisoquinoline),[91] neferine (bisbenzylisoquinline),[92] and oxysophoridine (quinolizidine)[93] are other alkaloids that have been found to have anti-lung damage impact in *in vitro* and *in vivo* studies. As a result, they regulated pro-inflammatory mediators and oxidative markers which show the chemical compositions of certain alkaloids and other phytochemicals that have defensive properties against lung damage, as well as a graphical diagram of their potential modes of operation. In general, alkaloids, especially quinolines and quinazolines, have shown therapeutic effects on lung injury by inhibiting the MAPK pathway and its interconnected mediators, such as TLR4, as well as inflammatory cytokines including IL-1, TNF-α, and IL-6. These compounds have also been shown to improve antioxidative stress indicators such as

Table 1. Phytoconstituents against the SARS-CoV-2 (*in silico* approaches)

Plant Name	Compounds	Structures	Virus acting	Reported Mechanisms	Ref.
Boenningh-ausenia sessilicarpa	Leptodactylone		SARS-CoV	potent antiviral action and protection against virus-infected cells	56
Panax ginseng	Ginsenoside-Rb1		SARS-CoV	Inhibits glycoprotein activity	43
Lycoris radiate	Lycorine		SARS-CoV	---	57
Aesculus hippocastanum	Aescin		SARS-CoV	-----	57
Rauwolfia serpentina	Reserpine		SARS-CoV	---	58
Stephaniae Radix Tetrandrae	Tetrandrine		HCoV-OC43	Inhibits p38 MAPK pathway, suppress HCoV-OC replication,	58
Bupleuri Radix,	Saikosaponin B2		HCoV	Invasion of cells by viruses and interference with the first stage of viral replication	59
Salviae Miltiorrhizae Radix	Dihydrotanshinone		MERS- CoV	viral passage inhibitory effects in MERS-CoV	58
Stephania japonica	Cepharanthine		SARS-CoV-2	ACE inhibitor	60
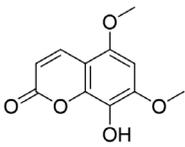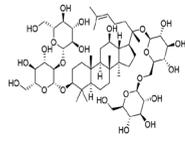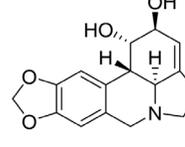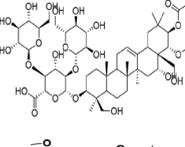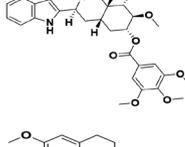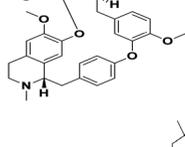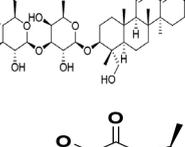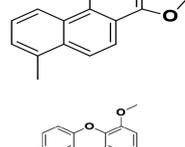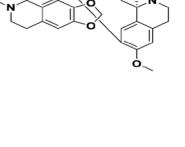
Camellia sinensis	Epigallocatechin (EGC)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Gallocatechin (GC)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Catechin (C)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Epicatechin (EC)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Catechin gallate (CG)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Epigallocatechin gallate (EGCG)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Epicatechin gallate		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Camellia sinensis	Gallocatechin-3-gallate (GCG)		HCoV, SARS, MERS	viral passage inhibitory effects in MERS-CoV	41
Clerodendrum spp	Taraxerol		HCoV, SARS, MERS	spike (S) glycoprotein	61
Curcuma longa	Curcumin I-III		SARS-CoV-2	spike protein	48

Cupressus sempervirens L	Amentoflavone		SARS-CoV-2	ACE2 to CASP-3 flagging pathway	43
Cryptolepis sanguinolenta	Cryptospirolepine		SARS-CoV-2	the primary protease and the RNA dependent polymerase	44
Cryptolepis sanguinolenta	Cryptoquindoline		SARS-CoV-2	the primary protease and the RNA dependent polymerase	44
Cryptolepis sanguinolenta	Biscryptolepine		SARS-CoV-2	the primary protease and the RNA dependent polymerase	44
Withania somnifera	Withanoside V		SARS-CoV-2	Mpro	46
Withania somnifera	Somniferine		SARS-CoV-2	Mpro	46
Zingiber officinale	(10) Gingerol		SARS CoV-2	Mpro	62
Piper nigrum	Piperanine		SARS CoV-2	Mpro	62
Piper nigrum	Piperadine		SARS CoV-2	Mpro	62
Curcuma longa	Cyclocurcumin		SARS CoV-2	Mpro	48
Curcuma longa	Curcumin		SARS CoV-2	Mpro	48
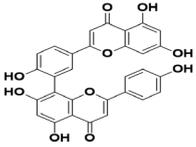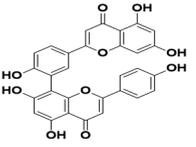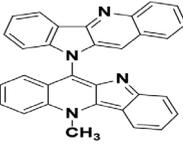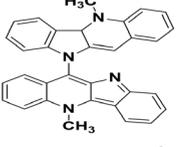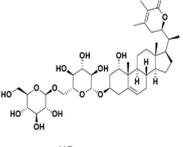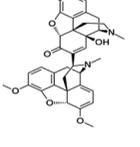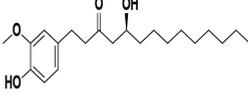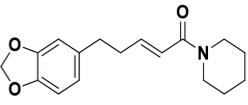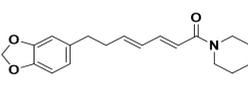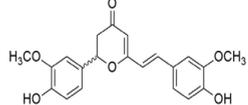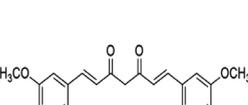
Androgrphis paniculata	Andrographolide		SARS CoV-2	Mpro	48
Androgrphis paniculata	Dihydroxy-dimethoxy flavone		SARS CoV-2	Mpro	48
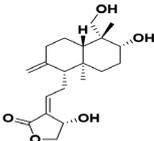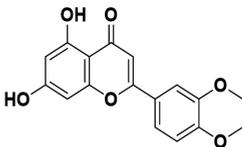
the glutathione, Nrf2/HO-1 pathway, and SOD. As a result of this impressive function in lung injury, as well as the alkaloids' other beneficial functions, especially their antiviral effects, these compounds are now being considered as multitarget agents for the treatment of coronavirus infection and its complications. Lycorine, tylophorine, ouabain, hypericin, myricetin, emodin, mycophenolate mofetil, silvestrol, scutellarein etc. demonstrated strong inhibitory effects against SARS-CoV-2 and other human coronaviruses.[94] Indigotica is sometimes used to cure a variety of infectious diseases in the laboratory. Immunomodulatory and antiviral effects were observed in isolated compounds from *I. indigotica* (indican, isatin, indirubin, and indigotin). Chang et al. found that indigo and indirubin, two alkaloids found in *I. indigotica* extracts, prevented Japanese encephalitis virus replication *in vitro*.[95] Various clinical trials of using colchicine have been announced are: (i) GRECCO-199 (ClinicalTrials.gov Identifier: NCT04326790) will recruit 180 COVID-19 diagnosed patients with the administration of colchicine for 21 days, (ii) Effects of colchicine in COVID-19 Pneumonia (ClinicalTrials.gov Identifier: NCT04322565) where n = 100, (iii) COLCORONA (ClinicalTrials.gov Identifier: NCT04322682) aims to recruit 6000 high-risk outpatients, (iv) Colchicine co-administration (or not) with lopinavir/ritonavir, 'The ECLA PHRI COLCOVID' Trial (ClinicalTrials. gov Identifier: NCT04328480) will recruit 2500 COVID-19 hospitalized patients.[96]

Flavonoids

Flavonoids are the common compounds in medicinal plants which containing various anti-viral and anti-bacterial activity[132] in pattern of particular chemical structure including hydroxylation, methoxylation and glycosylation.[133,134] The flavonoids, a promising group of compounds, have potentials to treat COVID-19. Chalcones, flavonols, flavones, and isoflavones are examples of this essential family of natural compounds.[135] Flavonoids have a flavan heart and a 15-carbon skeleton. A heterocyclic pyran ring (B ring) connects the two benzene rings (A and C rings). In hydroxylation, attachment of more hydroxyl group in particular ring of flavonoids decreases the activity such as luteolin has less inhibitory activity compared to apigenin due to presence of more −OH group in B ring whereas dinatin revealed unchanged activity like apigenin. Quercetin and myricetin depicted lower reduction effect comparison to kaempferol due to more −OH group in B ring. These results indicated that, more hydroxyl group in B ring decrease the activity of flavonoids (Figure).[136] In the case of methoxylation, addition of methoxy group in flavonoids ring plummated the antiviral activity such as 5,6,7,4'-tetramethoxyflavone and tangeritin exhibited minimum antibiotic activity compared to kaempferol and luteolin but tangeritin showed better antiviral activity than 5,6,7,4'-tetramethoxyflavone because of methoxy group in C-8 position. Although, attachment of methoxy group in flavonoids ring decrease the

antiviral activity but in C-8 position.[137] As for glycosylation, puerarin revealed greater antiviral activity compared to quercetin and ampelopsin.[138] It is estimated that flavonoids group shows grater antiviral effects in contrast to isoflavonoids. The resorcinol molecule, which has two hydroxyl groups in its aromatic ring configuration, and they are positioned at meta-positions with respect to another hydroxyl group, is the most important functional group of flavonoids that could be responsible for ACE2 inhibition. The benzene ring's behavior is largely determined by the position of
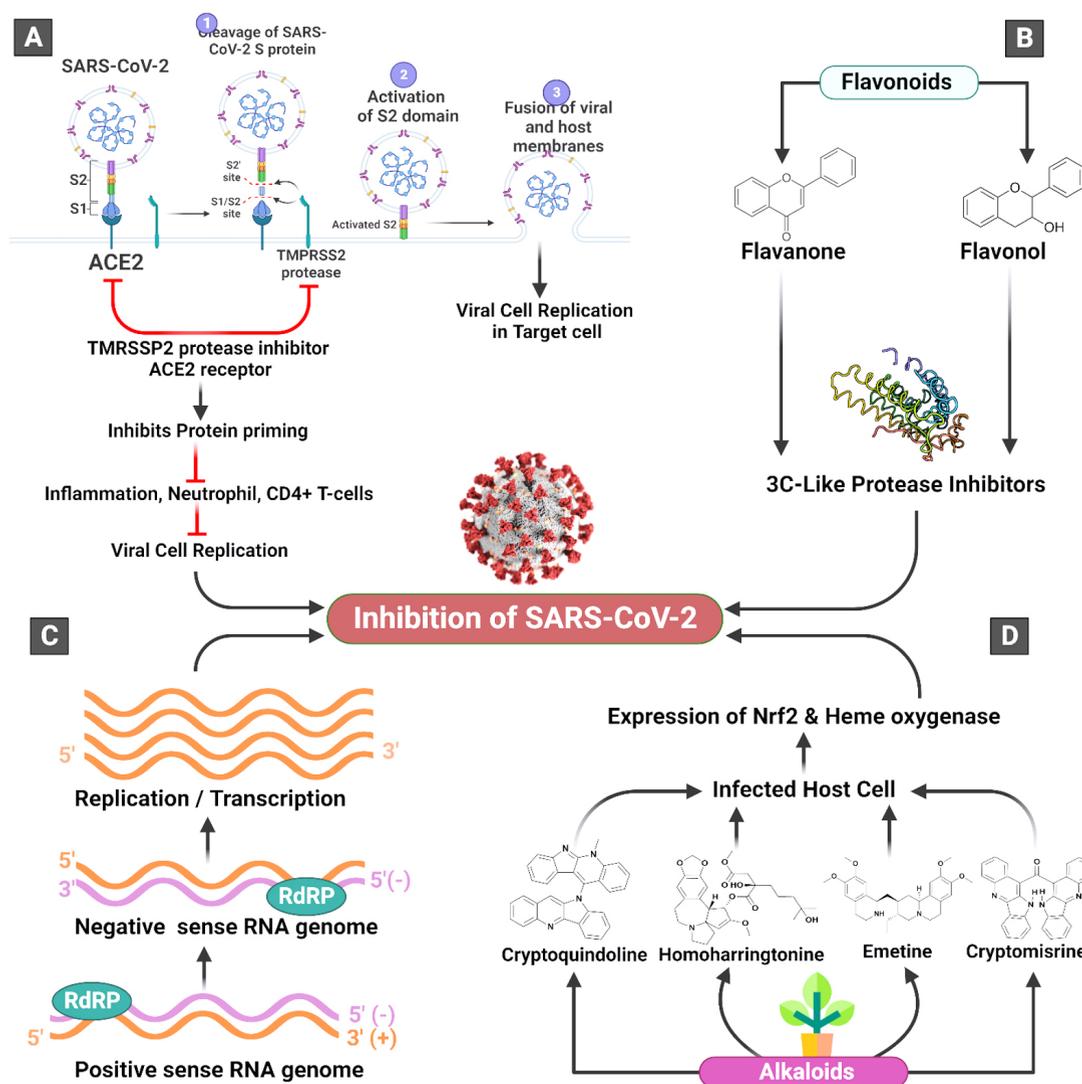

Figure. Exploring the potential role of alkaloids and flavonoids against SARS-CoV-2. A. The coronavirus replication loop and main steps for antiviral goals are depicted in this diagram. Antivirals that function extracellularly or intracellularly are shown by white text boxes. Membrane fusion, receptor binding, sub-genomic RNA transcription, viral RNA replication, and translation are all examples of phases in the coronavirus replication cycle. B. Flavonoids activate 3CL-like protease inhibitors which eventually inhibit SARS Cov-2. C. Flowchart of RNA synthesis by RNA-dependent RNA polymerase (RdRP) of positive-sense and negative-sense ssRNA viruses which inhibit SARS Cov-2. D. Natural alkaloids enter in the infected host cell and express Nrf2 and heme oxygenase which combat against SARS Cov-2 and inhibit it

these two hydroxyl groups.[139] Ring A's resorcinol moiety may be involved in ACE2 inhibition.[140]

In vitro studies have shown that flavonoids extracted from Angelica keiskei have a potent inhibitory effect on both 3CLpro and PLpro. Alkylated chalcones were able to inhibit PLpro in a manner that was not competitive. The compounds xanthoangelol E (IC50: 1.2 µM) and xanthoangelol F (IC50: 5.6 µM) proved to be the most effective in this regard. In accordance with the findings of the SAR analysis, the perhydroxyl component of a chalcone is an alkylated chalcone that has a more potent inhibitory action.[141] There are a variety of plants that contain the stilbenoid known as resveratrol, including *Vaccinium macrocarpon, Vitis vinifera,* and *Polygonum cuspidatum*. Resveratrol's pharmacological and therapeutic effects include, but are not limited to, hepatoprotective, cardioprotective, and neuroprotective abilities as well as anti-inflammatory and antibacterial activities. Resveratrol has been shown to greatly suppress the growth of MERS-CoV in vitro, as well as diminish MERS-CoV infection. As a direct result of this, resveratrol is an essential anti-MERS medicine and has the potential to be an effective SARS-CoV-2 antiviral.[142,143] The SAR analysis conducted on quercetin-3-galactoside and its analogues has revealed several key findings. Firstly, the presence of 4 OH groups on the quercetin moiety is crucial for eliciting biological activity. Secondly, removal of the 7-OH group results in a decrease in inhibitory effect on 3CLpro. Thirdly, the sugar moiety plays a significant role in the compound's activity. Lastly, alterations to the sugar moiety do not appear to have any impact on the efficacy of the inhibitor.[144] *Nigella sativa* is a source of myricetin and scutellarein, which have been the subject of numerous investigations. Myricetin and scutellarein exhibit inhibitory effects on SARS-CoV 3CLpro at concentrations ranging from 0.01 to 10 µM. Broussochalcone B, broussochalcone A, 4-hydroxyisolonchocarpin, papyriflavonol A, 4,7-trihydroxyflavane, kazinol A, kazinol B, broussoflavan A, kazinol F, and kazinol J are bioactive compounds derived from Broussonetia papyrifera. These compounds have been found to exhibit inhibitory effects against SARS-CoV, as reported in literature sources.[145,146]

A total of twelve geranylated flavonoids were discovered from *Paulownia tomentosa* (Thunb.) Steud., a traditional Chinese medicinal (TCM) plant. Among these compounds, five were newly identified as tomentin A-E (8) (2.39-2.43). These flavonoids were found to exhibit mixed-type inhibition against SARS Papain-Like Protease (PLpro), with IC50 values ranging from 5.0 to 14.4 µM. The study found that among the group of inhibitors tested, Tomentin A, B, and E exhibited the highest level of effectiveness in inhibiting PLpro, with IC50 values of 6.2, 6.1, and 5.0 µM, respectively. It was observed that each of the newly synthesised compounds containing dihydro-2H-pyran moiety exhibited superior inhibitory activity compared to their respective precursor compounds.[147] The seeds of *Cullen corylifolium* (L.) Medik. have been found to contain six flavonoids, namely bavachinin, neobavaisoflavone, isobavachalcone, 40-O-methylbavachalcone, psoralidin, and corylifol A. These flavonoids have been observed to exhibit mixed-type inhibition against SARS-CoV PLpro, with IC50 values ranging from 4.2 to 38.4 µM.[148] Amentoflavone, a bioflavonoid obtained from *Torreya nucifera*, has demonstrated noncompetitive inhibition of 3CLpro with IC50 values in the low micromolar range. Amentoflavone (2.6) was identified as the most potent inhibitor (IC50 = 8.3 µM), surpassing the parent compound apigenin (IC50 = 280.8 µM) in terms of inhibitory activity. Luteolin (2.23) and quercetin (2.29), which are flavones containing apigenin, were found to inhibit 3CLpro to a greater extent than the parent compound. The presence of the apigenin moiety at position C-30 of flavones was determined to be essential for their effectiveness. The IC50 values for luteolin and quercetin were 20.2 µM and 23.8 µM, respectively. The primary flavonoid present in honeysuckle, namely luteolin, has been identified as a constituent of *Lianhua qingwen*, a traditional Chinese medicine utilized for the treatment of COVID-19.[149]

The compound Quercetin has demonstrated noteworthy inhibition activity against SARS-CoV Mpro, which was expressed in Pichia pastoris, with an IC_{50} value of 73µM[150] The administration of Quercetin in conjunction with vitamin C has demonstrated anti-SARS-CoV-2 and immunomodulatory properties. The combined use of both agents exhibits a synergistic effect and may be utilized for prophylactic purposes in populations

Table 2. *In vitro* and *in vivo* evidence regarding the use of phytochemicals (alkaloids and flavonoids) in SARS-CoV-2

Phytochemicals	Class	Dose/conc.	Activity	Ref.
Baicalin	flavonoid	0.04 to 400 µM	↓ X4 and R5 HIV-1 Env-mediated fusion, CAT activity	97
Baicalin	flavonoid	20 µg/mL	↑ survival rate, IFN-α and IFN-β	98
Baicalin	flavonoid	20 µM	↓ viral replication	99
Baicalin	flavonoid	20–80 µg/mL	↓ virus replication, ↑ cell viability in MDCK cells	100
Baicalin	flavonoid	0.5–320 µM	↓ NP transcription, RIG-1, PKR, NS1 expression, viral replication	101
Baicalin	flavonoid	12.5–50 µg/mL	↑ mTOR phosphorylation, ↓autophagy	102
Baicalein	flavonoid	40–100 µM	↓ viral replication, IL6, CXCL10, and TNF-α	103
Baicalein	flavonoid	200 mg/kg	↑ respiratory function	104
Taxifolin	flavonoid	IC_{50} = 145.7 µM	Antimicrobial activities	105
Camellianin A	flavonoid	500 µg/mL	30.2% suppression at EC	106,107
Camellianin B	flavonoid	500 µg/mL	40.7% suppression at EC	106,107
Apigenin	flavonoid	500 µg/mL	30.3% suppression at EC	106,107
EGCG	flavonoid	50 µM	2-fold increase at EC by elevating intracellular Zn2+ level	108
Catechin	flavonoid	50 µM	2-fold increase at EC by elevating intracellular Zn2+ level	108
Purified flavonoids	flavonoid	3–30 µg/mL	↓ IL-6 and MCP-1, ↓ NA activity	109
Purified flavones	flavonoid		↓ HIV-1 protease	110
Purified flavonol glycosides	flavonoid	IC_{50} = 20–43 µM	↓ HIV-1 RDDP activity	111
EGCG	flavonoid	1–100 µM	↓ RT activity, protease activity,p24, viral entry, and viral production	112
EGCG	flavonoid	25–100 µM	↓ CD4 expression	113
EGCG	flavonoid	6–100 µM	↓ HIV-1 p24 antigen, ↓ HIV-1 infectivity	114
EGCG	flavonoid	1–50 µM	↓ virus replication	115
EGCG	flavonoid	0.2–20 µM	↓ HIV-1 gp 120 binding to the CD4+ T cells	116
Tetrandrine	Alkaloid	10 µM	Increased endolysosomal pH concentration dependently	117
Dauricine	Alkaloid	10 µM	Increased endolysosomal pH, impaired V-type ATPase activity	118
Daurisoline	Alkaloid	10 µM	Increased endolysosomal pH, impaired V-type ATPase activity	119
Tylophorine	Alkaloid	20 nM	3CLpro inhibitor, block the S and N proteins	120
Quinine	Alkaloid	10.7 µM	Mpro and S proteins inhibitor	121
Neferine	Alkaloid	10 µM	Decreased the levels of viral RNA	122
Lycorine	Alkaloid	0.47 µM	Mpro inhibitor	123
Hernandezine	Alkaloid	10 µM	Blocking the calcium transition	122
Fangchinoline	Alkaloid	1.01 µM	Blocked the expression of S and N proteins	58
Conessine	Alkaloid	10.75 µM	Mpro inhibitor	124
Tetrandrine	Alkaloid	2.05 µM	Mpro inhibitor, block the expression of S and N proteins	58
Oxysophoridine	Alkaloid	0.31 µM	Nucleotide biosynthesis inhibitor	125
Homohar-ringtonine	Alkaloid	0.46 µM	Blocked S proteins	126
Harmine	Alkaloid	13.46 µM	Mpro inhibitor	124
Emetine	Alkaloid	2.55 µM	Mpro inhibitor	127

Table 2. Cont...

Phytochemicals	Class	Dose/conc.	Activity	Ref.
Leelamine	Terpenoids	3 µM	Decreased cellular endocytosis	128
Pulsatilla saponin D	Terpenoids	1.25 µM	Downregulated cathepsins	129
Myrtenal	Terpenoids	100 µM	Suppressed the action of V-type ATPase	130
Saikosaponins	Terpenoids	0.25–25 µmol/L	Inhibitory effect on viral attachment and penetration	59
Ferruginol, betulonic acid	Terpenoids	0–80 µM	Reduced SARS-CoV replication substantially	131

at high risk.[151] Herbacetin, pectolinarin, and rhoifolin, flavonoids have been found to effectively inhibit the enzymatic function of SARS-CoV Mpro.[152] The methanolic extract of *Paulownia tomentosa* fruits was found to exhibit anti-papain protease activity through fractionation. This activity was attributed to various geranylated flavonoid derivatives, which were identified as potent inhibitors of the SARS-CoV papain protease.[153]

The evidence mentioned above suggests that certain flavonoids exhibit potential inhibitory activity against SARS-CoV-2 by potentially targeting crucial proteins involved in the virus's life cycle. Yet only a small number of flavonoids have undergone in vitro testing. Thus, it is necessary to verify the computational investigation by conducting a suitable biological assay.[154]

Terpenoids

The primary pharmacologically active triterpenoids, commonly in the form of glucosides, are saikosaponins. These are typically derived from traditional Chinese medicine (TCM) sources such as *Bupleurum spp., Heteromorpha spp.,* and *Scrophularia scorodonia*, and possess antiviral and immunomodulatory properties.[155] The antiviral activity of four saikosaponins (saikosaponin A, B2, C, and D) against human coronavirus-229E (CoV-229E) (alphacoronavirus) was investigated. The EC50 values of these saikosaponins were found to be 8.6, 1.7, 19.9, and 13.2 µM, respectively, at concentrations ranging from 5-25 M/L. Additionally, saikosaponin B2 was observed to inhibit viral adherence and penetration stages.[59] In 2012, an *in vitro* study was conducted to evaluate the anti-Human Coronavirus efficacy of

Triterpenoids and 3-friedelanol extracted from the leaves of *Euphorbia neriifolia*. The screening of a triterpenoid in combination with 3-Friedelanol revealed a heightened potential for antimicrobial activity and increased cellular viability following incubation with HCoV. Additionally, 3β-fridelanol exhibited potent inhibitory activity against 3CLpro.[156] The active constituents of Glycyrrhiza glabra, namely glycyrrhizin, exhibit antiviral properties against a range of viruses such as hepatitis A, B, and C, varicella-zoster, HIV, and herpes simplex type-1.[157] *Salvia miltiorrhiza* synthesizes tanshinones that possess an abietane diterpene framework. Tanshinones exhibit diverse biological activities such as anti-inflammatory, cardiovascular, and anti-neoplastic effects. The aforementioned compounds exhibit selective inhibition towards the SARS-CoV 3CLpro and PLpro enzymes, with their efficacy being predominantly influenced by the subtype of the enzyme. Several tanshinones have been found to exhibit greater potency in inhibiting PLpro, with IC50 values ranging from 0.8 to 30.0 µM.[158]

Miscellaneous

Marine microalgae belonging to the phyla Rhodophyta and Phaeophyta were discovered to contain phycocyanin, polysaccharides, lutein, vitamins, and other phenolics, which exhibit significant pharmacological effects such as antibacterial, anticancer, and anti-inflammatory properties.[118] The study conducted by Hirata et al. examined the antiviral and antioxidative characteristics of phycocyanobilins, which are a class of tetrapyrrole chromophores present in select marine cyanobacteria.[159] The potential application of Griffithsin, a lectin derived from

red algae, has been studied and its antiviral properties against HIV-1 and hepatitis C have been demonstrated through testing.[160,161] According to a recent in vitro investigation conducted by Millet et al., griffithsin exhibited inhibitory effects against MERS-CoV.[162] Axinella cf. corrugate, a marine sponge, has been found to contain esculetin ethyl ester, which has exhibited a significant affinity towards the SARS-CoV-2 protease. This compound has the potential to serve as a viable therapeutic agent for the treatment of COVID-19.[163] Carrageenans, a class of sulfated polysaccharides derived from marine sources, have been identified as potential antiviral agents. The mechanism of action involves the inhibition of viral attachment and internalization. Nagle and colleagues postulated that these compounds possess the potential to serve as coating agents on sanitary products for the purpose of impeding COVID-19 infection. The utilization of *in silico* analyses has recently played a significant role in identifying promising lead compounds for the development of treatments against the COVID-19 pandemic.[164]

CONCLUSION AND FUTURE PERSPECTIVES

Several herbal extracts and natural products can be useful in treating the symptoms of SARS-CoV-2 infection. Antiviral secondary metabolites have been isolated from a number of medicinal plants and global studies have been conducted to produce antiviral drugs that are effective against SARS-CoV-2. Searching the compounds that modify or disrupt every stage of the virus replication cycle may be the most effective way of preventing COVID-19 infections. Natural products with the ability to inhibit or change the structure of structural proteins (spike glycoprotein), non-structural proteins (3-chymotrypsin-like protease, papain-like protease, helicase, and RdRP), and accessory proteins encoded by the SARS-CoV-2 genome must be investigated. Phytochemicals, which have low toxicity and are used in the pharmaceutical industry for their bioactivity, including antiviral activity, could offer a solution to this problem. SARS-CoV-1 and COVID-19 have a lot in common, which may lead to the discovery of new medicines or even a vaccine. The potential anti-SARS-CoV-2 action of flavonols, flavanones, and flavones, as well as the fact that these metabolites are abundant in angiosperm plants, have given rise to a lot of optimism. Since the majority of current research is theoretical or lacks empirical validation, there is still a long way to go in terms of biological science and optimized extraction and development. Flavonoids and alkaloids combat COVID-19 in several ways like protease inhibition, spike protein inhibition, Nrf2 inhibition. This study initiative would be bolstered by the rigorous review outlined here. As pandemic situation is lasting for a long period, it is crucial to search for best drug candidates that have potentialities against SARS-CoV-2. Therefore, flavonoids and alkaloids may have such kind of potentialities to treat COVID-19. Flavonoids and alkaloids provide capabilities to fight against novel coronaviruses, and researchers can continue to investigate the mechanisms of action in order to develop effective preventions so that the planet will get rid of this deadly viral infection.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

KRAM and KRAJ conceptualized and designed the study, and performed statistical analysis. KRAM, GS and SJ performed acquisition of data. KD, MUK, TBE and HO performed analysis and interpretation of data. KRAM and TBE contributed in administrative, technical, and material support. KRAM, RB and KRAJ drafted the manuscript. KRAM, GS, MUK and HO revised the manuscript. All authors read and approved the final manuscript for publication.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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