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REVIEW ARTICLE

A review of natural products, their effects on SARS-CoV-2 and their utility as lead compounds in the discovery of drugs for the treatment of COVID-19

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Abstract

During the COVID-19 pandemic lasting now for well more than a year, nearly 247 million cases have been diagnosed and over 5 million deaths have been recorded worldwide as of November 2021. The devastating effects of the SARS-CoV-2 virus on the immune system lead to the activation of signaling pathways involved in inflammation and the production of inflammatory cytokines. SARS-CoV-2 displays a great deal of homology with other coronaviruses, especially SARS-CoV and MERS-CoV which all display similar components which may serve as targets, namely the Spike (S) protein, the main protease (M^{Pro}) which is a chymotrypsin-like protease (CL^{Pro}) and RNA-directed RNA polymerase (RdRp). Natural constituents found in traditional herbal medicines, dietary supplements and foods demonstrate activity against SARS-CoV-2 by affecting the production of cytokines, modulating cell signaling pathways related to inflammation and even by direct interaction with targets found in the virus. This has been demonstrated by the application of fluorescence resonance energy transfer (FRET) experiments, assays of cytopathic effect (CPE) and in silico molecular docking studies that estimate binding strength. Glycyrrhizin, flavonoids such as quercetin, kaempferol and baicalein, and other polyphenols are the most common constituents found in Traditional Chinese Medicines that modulate inflammation and cell signaling pathways, and bind viral targets demonstrating valuable effects against SARS-CoV-2. However, the bioavailability of these natural products and their dependence on each other in extracts make it difficult to assess their actual utility in the treatment of COVID-19. Therefore, more can be learned through rational drug design based on natural products and from well-designed clinical trials employing specific doses of standardized combinations.

Keywords COVID-19 · SARS-CoV-2 · Herbal · Botanical · Natural Products

Abbreviations

ACE2	Angiotensin Converting Enzyme Type Two
Ala	Alanine
AP-1	Activator Protein One
Arg	Arginine
Asp	Aspartic Acid
BCP	β-Caryophyllene
CB1	Endocannabinoid receptor type 1
CB2	Endocannabinoid receptor type 2
CBC	Cannabichromene
CBD	Cannabidiol
CBN	Cannabinol
CBV	Cannabivarin
CL^{Pro}	Chymotrypsin-like Protease
COVID-19	Coronavirus Disease, 2019
COX-2	Cyclooxygenase Two
CPE	Cytopathic Effect
Δ^9-THC	Delta-Nine Tetrahydrocannabinol
E	Envelope Protein
EC_{50}	Effective Concentration at 50% Maximal Effect
FRET	Förster or Fluorescence Resonance Energy Transfer
IC_{50}	Inhibitory Concentration at 50% Inhibition
IFN-γ	Interferon-gamma
IL	Interleukin
IL-1α	Interleukin 1-alpha
IL-1β	Interleukin 1-beta
iNOS	Intracellular Nitric Oxide Synthase

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IRF1	Interferon Regulatory Factor One
Kcal/mol	Kilocalories per mole
M^{Pro}	Main Protease
MAPK	Mitogen Activated Protein Kinase
MCP-1	Monocyte Chemotactic Factor One
MERS-CoV	Coronavirus that causes Middle-East Acute Respiratory Syndrome, in the outbreaks of 2012 and 2015
Mg	Milligram
μM	Micromolar
N	Nucleocapsid Protein
NAGA	N-Acetylglucosamine Amide
NFκB	Nuclear Factor Kappa B
NIH	National Institutes of Health (U.S.A.)
NO	Nitric Oxide
NRP1	Nucleosome Assembly Protein-1 Related Protein-1; Protein neuropilin 1
ORF	Open Reading Frame
PASC	Post-acute sequalae
PL^{Pro}	Papain-like Protease
PPAR	Peroxisome-proliferator activated receptor
RNA	Ribonucleic Acid
RdRp	RNA-directed RNA Polymerase
S	Spike Protein
S1	Spike Protein Segment One
S2	Spike Protein Segment Two
SARS-CoV	Coronavirus that causes Systemic Acute Respiratory Syndrome, in the epidemic of 2002-2003
SARS-CoV-2	Coronavirus that causes Systemic Acute Respiratory Syndrome, in the pandemic of 2020-2021
STAT1	Signal Transducer and Activator of Transcription Factor One
TCM	Traditional Chinese Medicine
TMPRS-S2	Transmembrane Serine Protease Type Two
TNF-α	Tumor Necrosis Factor-alpha
Trp	Tryptophan
TRP	Transient cation receptor potential channel
TTP	Thymidine Triphosphate
UTP	Uridine Triphosphate

Introduction

The COVID-19 pandemic has been with us now for more than a year. With nearly 247 million cases confirmed and more than 5 million deaths worldwide [1], science continues to learn more and more about how to treat the acute effects of mild, serious and severe infection and long-term sequelae of the virus. At this point there is much concern about the rise of new variants of SARS-CoV-2 that are transmitted more easily from to person. Worries persist about these variants being able to evade the protection offered by new vaccines that have entered the marketplace since late 2020, due to mutations affecting the ability to be recognized by antibodies [2, 3].

SARS-CoV-2 is a betacoronavirus spread by airborne droplets from the respiratory tracts of infected individuals. One reason why severe infection with SARS-CoV-2 is so dangerous is the effect the virus has on the immune system where the lungs are overrun with pro-inflammatory cytokines, often called "cytokine storm." Excessive production and release of cytokines such as Tumor Necrosis Factor Alpha (TNF-α), Interferon Gamma (IFN-γ), and Interleukins (IL-1α, IL-1β, IL-2, IL-6, IL-15 and IL-18) is believed to cause the symptoms of moderate to severe COVID-19 infection as well as multiple organ failure and cell death. Signaling pathways involved include the Nuclear Factor Kappa B (NFκB) and IFN pathways and the production of intracellular nitric oxide synthase (iNOS) and nitric oxide (NO) via the interferon regulatory factor 1/signal transducer and activator of transcription factor 1 (IRF1/STAT1) pathways [4]. Platanitis and Dekker have reviewed the roles of cytokines in these signaling pathways and their relationships to inflammation [5].

The genome of SARS-CoV-2 shares approximately 85% homology with SARS-CoV, the coronavirus that caused the SARS atypical pneumonia outbreak of 2002–2003. The proteins of SARS-CoV-2 share between 65% and 97% homology with those of SARS-CoV. The viral genome of SARS-CoV-2 also demonstrates 35–48% sequence homology with the envelope and nucleocapsid proteins and surface and membrane glycoproteins of MERS-CoV, the coronavirus that caused the Middle East Respiratory Syndrome outbreaks of 2012 and 2015 [6, 7]. MERS-CoV was originally isolated from the sputum of a man living in the Arabian Peninsula. Genetic analysis of MERS-CoV identified it as a betacoronavirus related to other betacoronaviruses transmitted by bats [8]. Civets and dromedary camels are believed to be the intermediate hosts of MERS-CoV [9].

The viral genome of SARS-CoV-2 is a single-stranded (+) RNA polymer coding for a number of proteins in open reading frames (ORFs) that play roles in viral structure, host cell penetration, replication and immunogenicity [10]. As such, SARS-CoV-2 has multiple targets for drug action that researchers are able to exploit in order to slow and diminish the effects of acute infection.

As targets, SARS-CoV-2 produces an envelope protein (E) and a nucleocapsid protein (N), important for viral structure, a main protease (M^{Pro}) which is a chymotrypsin-like protease (CL^{Pro}), a papain-like protease (PL^{Pro}), helicases and RNA-directed RNA polymerase (RdRp), all vital for viral replication. The spike protein (S), is integral for

viral entry into host cells by interacting with its host cell receptor, angiotensin converting enzyme 2 (ACE2). ACE2 is found on the cells of the pulmonary epithelium as well as many other tissues throughout the body such as kidney, brain, heart and the vasculature [11]. Herbal formulae contain plant materials whose constituents are able to inhibit the proteases, thus inhibiting viral replication, and interact with either the spike protein itself, the spike protein-ACE2 receptor complex or a transmembrane serine protease (TMPRSS2) found on host cells that cleaves the spike protein into S1 and S2 segments to facilitate viral entry into host cells [12].

Such targets can be affected by a number of drugs now being repurposed, such as dexamethasone and tocilizumab, and newly marketed drugs such as remdesivir and favipiravir. Dexamethasone is a glucocorticoid used routinely for its anti-inflammatory properties and tocilizumab is a monoclonal antibody whose target is the IL-6 receptor. It is believed that blocking the IL-6 receptor could reduce the effects of massive cytokine release during severe infection [13]. Remdesivir and favipiravir are inhibitors of RdRp found to be effective in the treatment of COVID-19 [13].

Even natural constituents found in herbal medicines, dietary supplements and foods demonstrate activity against SARS-CoV-2 and related coronaviruses, SARS-CoV and MERS [14]. In fact, since the early days of the pandemic clinicians in China have used botanically based Traditional Chinese Medicines as adjunct therapy in the treatment of patients infected with SARS-CoV-2 with remarkable success in decreasing the severity of disease and the length of stay in the hospital [15–24]. However, much remains to be learned from conducting well designed clinical trials of scope and magnitude large enough to explain with certainty that natural medicines, dietary supplements and foods rich in certain phytochemicals have a place in the therapy of COVID-19 [25].

What then are the common phytochemicals and chemical classes of interest from natural sources that have activity against SARS-CoV-2, how do they work, what are their targets and how do we assess their activity? Moreover, why is it important that we understand that this activity exists and how can we exploit it? Physicians in the west may not be ready, able or willing to employ Traditional Chinese Medicine (TCM) as a modality of practice, but if we were to understand the activity of these natural constituents it may be possible to develop new drugs capable of reducing the symptoms and severity of acute infection, reduce the length of stay in hospitals and improve the quality of life in patients infected with SARS-CoV-2 [25]. The NIH Center for Complementary and Integrative Health is also looking for insight into complementary and integrative methods that may even include the use of herbs, dietary supplements and adjustments to the diet in order to mitigate the post-acute sequelae (PASC) of SARS-CoV-2 [26]. In this review, Traditional Chinese Medicines and their most common chemical constituents having activity against coronaviruses, including SARS-CoV-2, are surveyed with discussion relating to their possible mechanisms of action against SARS-CoV-2.

Traditional Chinese medicine (TCM)

During early 2020 physicians in China, where the outbreak of SARS-CoV-2 originated, began using formulae known and used in TCM to treat viral infections, or what are commonly referred to in TCM as “pestilence” [27]. TCM uses multi-component herbal formulae to achieve treatment of disease. Several formulae were employed that were found to modulate reproducibility of the virus by affecting viral protease enzymes, and modulate the concentration of cytokines in the host, thus affecting the host immune response to the virus [25].

There are at least 116 different, multicomponent TCM formulae and patent medicines composed of more than 215 different plants, plant parts and extracts used in various combinations with one another [25, 28–32]. Although vaccines are now widely used in China and around the world [33], these herbal formulae have been employed as adjuncts in the treatment of patients infected with SARS-CoV-2 for various purposes with some success [26]. Many of the plants found in these formulae are not necessarily found commonly as dietary supplements in the US, but many of their chemical constituents that have activity against the targets of SARS-CoV-2, such as kaempferol and quercetin, can be found in dietary supplements. For example, *Ginkgo biloba* is a popular dietary supplement that is rich in both kaempferol and quercetin [34]. The question then becomes, how can one classify these herbal formulae into a more meaningful subset of information of which to take advantage, chemically? We need to examine the constituents of plants and their activity in inhibiting SARS-CoV, MERS-CoV and SARS-CoV-2. Doing so will allow us to learn how these phytochemicals could be used as lead compounds in the development of drugs that can be used to treat and diminish the severity of COVID-19.

Assessment of activity in vitro

There are many ways to determine and analyze the interactions of various phytochemicals with the targets of SARS-CoV-2. FRET-Förster or Fluorescence resonance energy transfer (FRET) experiments use confocal microscopy to analyze the transfer of photons from a donor dye to an acceptor dye over distance through space during excitation

by light in order to describe the binding strength of a labeled ligand to its labeled target [35]. Binding is often expressed as an IC_{50} value, the concentration necessary to inhibit 50% of target activity.

An assay of cytopathic effect (CPE) is a controlled colorimetric assay where cells are incubated in a well plate, exposed to a virus and a suspected antiviral compound in varying concentrations. A log dose-response curve is generated and the EC_{50} value represents the concentration of the test compound necessary to inhibit 50% of viral cell death. A lower the EC_{50} value indicates better ability of the test compound to inhibit viral cell death.

In Silico molecular modeling uses the established crystal structure of viral targets from SARS-CoV-2, or closely related targets of related viruses such as SARS-CoV, docked with a known subset of ligands to establish the binding strength of competitive inhibitors of the target. A variety of targets from both SARS-CoV and SARS-CoV-2 are noted in Table 1 [36–46]. Binding strength is expressed in terms of kcal/mol. It is best for the binding strength of a test compound to be as close as possible to the binding strength of a known inhibitor or control. It is also important to note that in silico docking is no indication that a compound will absolutely inhibit a target, but it offers a good start for engaging in drug design [47].

Glycyrrhizin

In reviewing formulae from TCM, the most commonly used herb was *Glycyrrhizae radix et rhizoma*, from *Glycyrrhiza glabra* L. and other *Glycyrrhiza* species, also known in the West as licorice root. This herb, with its anti-inflammatory properties also activates granulocytes, natural killer cells and eosinophils, appears to inhibit both viral entry into host cells and SARS-CoV-2 replication [29, 48–50]. Glycyrrhizin, the major triterpenoid saponin found in licorice root (Fig. 1A), inhibits the binding of SARS-CoV S proteins to ACE2 by binding four residues of ACE2 with a binding free energy similar to flavonoids, thus blocking the ability of SARS-CoV-2 to enter host cells [51]. Glycyrrhizin and its aglycone, 18β-glycyrrhetinic acid, also affect cell signaling pathways involving protein kinase C (PKC), activator protein 1 (AP1) and NFκB. These two phytochemicals mediate the production of cytokines, inflammation and apoptosis resulting from their production. By decreasing neutrophil infiltration, decreasing nitric oxide synthase and nitric oxide (NO) production, free radical sequestration the production of protective IFN-γ and apoptosis increase, while the production of pro-inflammatory cytokines IL-6, IL-10 and TNF-α decrease [28, 48, 50–53]. As used, when taken orally glycerrhizin is dosed as tablets containing approximately 300 mg of glycyrrhizin, capsules containing 150 mg diammonium glycyrrhizinate [31] or as the 1700 mg of the crude herb containing 5.65% glycyrrhizin. When administered intravenously the dose of glycyrrhizin is approximately 240 mg [51].

In a CPE assay glycyrrhizin's EC_{50} was 365 μM and the EC_{50} for 18β-glycyrrhetinic acid (Fig. 1B) was >20 μM, but only glycyrrhizin was selective in maintaining cell viability with a selectivity index of >65. Interestingly, the 2-acetimido-β-*D*-glucopyranosylamine (N-acetylglucosamine amide-NAGA) derivative of glycyrrhizin (Fig. 1C), demonstrated an EC_{50} value of 40 μM with a selectivity index of >75, compared to 13 other glycyrrhizin derivatives, 6 of which were potent, but none of which were selective in their cytopathic activity. Presumably, the NAGA derivative binds well with the highly glycosylated S-proteins of SARS-CoV thus increasing the potency of this derivative [54].

Molecular docking studies were carried out in silico with glycyrrhizin and glycyrrhizic acid, and a number of SARS-CoV-2 targets. Lower docking scores indicate better binding of the compound with its putative targets. The results of molecular docking studies with glycyrrhizin and glycyrrhizic acid are shown in Table 2. These encouraging results should shed light into possible modifications relative to the rational design of anti-coronavirus agents based on the triterpenoid saponin, glycyrrhizin [55, 56].

Table 1 Targets of SARS-CoV and SARS-CoV-2 for in silico binding studies

Target	PDB Code	Target	PDB Code
SARS-CoV M^{Pro}	1WOF [36]	SARS-CoV-2 M^{Pro}	7K3T [37]
SARS-CoV PL^{Pro}	2FE8 [38]	SARS-CoV-2 PL^{Pro}	6W9C [39]
SARS-CoV RdRp	6NUR [40]	SARS-CoV-2 RdRp	7BV2 [41]
SARS-CoV N	2GIB [42]	SARS-CoV-2 N	6YVO [43]
SARS-CoV S	3JCL [44]	SARS-CoV-2 S	6VXX [45]
Human ACE2	7A98 [46]		

Flavonoids and polyphenolics

Flavonoids (Fig. 2) and other polyphenolic compounds are some of the most widely found chemical compounds in plants used both as medicinal herbs in TCM and other systems of herbal medicine, and from plants eaten in the diet [57]. Flavonoids are polyhydroxylated 2-phenylchromones. They, their glycosides and some bioisosteres demonstrate antiviral activity against SARS-CoV, MERS-CoV and other human coronaviruses as well as influenza A virus [58]. Flavonoids not only stimulate host immune responses to viral exposure; they also suppress excessive inflammatory reactions and modulate autophagy and immunoproteasome effects [57, 59, 60].

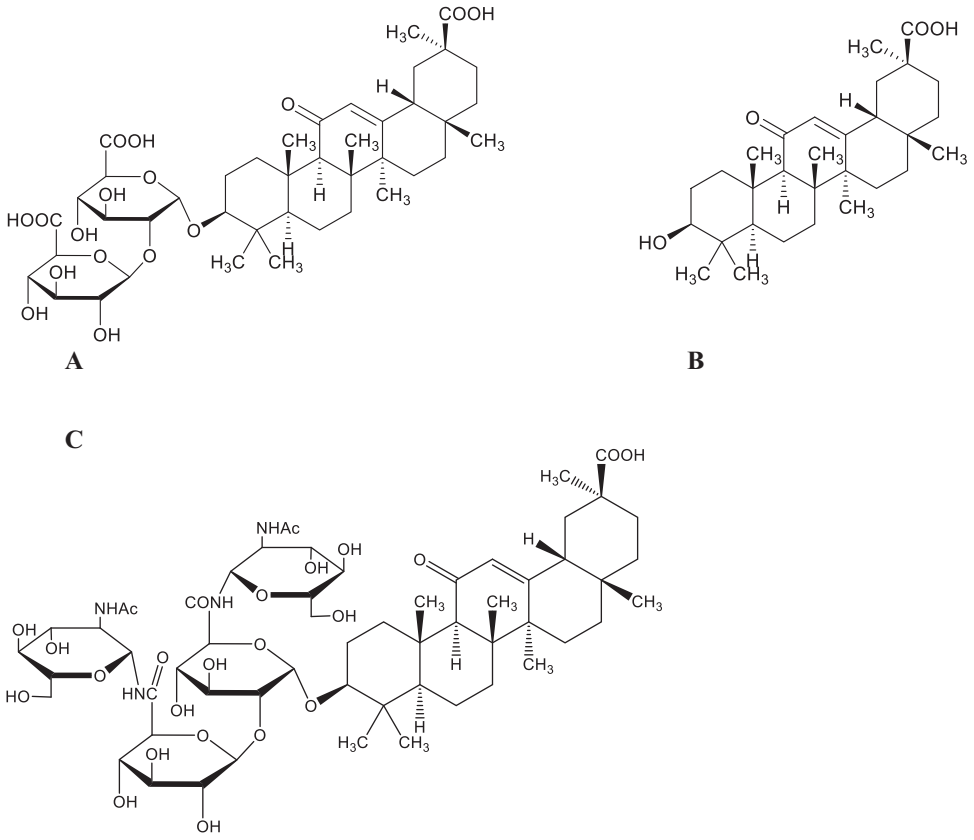


Fig. 1 **A** Glycyrrhizin. **B** Glycyrrhetinic acid. **C** 2-acetamido-β-D-glucopyranosylglycyrrhizin

Table 2 Binding energies of glycyrrhizic acid and glycyrhhizin with SARS-CoV-2 target proteins

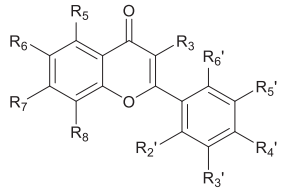
Target/PDB Code	Glycyrrhizic Acid [55]	Glycyrrhizin [56]
M^{Pro} / 7K3T	−8.7	−8.1
PL^{Pro} / 6W9C	−8.2	−7.9
RdRp / 7BV2	−9.9	–
N / 6YVO	–	−7.9
S / 6VXX	−9.3	–
Human ACE2 / 7A98	−9.5	–

M^{Pro}-Main Protease ($3CL^{Pro}$, Chymotripsin-like Protease); PL^{Pro}-Papain-like Protease; RdRp-RNA-dependent RNA polymerase; N-Nucleocapsid protein; S-Spike protein; Human ACE2-Angiotensin Converting Enzyme 2 (human host cell surface)

The flavonoids apigenin chrysin, galangin, hesperetin, kaempferol, luteolin, naringenin and quercetin (Fig. 2), the flavonoid glycoside rutin (Fig. 3A), the isoflavone phytoestrogen daidzein (Fig. 3B), neobavaisoflavone (Fig. 3C) and the catechins from dietary sources, such as green tea (Fig. 4), are flavonoids or closely related compounds found in a variety of fruits and vegetables. These compounds diminish a number of inflammatory processes related to cyclooxygenase-2 (COX-2) and iNOS activity, NFκB, Activator Protein-1 (AP-1) and mitogen activated protein kinase (MAPK) activities [57]. Such activities reduce the synthesis of inflammatory markers such as IL-1β, IL-6, IFN-γ and TNF-α, whose elevated concentrations are noted in patients experiencing severe symptoms of SARS-CoV-2 infection [57]. Non-flavonoid anti-oxidants and anti-inflammatories found in fruits, vegetables, grains and cereals such as caffeic, ferulic, *p*-coumaric, syringic and vanillic acids, eriodictyol, polydatin and resveratrol (Fig. 5), also play roles in inhibiting lipid peroxidation and free radical scavenging. These activities lead to the decreased synthesis and effects of the aforementioned markers of inflammation in SARS-CoV-2. In fact, eriodictyol, one of its glycosides, and polydatin, bind ACE2 and inhibit SARS-CoV-2 main protease (M^{Pro}) [57].

A flavonoid enriched extract of the skullcap root, *Scutellaria baicalensis*, rich in the flavonoids, scutellarein, baicalein and its glycoside, baicalin, as well as other flavonoids decreased the production of inflammatory cytokines TNF-α, IL-6, monocyte chemotactic factor-1 (MCP-1) and nitric oxide in mouse lung tissues exposed to influenza A virus, while increasing the synthesis of protective cytokines IFN-γ and IL-10 [61]. In examining a TCM formula rich in flavonoids (baicalein, isorhamnetin, kaempferol, luteolin, naringenin, quercetin and wogonin), extracts rich in these compounds suppressed IL-6 production in macrophages in vitro, and downregulated TNF-α and NFκB

Fig. 2 Flavonoids



	R_3	R_5	R_6	R_7	R_8	R_2'	R_3'	R_4'	R_5'	R_6'
Apigenin	H	OH	H	OH	H	H	H	OH	H	H
Baicalein	H	OH	OH	OH	H	H	H	H	H	H
Caflanone	H	OH	H	OH	C_5H_9	H	OCH_3	OH	H	H
Chrysin	H	OH	H	OH	H	H	H	H	H	H
Galangin	OH	OH	H	OH	H	H	H	H	H	H
Herbacetin	OH	OH	H	OH	OH	H	H	OH	H	H
Hesperetin (2,3 dihydro)	H,H	OH	H	OH	H	H	OH	OCH_3	H	H
Isorhamentin	OH	OH	H	OH	H	H	OCH_3	OH	H	H
Kaempferol	OH	OH	H	OH	H	H	H	OH	H	H
Luteolin	H	OH	H	OH	H	H	OH	OH	H	H
Morin	OH	OH	H	OH	H	OH	H	OH	H	H
Myricetin	OH	OH	H	OH	H	H	OH	OH	OH	H
Naringenin (2,3 dihydro)	H,H	OH	H	OH	H	H	H	OH	H	H
Nobiletin	H	OCH_3	OCH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	H	H
Quercetin	OH	OH	H	OH	H	H	OH	OH	H	H
Rhamentin	OH	OH	H	OCH_3	H	H	OH	OH	H	H
Scutellarein	H	OH	OH	OH	H	H	H	OH	H	H
Tangeretin	H	OCH_3	OCH_3	OCH_3	OCH_3	H	H	OCH_3	H	H
Wogonin	H	OH	H	OH	OCH_3	H	H	H	H	H

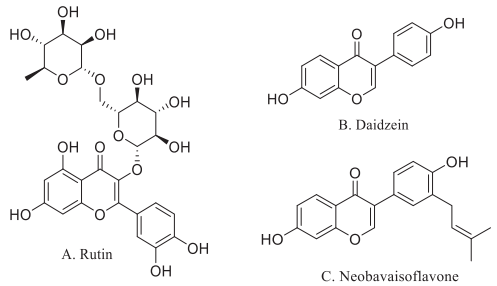


Fig. 3 Flavonoid-related compounds. **A** rutin. **B** daidzein. **C** neobavaisoflavone

signaling in addition to attenuating a host of other inflammatory signaling pathways [62].

Flavonoids interact with a number of viral targets including those involved with entry into host cells, genome transcription, post-translational modification and others related to viral viability. Solnier and Fladerer [59] summarized the results of flavonoids and related compounds binding to CL^{Pro} (M^{Pro}) and PL^{Pro} of SARS-CoV and MERS-CoV in FRET assays. With the lowest IC_{50} values being the best, flavonoids bound SARS-CoV CL^{Pro} with IC_{50} value ranges of 8.3–381 µM and MERS CoV CL^{Pro} with IC_{50} value ranges of 34.7–125.7 mM. Chalcones, dimeric structures of flavonoids, bound SARS-CoV CL^{Pro} with IC_{50} value ranges of 11.4–202.7 µM and MERS CoV CL^{Pro} with IC_{50} value ranges of 27.9–193.7 mM. Flavonoids bound SARS-CoV PL^{Pro} with IC_{50} value ranges of 3.7–66.2 µM and MERS-CoV PL^{Pro} with IC_{50} value ranges of 48.8–206.6 mM. Chalcones bound SARS-CoV PL^{Pro} with IC_{50} value ranges of 1.2–46.4 µM and MERS-CoV PL^{Pro} with IC_{50} value ranges of 42.1–171.6 mM (Table 3) [59]. Binding to CL^{Pro} is somewhat more erratic for flavonoids and chalcones, but binding to PL^{Pro} is less erratic and somewhat more potent. From this data, it may be more beneficial to base the development of PL^{Pro} inhibitors on chalcones, rather than flavonoids and to use flavonoids as the basis for the development of either CL^{Pro} or PL^{Pro} inhibitors.

Goyal and colleagues [63] completed molecular docking studies of SARS-CoV-2 RdRp with various flavonoids and triterpenes and compared them with uridine and thymidine triphosphates (UTP, TTP) and remdesivir, an effective RdRp inhibitor used in the treatment of COVID-19, as controls. Docking scores for the twenty compounds tested were all within 4 kcal/mol of the controls, and their binding free energies were on par with controls or at least within 80 kcal/mol of controls. The controls and the compounds tested appear to interact with the same amino acid residues in RdRp, namely serine, lysine, arginine, aspartate and isoleucine (Table 4). Molecular modeling demonstrates weak intermolecular interactions occurring between hydroxyl groups, ether oxygens and carbonyl oxygen atoms of the flavonoid and triterpene structures with amino acid residues of RdRp [63]. With respect to RdRp and ACE2,

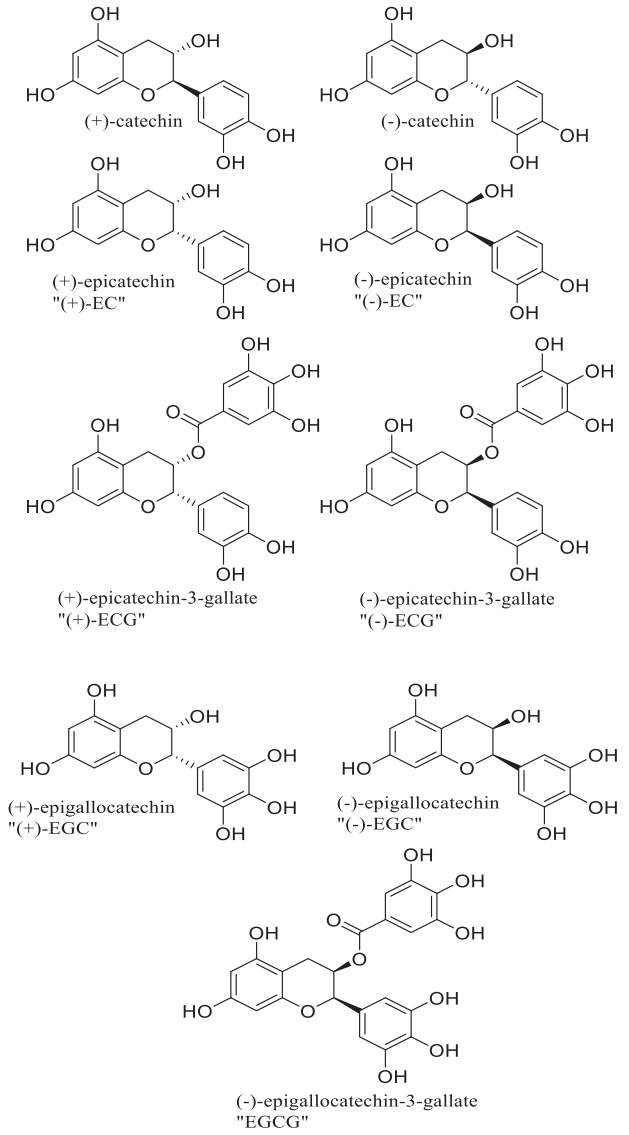


Fig. 4 Catechins from green tea

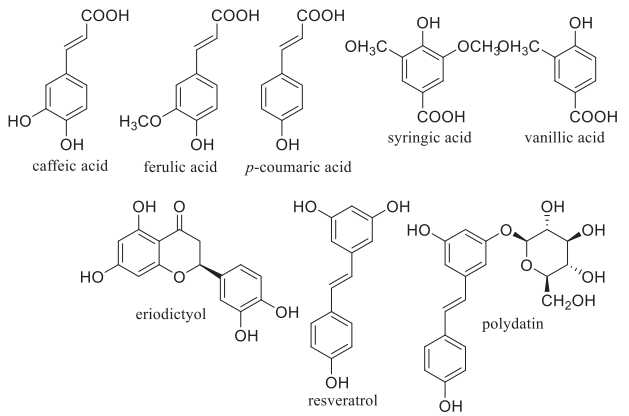


Fig. 5 Non-flavonoid anti-oxidants and anti-inflammatories from the diet

Table 3 IC_{50} value ranges of flavonoids and chalcones with SARS-CoV and MERS-CoV CL^{Pro} and PL^{Pro} [59]

	IC_{50} Value Ranges (μM)			
	SARS-CoV CL^{Pro}	SARS-CoV PL^{Pro}	MERS-CoV CL^{Pro}	MERS-CoV PL^{Pro}
Flavonoids	8.3–381	3.7–66.2	34.7–125.7	48.8–206.6
Chalcones	11.4–202.7	1.2–46.4	27.9–193.7	42.1–171.6

Table 4 Binding interactions common to flavonoids and glycyrrhizic acid in RdRp, and flavonoids and glycyrrhizinic acid in ACE2 [55, 63]

RdRp (PDB Codes 6M71 and 7BV2) [41, 89]		ACE2 (PDB Codes 6M17 and 2AJF) [90, 91]
Glycyrrhizic Acid [55]	Flavonoid[a]/ Flavonoid Glycoside[b] [63]	Glycyrrhzinic Acid [55]
Arg^{555}, Ser^{682}	Apigenin[a]	Ala^{348}
Arg^{555}, Ile^{548}	Apigenin-7-*O*-glucoside[b]	Ala^{348}, Arg^{393}, Asn^{394}
Arg^{555}	Galangin[a]	Asn^{394}, Asp^{350}, Arg^{393}
Arg^{555}, Ser^{682}	Hesperetin[a]	Ala^{348}, Arg^{393}, Asn^{394}
Lys^{545}, Ile^{548}	Hesperidin[b]	Tyr^{385}, Ala^{348}, Arg^{393}
Arg^{555}	Kaempferol[a]	Asn^{394}
Ile^{548}	Luteolin[a]	Ala^{348}
Ile^{548}	Luteolin-7-*O*-glucoside[b]	Glu^{402}
Ser^{682}	Naringenin[a]	–
Ser^{549}, Asp^{623}	Naringin[b]	Ala^{348}, Arg^{393}
Ser^{682}	Quercetin[a]	Ala^{348}
Ile^{548}, Asp^{623}, Lys^{551}, Arg^{555}	Rutin[a]	Asn^{394}

[a]Flavonoid

[b]Flavonoid glycoside

Goyal and colleagues found a number of binding interactions between various flavonoids/flavonoid glycosides and amino acid residues that share commonality with residues to which glycyrrhizic acid and glycyrrhizinic acid bind as noted by Vardhan and Sahoo (Table 4) [55, 63]. While molecular docking studies are not a guarantee that such compounds would interact with the target in vivo, there is some likelihood that they can, and by examining these commonalities in binding interactions these molecules such as these could serve as useful templates for antiviral drug development.

Molecular docking studies of flavonoid and triterpene binding to ACE2 gave docking scores within 3 kcal/mol of control and binding free energy values within 30 kcal/mol of control. Compounds tested bound key alanine, aspartate and arginine residues in binding models. These residues were among those bound by the known ACE2 inhibitor,

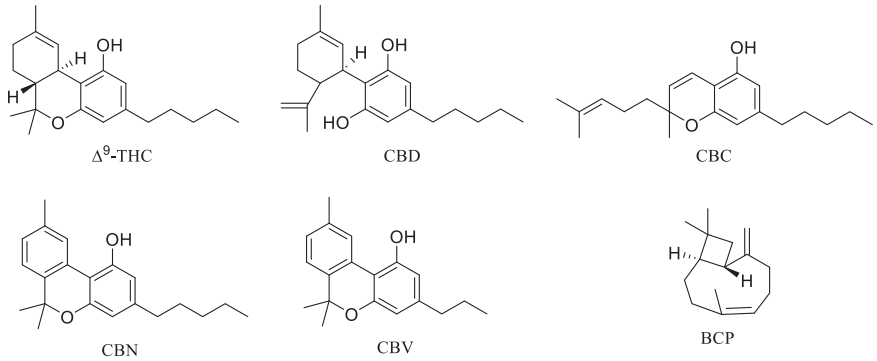


Fig. 6 Selected constituents of *Cannabis sativa* L

GL1001 (Ala[348], Trp[349], Asp[350], Asp[382] and Arg[393]). Again, models reveal weak intermolecular interactions occurring between hydroxyl groups, ether oxygens and carbonyl oxygen atoms of the flavonoid and triterpene structures with amino acid residues of ACE2 [63]. The structures of such flavonoids and triterpenes could be optimized to serve as potential leads for drug development.

Su and colleagues studied the effects of a Chinese patent medicine, whose name is Shuanghuanglian, on SARS-CoV-2 in vitro [64]. Shuanghuanglian is a multicomponent composition rich in the flavonoid, baicalein, found in *Scutellaria baicalensis*, and a number of other related compounds from *Forsythia suspensa*. As determined by molecular modeling studies, baicalein binds to a core region of the SARS-CoV-2 CL^{Pro} (M^{Pro}), by hydrogen bond interactions with leucine and glycine, glutamate and serine and glycine with the assistance of water, and by hydrophobic and/or pi stacking interactions with glutamine, arginine, methionine, cysteine and histidine residues. Baicalein inhibits SARS-CoV-2 M^{Pro} with an IC_{50} of ~0.94 µM, as well. Baicalein's glycoside, baicalin, also inhibited SARS-CoV-2 M^{Pro}, but inhibition was nearly 10-fold weaker at ~6.41 µM. Interestingly, seven other compounds from Shuanghuanglian, namely the catecholic glycosides forsythoside A, B, E, H, I, isoforsythoside and scutellarein, a flavonoid closely related to baicalein, also inhibited SARS-CoV-2 M^{Pro}, albeit with potency less than that of baicalein, with IC_{50} values ranging from 2.88 to 10.17 µM. These compounds could also serve as initial leads for anti-SARS-CoV-2 drug development.

A number of other compounds whose structures resemble the scaffolds of natural products have been found to inhibit SARS-CoV-2 M^{Pro} in the COVID Moonshot project. The COVID Moonshot project is a crowdsourced consortium of scientists from around the world using molecular modeling and crystallographic techniques, high-throughput synthesis, solubility and screening methodology, and artificial intelligence in the effort to find lead compounds active against SARS-CoV-2 M^{Pro} [65].

Not only do flavonoids and triterpenes display potential to bind ACE2, the cell surface receptor for SARS-CoV and SARS-CoV-2, flavonoids and their glycosides, gingerols and cannabinoids all demonstrate binding to the main protease M^{Pro} and S protein of SARS-CoV-2. Recall that the S protein of the virus interacts with ACE2 on the cell surface, whereby viral entry to the cell is gained. Binding free energies of flavonoids and their glycosides, gingerols and cannabinoids are low and comparable. The best binding to S protein was accomplished by epigallocatechin gallate, a well-known constituent of green tea, the flavonoid glycosides hesperidin, rhoifolin, pectolinarin and the cannabinoids, cannabidiol and Δ^9-THC [66]. Thus, all of these compounds could serve as useful scaffolds for drug design and lead development of anti-SARS-CoV-2 drugs.

Cannabis

Cannabis sativa L. has been used as a phytomedicinal substance for centuries, dating back to the Han Dynasty in China [67]. Of more than 550 compounds identified from *C. sativa*, there are at least 113 cannabinoids, 140 terpenes and at least 23 flavonoids [68, 69]. Cannabinoids derived from *Cannabis sativa* L. bind CB1 and CB2 receptors in the endocannabinoid system [70]. While the psychoactive cannabinoid, Δ^9-THC (Fig. 6) is known to bind CB1 receptors, promote relaxation of the vasculature and inhibit IL-1β production [71–73], cannabidiol (CBD, Fig. 6), cannabichromene (CBC, Fig. 6) and cannabinol (CBN, Fig. 6) bind CB2 receptors with resulting decreases in the proinflammatory cytokines [73, 74]. CBD has been shown to stimulate peroxisome-proliferator activated receptors alpha and gamma (PPAR-α and PPAR-γ) to attenuate the pathways leading to proinflammatory cytokine release [70, 73, 75, 76]. Through their actions at inflammasomes and the transient cation receptor potential channels (TRPs) these non-psychoactive cannabinoids depress the NFκB signaling pathway, decreasing the release of IL-6, IL-1β, IFN-γ and TNF-α in animal and in vitro models [77–79]. Thus, the interest in cannabinoids to diminish the effects of the cytokine storm as a serious manifestation of SARS-CoV-2 infection is pronounced, of late.

In molecular docking studies of cannabinoids and their binding to ACE2, TMPSS2, IL-6 and the histone chaperone NRP1, CBD and cannabivarin (CBV, Fig. 6) demonstrated significant binding affinity with binding free energies between −8.2 and −8.9 kcal/mol [80]. Binding of the cannabinoid with the these target proteins results in down-regulation of corresponding activity and an implied competition between binding of cannabinoids and the endogenous ligand [80].

Not only do cannabinoids diminish the release of proinflammatory cytokines, extracts high in CBD concentration also downregulate expression of the ACE2 receptor and TMPSS2 [81–83]. However, the effects on ACE2 and TMPSS2 expression cannot be related solely to CBD concentration [75, 82]. Extracts of cannabis contain bioactive terpenes as well. The relatively higher biological activity of cannabis extracts containing a combination of cannabinoids and terpenes may be explained by the entourage effect, where a complex mixture of compounds in a plant extract demonstrates greater biological activity than a single constituent alone [73, 82].

Terpenes are noted for the aromatic character and flavor they impart to cannabis plants [67]. Mentioned previously, terpenes found in cannabis extracts may account for an entourage effect. β-Caryophyllene (BCP, Fig. 6) is a terpene found in cannabis as well as a number of other plant species, and is a full agonist of CB2 receptors [84]. BCP also activates peroxisome-proliferator activated receptors alpha and gamma (PPAR-α and PPAR-γ) leading to attenuation of the pathways causing proinflammatory cytokine release [84]. Interestingly, BCP also binds SARS-CoV-2 M^{Pro} with a binding free energy of −7.2 kcal/mol, which is comparable to that of glycyrrhizin, −8.1 kcal/mol [69].

As stated, at least 23 flavonoids have been isolated from cannabis. Caflanone, a.k.a. isocannflavin B (Fig. 2), a flavonoid derived from cannabis, was shown to bind the metalloproteinase domain of ACE2 [85]. Other flavonoids and chloroquine also bind the metalloproteinase domain, however caflanone's binding free energy of −7.9 kcal/mol is lower than that of chloroquine (−4.1 or −4.7 kcal/mol), implying better binding in the ACE2 metalloproteinase domain. Other flavonoids discussed above, such as myricetin and hesperitin, bind the ACE2 metalloproteinase domain with free energies of −8.9 kcal/mol and −9.1 kcal/mol respectively, comparable to that of caflanone [85].

Given the effects of cannabis constituents on systems involved in the serious complications of COVID-19 and the wide availability of cannabis in the community today, it is no wonder that there is so much interest in cannabis as a potential therapy for the severe complications of SARS-CoV-2 infection. However, the effects of smoking and/or vaping cannabis can be deleterious to the lungs, many unsubstantiated claims have been made in the media and there has not been adequate clinical research to support the use of cannabis as a treatment or preventive therapy for COVID-19 [86, 87].

Conclusion

While the flavonoids and their related compounds, and other naturally occurring anti-oxidants and anti-inflammatories discussed display these beneficial properties, it is important to realize their bioavailability from the diet is limited. When ingested these compounds are subject to hepatic first-pass metabolic transformations and conjugation reactions that decrease their absorption and promote their elimination from the body. Dabeek and Marra have reviewed the bioavailability of the flavonoids, quercetin and kaempferol. In their work they detailed a number of food sources for these flavonoids and their glycosides, and discussed the kinetics behind their absorption, metabolism and excretion [88]. Complicating matters is the notion that extracts of natural products contain constituents that often act in synergy to illicit their effects, and that when individual constituents are purified their activity diminishes or disappears. With this in mind, a diet consistently rich in fruits, vegetables, grains and cereals affords the best chances for these bioactive compounds to be present in order to have and maintain their effects on viral entry and replication, and the inflammatory processes related to the consequences of moderate to severe infection. As claims are concerned, we must be reminded that US Federal Law does not permit claims for the treatment, cure or diagnosis of diseases such as COVID-19. Regardless, at this point it would be desirable to conduct well-designed clinical trials with specific doses of standardized products in order to determine the actual utility of natural compounds in the treatment of COVID-19.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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