

Systematic review

Phytochemicals Against COVID -19, Pharmacological Perspectives: A Systematic Review

ABSTRACT

Background: Many publications discussed the potential role of medicinal plants in the management of COVID-19. However, clinical studies of the efficacy and safety of specified phytochemical(s) are limited.

Objectives: To explore the pharmacological profile of specified compounds against COVID-19

Method: Systematic literature search of free academic databases .to explore phytochemical(s) for the management of COVID-19 using appropriate search terms and advanced search. Rayyan software was used to organize 786 citations of which. 236 articles were included

Results: Initially 70 compounds were identified to have a potential role in the management of COVID-19. In this review, 18 compounds were selected for further search

Conclusion: In vitro anti-SARS-CoV-2activity has been indicated for a variety of natural compounds. However, preclinical research is scarce, and only a few phytochemicals have been evaluated in clinical trials against COVID-19. A comprehensive pharmacological profile of these phytochemicals is urgently needed.

Keywords: Phytochemicals; COVID-19; SARS-CoV-2; Flavonoids; Alkaloids; Essential oils

1. Introduction

Coronavirus disease 2019 (COVID-19), which was first reported in Wuhan, China, in December 2019, is an ongoing global pandemic, highly infective respiratory viral illness. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It leads to extreme human and economic losses. As of 29 June 2021, more than 181 million cases have been identified, with more than 3.92 million confirmed deaths[1]. More details are available in these reviews[2-4]. The development of diagnostic tests, vaccinations, and medications for COVID-19 management has received a lot of attention.[5].

Numerous meta-analyses have shown the potential beneficial role of medicinal plants in reducing the severity of COVID-19 when combined with standard pharmacological therapy. [6-30]. Most clinical trials involved Chinese herbs [10, 12-15, 17, 18, 20, 22-29], few studies discussed the role of herbal medicine in specific countries, such as Nigeria [16] or India,[19]. Some clinical trials focused on a single plant or food as bee products [7, 11], plant-derived food-grade substances[21], Lianhua Qingwen (a Chinese herbal medicine) [28, 30]. However, it should be noted that integrated research on isolated phytochemicals (pure substances) is sparse, which may explain why most decision-makers are reluctant to study the efficacy and safety of phytochemicals in COVID-19 clinical studies. Therefore, the goal of this systemic review is to explore the potential role of phytochemicals in the management of COVID-19.

2-Method

Two databases were used, namely PubMed (NCBI), Lit-COVID 19, last accessed in November 2021. The research was restricted to 2019-2021, full text, and English language. All citations were imported to endnote 8, duplicates were excluded. Rayyan program (for Systemic review) was used to organize and select the relevant articles [31]. [PRISMA flow chart is shown in diagram 1\[32\]](#)

The first objective was to identify phytochemical(s) for the management of COVID-19. The 2nd objective explores the efficacy and safety, pharmacology of specified phytochemicals. The study was conducted in two phases, search terms in phase one were: # 1 " SARS-CoV-2" OR" COVID-19 ", OR" coronavirus". # 2: "Phytochemical*" OR" medicinal plants", OR "herbal medicine" followed by advanced (combined) search: #1 AND#2. 70 compounds were identified to have potential activity against the coronavirus (table 1-3). 18 compounds were selected by two investigators: given their low IC₅₀ against SARS-CoV-2, immunomodulating effect and good safety profile. Key terms in phase 2: each of the phytochemicals e.g. # 3Thymoquinone, 4 # " clinical trial " OR " antiviral " OR " anti-inflammatory " OR "lung injury" OR "Pharmacokinetic" OR "Formulation" OR "safety". Followed by advanced search #3 AND #4

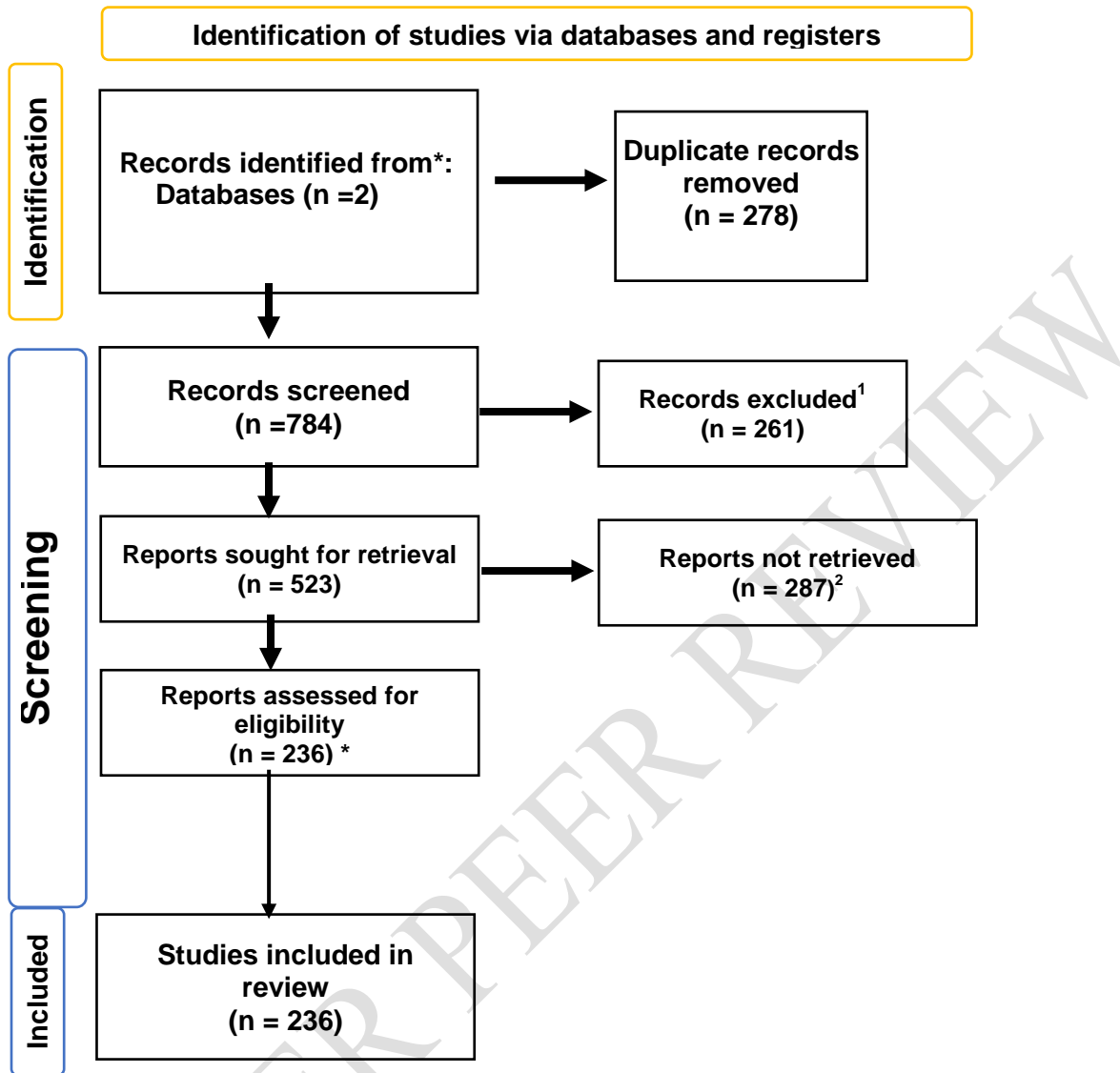


Diagram 1: PRISMA flow chart of the search for safety and efficacy of specified phytochemicals against COVID 19

*1- Only journals were included, 2- Only review articles, systemic reviews, clinical trials were included

Abbreviations and glossary of terms

ACE2: Angiotensin converting enzyme-2

ALI: Acute lung injury.

COVID-19: Coronavirus disease 2019

CPE: Cell-protective effects.

FDA: Food and Drug Administration.

IC₅₀/EC₅₀ values: The 50% inhibitory and effective concentration respectively.

LPS: Lipopolysaccharide.

M Wt.: Molecular weight.

Mpro: Main protease.

PK: Pharmacokinetics; describes absorption, distribution, metabolism, and elimination of drugs.

PLpro: Papain like proteases, and 3CLpro: 3-chymotrypsin like protease: enzymes essential for viral replication.

SARS: Severe acute respiratory syndrome.

SARS-CoV or SARS-CoV-1: severe acute respiratory syndrome coronavirus 1, is a strain of virus that causes SARS.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, that causes COVID-19.

3. Potential role of phytochemicals in the management of COVID-19

3.1 Overview

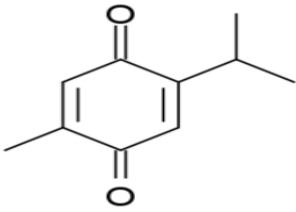
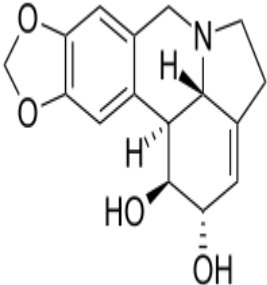
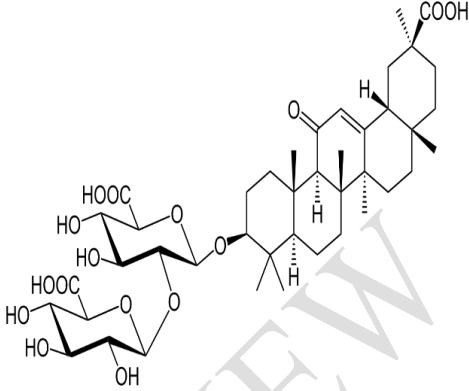
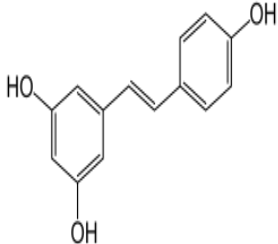
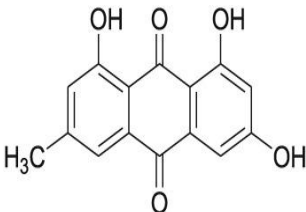
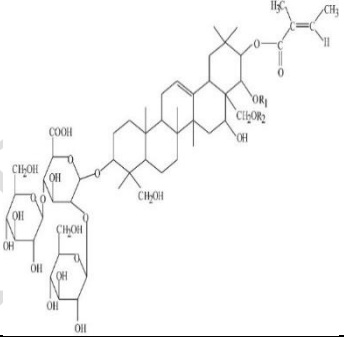
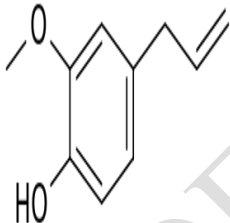
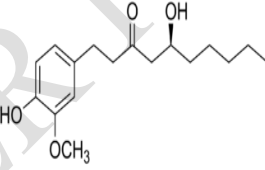
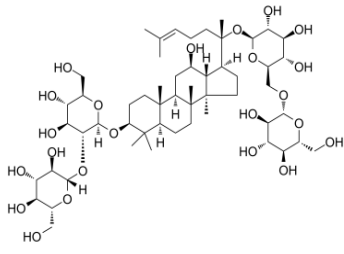
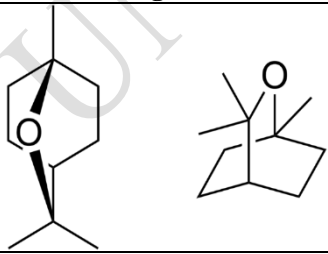
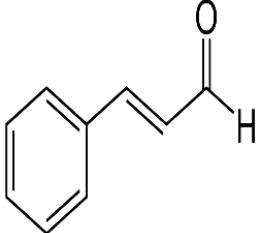
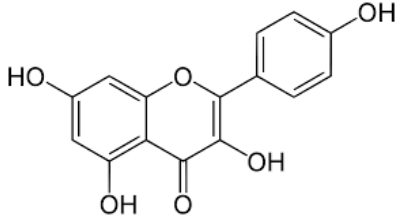
A comprehensive web-based resource for natural products (about 200 compounds) was launched in 2020 [33]. Several review articles included an extensive search for medicinal plant extracts, compounds that have been identified and proven to suppress the life cycle of the coronavirus. These reviews summarized the IC₅₀, selectivity, mechanisms of action and structure of specified compounds as polyphenols[34-36], flavonoids[37, 38] of which myricetin and scutellarin[39] were highlighted. Alkaloids [40, 41] particularly lycorine [42, 43] was of considerable interest, other alkaloids include tetrandrine, tangchinoline, cepharanthine [44] and reserpine[45]. Other classes of phytochemicals include : sterols[46], terpenoids[47, 48], stilbenoid, resveratrol[49], triterpene glycoside (saponin) glycyrrhizin [50], and saponin (Aescin)[45]. Tannins (tannic acid), 3-isotheaflavin-3-gallate, theaflavin-3,3'-digallate [51], and essential oils[52-54].

Many publications provided an overview of the utility of phytochemicals against COVID-19 [55-57]. Some provided a detailed description of a specified compound(s) e.g.,

Final version

curcumin[58], valinomycin [59], tanshinones[60], resveratrol [61] and glycyrrhizin [62]; or plant e.g. *Nigella sativa*[63]. A non-comprehensive list (about 70 compounds) was provided in tables 1-3. From this list, 18 compounds were selected for further search to explore their pharmacological profile (their structure is provided in figure 1.). The selection was based on low IC_{50} , immunomodulating effect and known safety profile by two authors.

UNDER PEER REVIEW

		
Thymoquinone	Lycorine (LYC)	Glycyrrhizin
		
Resveratrol	Emodin	Aescin (Esc) (N-3)
		
Eugenol	Ginger	Ginsenoside-Rb1
		
Eucalyptol	Cinnamaldehyde	Kaempferol
Figure 1: Structure of selected phytochemicals of a potential role in the management of COVID		
19		

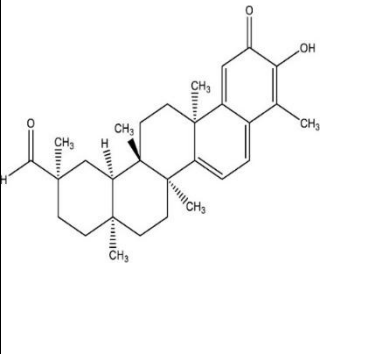
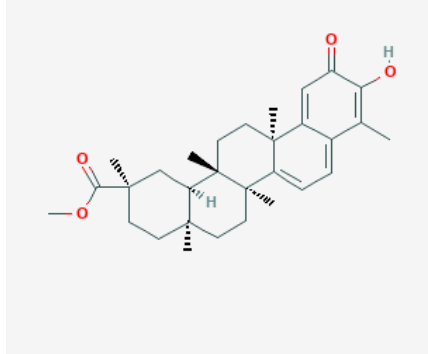
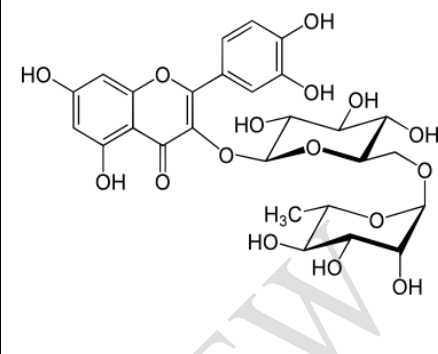
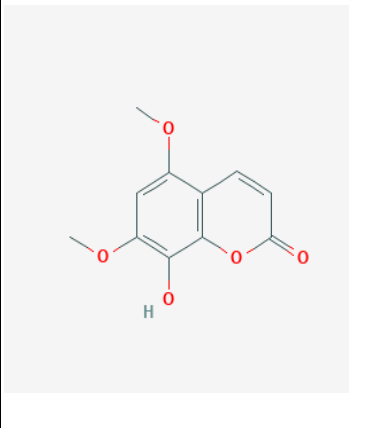
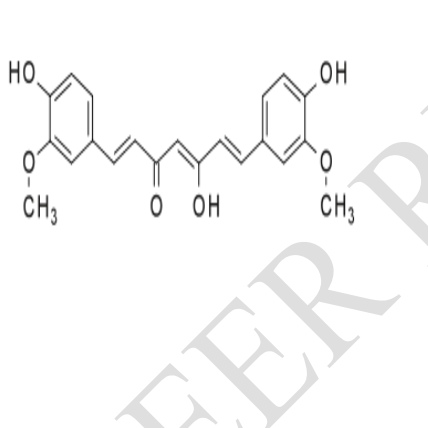
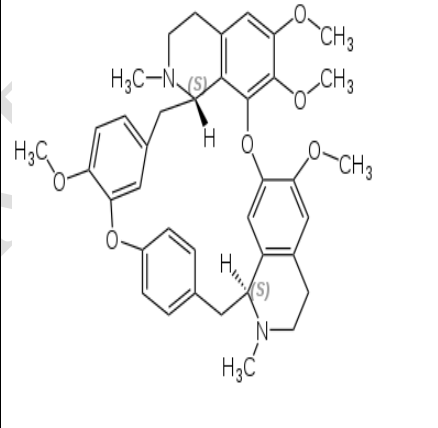
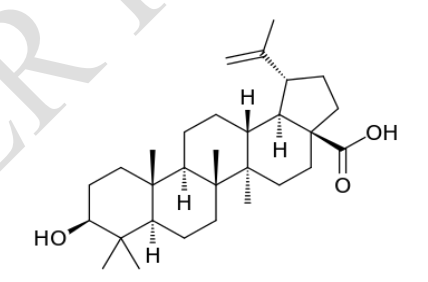
 <p>The structure of Celastrol is a complex polycyclic molecule with a decalin core, a cyclohexane ring, and a decalin ring system. It features several methyl groups, a ketone group, and a hydroxyl group.</p>	 <p>The structure of Pristimerin is a complex polycyclic molecule with a decalin core, a cyclohexane ring, and a decalin ring system. It features several methyl groups, a ketone group, and a hydroxyl group.</p>	 <p>The structure of Rutin is a flavonoid glycoside. It consists of a flavanone core (quercetin) linked to a rhamnose sugar and a glucose sugar.</p>
<p>Celastrol</p>	<p>Pristimerin</p>	<p>Rutin</p>
 <p>The structure of Leptodactylone is a complex polycyclic molecule with a decalin core, a cyclohexane ring, and a decalin ring system. It features several methyl groups, a ketone group, and a hydroxyl group.</p>	 <p>The structure of Curcumin is a polyphenolic compound consisting of two phenolic rings connected by a central heptadiene chain. It features two hydroxyl groups and two methoxy groups on each phenolic ring.</p>	 <p>The structure of Tetrandrine is a complex polycyclic molecule with a decalin core, a cyclohexane ring, and a decalin ring system. It features several methyl groups, a ketone group, and a hydroxyl group.</p>
<p>Leptodactylone</p>	<p>Curcumin</p>	<p>Tetrandrine</p>
 <p>The structure of Betulinic acid is a complex polycyclic molecule with a decalin core, a cyclohexane ring, and a decalin ring system. It features several methyl groups, a ketone group, and a hydroxyl group.</p>		
<p>Betulinic acid</p>		
<p>Figure 1: Structure of selected phytochemicals of a potential role in the management of COVID- 19</p>		

Table 1: Compounds suggested to interact with the specified target(s) of SARS-CoV-2: Spike protein, 3CLpro or PLpro [33].		
Compound	Class/ source	mechanism
Betulinic acid	Pentacyclic triterpenoid	3CLpro
Dihomo- γ -linolenic acid	ω -6 fatty acid.	3CLpro
Dihydrotanshinone	<i>Salvia miltiorrhiza</i>	Spike protein
TanshinoneIIa	<i>Salvia miltiorrhiza</i>	PLpro and 3CLpro
Cryptotanshinone	Quinone	PLpro and 3CLpro
Lignan	Low M Wt. polyphenols	3CLpro
Moupinamide	A phenolic amide	PLpro
N-cis-feruloyl tyramine	A phenolic amide	PLpro and 3CLpro
Coumaroyl tyramine	A phenolic amide	PLpro and 3CLpro
Quercetin	Flavonol	PLpro and 3CLpro
Kaempferol	Flavonol,	PLpro and 3CLpro
Sugiol	A diterpene	3CLpro

Table 2: Example of compounds with IC ₅₀ /EC ₅₀ values tested against an infectious coronavirus [64]			
Compound	Chemical group	IC ₅₀ /EC ₅₀ values	Coronavirus type targeted
Glycyrrhizin	Saponin	EC ₅₀ = 364.5 μM	SARS-CoV
Tetra-O-galloyl-β-D-glucose	Polyphenol	EC ₅₀ = 4.5 μM	SARS-CoV
Luteolin	Flavonoid	EC ₅₀ = 10.6 μM	SARS-CoV
Sinigrin	Polyphenol	IC ₅₀ = 217 μM	SARS-CoV
β-Sitosterol	Phytosterol	IC ₅₀ = 1210 μM	SARS-CoV
Hesperetin	Flavonoid	IC ₅₀ = 8.3 μM	SARS-CoV
Amentoflavone	Flavonoid	IC ₅₀ = 8.3 μM	SARS-CoV
Luteolin	Flavonoid	IC ₅₀ = 20.2 μM	SARS-CoV
Quercetin	Flavonoid	IC ₅₀ = 23.8 μM	SARS-CoV
Isobavachalcone	Flavonoid	IC ₅₀ = 7.3 μM	SARS-CoV
Psoralidin	Flavonoid	IC ₅₀ = 4.2 μM	SARS-CoV
Tomentin A	Flavonoid	IC ₅₀ = 6.2 μM	SARS-CoV
Tomentin B	Flavonoid	IC ₅₀ = 6.1 μM	SARS-CoV
Tomentin E	Flavonoid	IC ₅₀ = 5.0 μM	SARS-CoV
3'-O-Methyldiplacol	Flavonoid	IC ₅₀ = 9.5 μM	SARS-CoV
Isoliquiritigenin	Flavonoid	IC ₅₀ = 61.9 μM	SARS-CoV
Kaempferol	Flavonoid	IC ₅₀ = 116.3 μM	SARS-CoV
Kazinol F	Flavonoid	IC ₅₀ = 43.3 μM	SARS-CoV
Brousochalcone B	Flavonoid	IC ₅₀ = 57.8 μM	SARS-CoV
Papyriflavonol A	Flavonoid	IC ₅₀ = 103.6 μM	SARS-CoV
Terrestimine	Cinnamic amide	IC ₅₀ = 15.8 μM	SARS-CoV
Blancoxanthone	Xanthone	EC ₅₀ = 3 μg/ml	HCoV 229E
Pyranojacareubin	Xanthone	EC ₅₀ = 15 μg/ml	HCoV 229E

Table 2: Example of compounds with IC ₅₀ /EC ₅₀ values tested against an infectious coronavirus [64]			
Compound	Chemical group	IC ₅₀ /EC ₅₀ values	Coronavirus type targeted
Lycorine	Alkaloid	EC ₅₀ = 15.7 IU/ml	SARS-CoV
Tingenone	Triterpene	IC ₅₀ = 9.9 μM	SARS-CoV
Iguesterin	Triterpene	IC ₅₀ = 2.6 μM	SARS-CoV
Pristimererin	Triterpene	IC ₅₀ = 5.5 μM	SARS-CoV
Dihydrotanshinone I	Diterpene	IC ₅₀ = 4.9 μM	SARS-CoV
Cryptotanshinone	Diterpene	IC ₅₀ = 0.8 μM	SARS-CoV
Tanshinone IIA	Diterpene	IC ₅₀ = 1.6 μM	SARS-CoV
Xanthoangelol	Chalcone	IC ₅₀ = 11.4 μM	SARS-CoV
Hirsutenone	Diarylheptanoid	IC ₅₀ = 3.0 μM	SARS-CoV
Rubranoside	Diarylheptanoid	IC ₅₀ = 7.2 μM	SARS-CoV
Curcumin	Diarylheptanoid	IC ₅₀ = 5.7 μM	SARS-CoV
Flt3 receptor-interacting lectin (FRIL).	Lectin	EC ₅₀ = 6.25 μg/ml	SARS-CoV-2
Abrus precatorius (APA) Lectin	Lectin	EC ₅₀ = 0.45 μg/ml	SARS-CoV
Urtica dioica agglutinin (UDA) Lectin	Lectin	EC ₅₀ = 1.3 μg/ml	SARS-CoV
<p>Other compounds are not listed above. Resveratrol, Emodin, Aescin, Ginsenoside-Rb1, Leptodactylone, Celastrol, Tetrandrine, Cepharanthine, S-aikosaponin B₂, Quercetin-3-O-galactoside, Chalcones, Theaflavin, Myricetin, Scutellarein [40, 65-70].</p> <p>Essential oils with potential antiviral and immunomodulating activity, 8-cineole (eucalyptol), allyl sulfide, farnesene, farnesol, nerolidol; eugenol, menthol, carvacrol, cinnamaldehyde [71-74].</p>			

3.2 Pharmacological Profile of Selected Phytochemicals.

Out of 18 selected phytochemicals (Fig 1), two clinical trials were found, the 1st trial revealed that resveratrol, reduces angiotensin converting enzyme-2 (ACE2) expression in human adipose tissue [75]. The 2nd trial documented that, nano-curcumin treatment is a promising technique for controlling inflammatory cytokines in COVID-19 patients [76]. Aescin (was registered in China and Italy for clinical trials to demonstrate its potential role as an adjuvant in the management of COVID-19 [77].

The following is a summary of what has been collected regarding the pharmacology profile of these compounds, with a focus on their potential role against COVID-19

3.2.1. Thymoquinone

It is a quinone compound found in the seeds of *Nigella sativa (Ranunculaceae)* It has a broad pharmacological activity, and a good safety profile [78]. Its potential role in the management of COVID -19 was suggested based on its antiviral activity and ability to attenuate lung injury and inflammation [79-82]. Thymoquinone has poor oral bioavailability [83] likely due to its low solubility in water. Pharmaceutical formulations and nano delivery systems were suggested to improve their bioavailability and distribution [84-86].

3.2.2. Lycorine

Lycorine is a phenanthridine alkaloid isolated from the bulbs of *Lycoris radiata (Amaryllidaceae)*. It has broad pharmacological activity[87], it has potent activity against SARS-CoV[42]. Its ability to suppress SARS-CoV-2 replication was confirmed in Viro-6 cells, the EC₅₀ of lycorine, and chloroquine was, 0.18 and 1.36 µM, respectively, CC value >40 µM [69]. An animal study showed its very high volume of distribution and short half-life[88]. More, pre-clinical investigations are needed to determine other PK parameters such as protein binding and metabolism. Lycorine, in particular, has a wide range of pharmacological effects on a variety of disorders while having relatively low toxicity and minimal side effects [89].

3.2.3. Glycyrrhizin

It is triterpene glycoside (saponin), which is also known as glycyrrhizinic acid isolated from the roots of *Glycyrrhiza glabra (Fabaceae)*. It has several pharmacological activities [90]. The compound or its active metabolite expresses antiviral effects against SARS-CoV in cell

culture[91]. *In vitro* studies demonstrated that glycyrrhizin potently neutralizes SARS-CoV-2 by inhibiting the viral main protease (Mpro)[92]. It exhibited anti-inflammatory potential by several mechanisms including suppression of several proinflammatory mediators [93]. Its low bioavailability, low volume of distribution suggest that it is not likely to achieve an effective antiviral concentration of glycyrrhizin in lung tissues by oral or IV administration of safe doses 150-300 mg/day. An advanced delivery system such as inhalation can be considered to enhance its access to lung tissues.

3.2.4. Aescin(escin)

It's a blend of triterpene saponins extracted from the seeds of the horse chestnut tree; *Aesculus Hippocastanum (Sapindaceae)*. It has a high molecular weight [94]. It possesses antiviral and immunomodulatory activities[95]. It has been widely used in the treatment of traumatic induced oedema, and chronic venous insufficiency [96]. It was demonstrated to inhibit acute inflammation similar to corticosteroids [45]. Its EC_{50} against SARS-CoV was 6 μ M[45]. Given these pharmacological characteristics; it was suggested to consider escin as an add-on therapy in acute lung injury (ALI) associated with severe COVID-19 infection[96]. Injection formulation was registered in China and Italy for clinical trials to treat patients with COVID-19 pneumonia[77]. Aescin is not absorbed orally (bioavailability < 0.3%); likely due to extensive first-pass metabolism[97]. Aescin PK features were studied in rats following IV injection at dosages ranging from 0.5 to 2.0 mg/kg. The half-life of Aescin was about 7-12 hr., V_d : 3-6 L/Kg[97]. PK data in humans not available.

3.2.5. Resveratrol

Resveratrol, a polyphenol compound (3,5,4'-trihydroxystilbene) found in grapes; *Vitis vinifera (Vitaceae)*; Mulberry or *Morus nigra (Moraceae)* and Peanuts or *Arachis hypogaea (Fabaceae)*. It possesses antioxidant, antitumor, antiviral and free radical scavenging properties[98]. Among the seven drugs tested against HCoV-229E *in vitro*, resveratrol demonstrated a favourable antiviral effect (EC_{50}) = 4.6 μ M which was superior to two drugs namely lopinavir/ritonavir (EC_{50} = 8.8 μ M), and Chloroquine (EC_{50} = 5 μ M). Resveratrol has also the best selectivity index (SI) of 45.65 [70]. It showed the ability to attenuate lung injury in animal models [99]. In this context,

studies documented its ability to reduce biomarkers of inflammation, tumor necrosis factor (TNF- α), and C-reactive protein[100].

Resveratrol has poor oral bioavailability due to extensive metabolism in gastro-intestinal tract (GIT) and liver. It has a very short half-life, but its active sulfate metabolites showed a half-life of about 8 hr. It was speculated that levels of resveratrol in serum after oral administration are not likely to achieve an effective antiviral level[99]. However, the optimized pharmaceutical formulation may solve this limitation e.g., nanotechnology-based formulations and liposomes [72, 101]. Clinical studies showed favorable safety outcomes of resveratrol. A good safety profile was assured with doses up to 500 mg/d for 60 days [102]. Most reported adverse effects are mild GIT symptoms such as diarrhea [103]. However, an advanced delivery system is needed to improve its PK profile.

3.2.6. Emodin

Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) is found in many plants such as Chinese rhubarb; *Rheum palmatum* (Polygonaceae) [104]. It has many effective preventive and therapeutic effects [105]. Emodin was demonstrated to block the binding of SARS-CoV spike protein binding to its ACE2 receptors, hence it is likely to block viral entry into host cells [66]. It is one of the top 16 network-predicted re-purposed drugs against SARS-CoV and is suggested among drug combinations (toremifene plus emodin) [106]. It is included among **traditional Chinese medicine** against viral infections [107]. Its ability to attenuate lung injury is well documented in an animal model[108]. In animal studies, it has poor oral bioavailability due to extensive metabolism by glucuronidation. Emodin can cause reproductive, liver, and kidney toxicity, especially after chronic use[109].

3.2.7. Ginsenoside-Rb1 (G-Rb1)

G-Rb1 appears to be most abundant in ***Panax quinquefolius* (Araliaceae)** (American Ginseng). Ginsenosides possess a variety of potential health effects[110]. The ability of ginseng to attenuate experimentally induced lung injury are well documented and several mechanisms were suggested to explain its pharmacological effect [111]. Molecular docking analysis indicated that ginsenosides have the potential to inhibit the SARS-CoV-2 Mpro receptor [112]. Ginsenosides have very low bioavailability after oral administration [113]. Several studies documented the feasibility of enhancing its bioavailability by adopting several pharmaceutical technology

approaches[114, 115]. When ginseng extract was standardized at a concentration of 4 mg ginsenosides/100 mg capsule and given at a dose of up to 114 g ginsenoside/kg to humans for up to 12 weeks, no significant adverse effects were demonstrated [116].

3.2.8. Eugenol

It is a phenolic molecule (methoxy phenols, M Wt 164.2) found in several plants such as cinnamon *Cinnamomum (Lauraceae)*, clove *Syzygium aromaticum (Myrtaceae)*, Tulsi *Ocimum tenuiflorum (Lamiaceae)*. The potential value of clove and eugenol against COVID-19 was suggested based on their antiviral, anti-inflammatory, and antithrombotic effects [117]. Docking analysis indicated the possible interaction of α -pinene and eugenol with SARS-CoV spike protein [118]. The ability of eugenol to attenuate experimentally acute induced lung injury was documented [68]. It is likely mediated by the inhibition of lipoxygenase and cyclooxygenase pathways[119].

In mice, eugenol was readily absorbed after oral administration. The mean plasma half-life was about 14 hrs. suggesting a potential accumulation of the drug following repeated administrations[120]. A good safety profile was demonstrated in animal toxicity studies [121]. It is generally recognized as safe by the food and drug administration (FDA)[122]. However, local hypersensitivity reaction was reported in dental practice [123]. Based on its pharmacology profile, it is strongly recommended for pre-clinical studies and clinical studies, optimized formulations to explore its utility in the management of respiratory viral infections.

3.2.9. Gingerol

Gingerol, or [6]-gingerol, is a phenolic compound found in fresh ginger, *Zingiber officinale (Zingiberaceae)*. Pre-clinical *in vitro* and animal models documented a broad spectrum of therapeutic values[124]. The favorable impact of ginger and its active ingredients on the immune system are extensively studied, *in vitro* studies included; modulation of inflammatory cytokines levels[125], inhibition of lipopolysaccharide (LPS)-induced inflammatory responses in macrophages[126], the potential of the anti-inflammatory effect of some drugs such as paracetamol[127]. Other studies documented the therapeutic benefits in the management of allergic asthma and allergic rhinitis[128, 129]. Pharmacokinetic (PK) studies showed that, in general, is well absorbed orally and has good tissue distribution [130, 131]. A good safety profile was reported in clinical trials[132], several pharmaceutical nanotechnology approaches were

suggested to enhance its systemic availability or distribution[133, 134].

3.2.10. Eucalyptol (1,8-cineole)

It is a cyclic ether and monoterpenoid, it controls airway mucus hypersecretion and asthma via anti-inflammatory cytokine inhibition. It is abundant in many *Eucalyptus species (Myrtaceae)* [135]. It has low toxicity (LD₅₀ for rats 2.5 g/kg) [116]. It showed the ability to attenuate ALI in an animal model by different mechanisms [136, 137]. A comprehensive review of the ability of essential oil to suppress several respiratory viruses was studied by Wani et al.[138]. *Eucalyptus* essential oils have been used to treat a variety of respiratory diseases, including sinusitis, pharyngitis, and bronchitis. One of its active ingredients (1,8-cineole), showed smooth muscle relaxant effects[139]. Furthermore, investigations have shown that inhaling cineole has analgesic and anti-inflammatory properties, suggesting that it could be utilized to treat chronic obstructive pulmonary disease (COPD) and asthma[140]. Sharma et al. [141]used molecular docking to show that eucalyptol (1,8-cineole) may bind to Mpro and suppress viral multiplication. Strong ionic, hydrogen bonds and hydrophobic interactions have been described in the eucalyptol/Mpro complexes.

Several investigations found that eucalyptus oil and its active component, eucalyptol, have strong immunomodulatory activities. They were able to reduce the release of pro-inflammatory cytokines from macrophages and monocytes while maintaining their phagocytic properties[142]. In conclusion, it has an anti-inflammatory, bronchodilator, antibacterial effect, mucolytic, and antiviral activity. It is well absorbed orally, can be inhaled, and has good lipophilicity which suggests adequate access to lung cells. It has a good safety profile; therefore, the compound is suggested for more investigations in the management of respiratory viral infections.

3.2.11. Cinnamaldehyde

Cinnamaldehyde is an active ingredient in the bark of *Cinnamon* trees *Cinnamomum verum (Lauraceae)*. The essential oil of cinnamon bark contains > 90% cinnamaldehyde (predominantly the Trans E- isomer) synthetic compound is also available. According to docking experiments, cinnamaldehyde may prevent *SARC-CoV-2* from attaching to its target receptors [143]. Cinnamaldehyde's preventive benefits in the animal model of ALI have been demonstrated[144]. Different mechanisms were demonstrated; including neutrophils, macrophages, and total cell

number in bronchoalveolar lavage fluid is inhibited. It reduced the levels of inflammatory cytokines such TNF-, interleukin (IL-6), IL-13, and IL-1[145].

Cinnamaldehyde is approved by the FDA for use within allergenic percutaneous patch tests[146]. It has had a low potential for toxicity but weak sensitization reactions in animals and human skin allergy were reported[147]. It is metabolized to cinnamyl alcohol and methyl cinnamate and cinnamic acid, these compounds are potentially toxic[146]. In acute studies, these materials have a low to moderate order of oral toxicity (LD₅₀ values of 1.5–39 g/kg body weight)[148].

About 52% of cinnamaldehyde is absorbed through the skin and shown to be rapidly absorbed from the gut. It is metabolized and excreted as polar metabolites, the final major urinary metabolite is hippuric acid [148]. Novel intravenous sub-micrometre emulsion showed good tissue distribution and enhanced antitumor efficacy without significant toxicity in an animal model of cancer [149].

3.2.12. Kaempferol (KMF)

Kaempferol (3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) is a polyphenol abundant in fruits and vegetables, herbal medications, and beverages derived from plants. It's used to treat a variety of diseases [150]. Several studies suggested KMF has superior efficacy compared to many other natural compounds against SARS-CoV-2[151, 152]. KMF shares structural similarities with other flavonoids such as myricetin and dihydromyricetin, which showed strong inhibitory activity against the 3-chymotrypsin like protease(3CLpro) of SARS-CoV-2 [153]. KMF was shown to inhibit MERS 3CLpro (IC₅₀ = 35.3 μM) and SARS 3CLpro (IC₅₀ = 116.3 μM)[154]. Molecular docking documented strong interaction of KMF with SARs-CoV-2 Mpro 3CLpro[155]. This finding was confirmed by another docking study, which also documented an inhibition rate of about 90 % at a concentration of 62.5 μM cell protective effect (CPE) inhibition assay. The authors concluded that KMF was found to protect cells against virus-induced cell death, suggesting that it could be a promising SARS-CoV-2 antiviral treatment[151].

The ability of KMF to attenuate the experimentally induced lung injury are well documented, various mechanisms were suggested [156, 157]. KMF is expected to show low bioavailability,

therefore several studies suggested the utility of pharmaceutical approaches such as phospholipid complexes; solid dispersion, self-emulsifying formulation to enhance its bioavailability[158], Nano formulations were also investigated to improve PK characteristics of KMF [159]. On the other hand, KMF was found to enhance the bioavailability of some drugs after oral administration[160].

3.2.13. Rutin

Rutin, (a glycoside) also known as rutoside or quercetin-3-O-rutinoside, is a citrus flavonoid found in a range of plants, including **Citrus (Rutaceae)** and **Buckwheat or Fagopyrum esculentum (Polygonaceae) species** [161]. Several computations and *in vitro* testing suggest its activity against **SARS-CoV-2** [162, 163]. Based on the crystal structures of 3CLpro and RdRp, docking studies revealed that sulfate or glucuronide metabolite of rutin can inhibit these enzymes; which are essential for replication of **SARS-CoV-2**[164]. Moreover, it demonstrated a good ability to attenuate experimentally induced ALI[165], and potent thrombolytic activity[166].

Before being absorbed into the circulation, rutinosides like rutin and nicotiflorin are deglycosylated and subsequently conjugated mostly with glucuronate and sulfate, which are the predominant forms in plasma [167]. Intravenous or intranasal administration was suggested to improve the delivery of rutin [164]. Despite several preclinical mechanistic studies on its anticancer activities, the lack of well-designed randomized clinical trials on rutin's safety and therapeutic activity highlights the need for greater clinical research [168].

3.2.14. Leptodactylone

It is a coumarin isolated from **Leptodactylon pungens (Polemoniaceae)** and **Linanthus demissus (Polemoniaceae) species**, [169]. *In vitro* study was applied in Vero-E6 cells infected by SARS-CoV and measured the CPE by fluorescence microscope revealed that it produced 60 % protection of the infected cells (EC %) at 100 micro mols [170]. PK and safety data of **Leptodactylone** are not available.

3.2.15. Celastrol

It is a pentacyclic triterpenoid (belong to triterpene quinone methides) extracted

from *Tripterygium wilfordii* (Celastraceae)[171]. It has broad pharmacological activities [172]. Celastrol inhibits SARS-CoV-2 Mpro 3CLpro and acts as a superoxide radical scavenger, according to docking and other relevant studies[173]. Moreover, it showed promising *in vivo* results in animal models for inflammatory pulmonary diseases[174]. In rats, the pure compound showed poor bioavailability which improved after using an optimized tablet dosage form [175]. Several studies showed the utility of pharmaceutical techniques to enhance its PK characteristics [176, 177]. However, liver and kidney induced toxicity was demonstrated in animal studies[178]. More studies are needed to clarify the safety concern.

3.2.16. Tetrandrine (TET)

It is a bis-benzylisoquinoline alkaloid calcium channel blocker. It is isolated from the plant *Stephania tetrandra* (Menispermaceae). It has immunomodulatory effects and was found to be beneficial against inflammation, and lung cancer in clinical trials, with a favorable safety profile. It was demonstrated as effective against Ebola virus, Mycobacterium TB, Plasmodium falciparum, and Candida albicans. Tetrandrine's pharmacological properties have been demonstrated by its effects on many signaling pathways, including, calcium channel, suppression of formation of reactive oxygen species, increased autophagy, reversal of multidrug resistance, and caspase pathway[179]. It was suggested to act against the coronavirus by antagonism of the two-pore channel 2 (TPC2)[180]. It also decreased human coronavirus strain OC43 (HCoV-OC43) infection of MRC-5 human lung cells *in vitro*, with an inhibitory concentration (IC₅₀) of 0.33 µM/L [40]. It showed promising effects in the management of silicosis, and in one study it was given by inhalation to ameliorate lung fibrosis[181].

A published hypothesis, discussed in detail that TET can be considered a promising treatment for COVID-19. The research reviewed the multiple properties of the drug, including its ability to inhibit replication of related coronavirus at very low concentrations. Then, the researcher also discussed its PK and the possibility of achieving an effective concentration in lung tissue. They also reviewed the expected side effects; drug interactions and precautions to be considered in certain situations[180].

3.2.17. Pristimerin (Pris)

Pristimerin, a quinonoid triterpene, isolated from the Chinese herbal plant *Tripterygium wilfordii*

(**Celastraceae**), and it has been claimed that pristimerin has anti-fungal, anti-oxidant, anti-bacterial, and antiviral characteristics [182, 183]. It is active against SARS- CoV with an $IC_{50} = 5.5 \text{ } 0.7 \text{ M}$ According to several studies, pristimerin and its biological counterpart URB602 are monoglyceride lipase inhibitors, [184]. The formation of proteasomes was suppressed, NF-B activity and cyclin D1 expression were downregulated, and Bax, caspase, and cleavage of poly (ADP-ribose) polymerase PARP-1 were activated as part of pristimerin's anticancer activities.[185]. **Studies in animals showed that Pris has a half-life of about 2 hours and poor bioavailability of about 28 % after oral administration. It is primarily metabolized by phase I enzymes [186].**

3.2.17. Curcumin

It is described as a drug with multitarget for multiple chronic diseases. It has broad pharmacological activity. Its potential role in the management of COVID -19 was suggested [187, 188]. Curcumin **is a bright yellow chemical produced by plants of the *Curcuma longa* (**Zingiberaceae**) that** could potentially block ACE2 to prevent COVID-19 entrance into host cells, [189]. It also has a potential inhibitory effect on COVID-19 Mpro [190]. An *in vitro* study showed that treatment with cationic carbon dots based on curcumin can suppress coronavirus replication by stimulating the production of interferon-stimulating genes (ISGs) and cytokines (IL8 and IL6) of Vero cells by triggering the innate immunity of the host[191]. Curcumin has been shown to lower influenza A virus infection and its associated pneumonia. It suppresses virus-induced activation of several inflammatory pathways (TLR2/4, MAPK, and NFB). Given these findings, it was suggested that curcumin has a potential role in the treatment of COVID-19 induced lung complications[192]. Curcumin has anti-inflammatory and anti-fibrotic effects by several mechanisms[193]. Furthermore, in experimental models of lung fibrosis, curcumin has been demonstrated to decrease collagen formation[194]. A study showed that prophylactic application of curcumin decreased the inflammation and reduces the influx of fluid in the lungs of a rat model of induced hypoxia [195].

Curcumin has poor bioavailability and as such, it is not likely to show good tissue distribution. [196]. Some clinical trials suggested its good safety profile after oral administration [197]. However, it is considered unsafe for pregnant women. It can cause GIT side effects, and there are some reports of liver injury [198, 199].

3.2.18. Betulinic acid (BTA)

BTA is lupine-type pentacyclic triterpenoid saponin (3 β -hydroxy-lup-20). It is found in the bark of several natural plants, primarily *Betula pendula* (*Betulaceae*). Its anti-inflammatory, anti-angiogenic, and immunomodulatory properties, as well as its anti-human immunodeficiency virus effects, have been demonstrated. The majority of studies focused on its anticancer effects and postulated the underlying mechanisms [200, 201]. BTA was discovered to be a strong inhibitor of (SARS-CoV) *in vitro* [202]. Molecular modelling analysis indicated that BTA interacts with coronavirus (SARS-CoV) 3CL protease [203]. Several studies suggested BTA ability to attribute experimentally induced lung injury by several mechanisms [204, 205]. BTA has very low water solubility that explains its low bioavailability. Some derivatives were suggested to improve its bioavailability while retaining its antitumor activity [206]. Other studies utilized pharmaceutical techniques such as liposomes, nanosuspension, nanoencapsulation analogue [5, 207] to improve its bioavailability. In animal experiments, a good safety profile was documented [208].

4. Conclusion:

- 1) Many phytochemicals have been suggested to have potent anti-SARS-CoV-2 activity based on *in vitro* testing. However, preclinical research is sparse, and only a few compounds were tested in clinical trials against COVID-19.
- 2) Extensive research is needed to provide a full pharmacological profile of phytochemicals that showed promising efficacy against SARS-CoV-2.
- 3) The pharmacokinetics (PK) features of phytochemicals could be improved with pharmaceutical technologies. Table 3 summarizes the bioavailability of several substances as well as techniques to improve them.
- 4) Decision-makers, researchers, and pharmaceutical companies will benefit from this study.

plasma concentration of phytochemicals	Oral	Nasal/ Rectal	Intravenously (IV)/ Intrapertoneal Route (IP)	Enhancer and notes
Glycyrrhizin	Extremely low	Nasal-80-fold greater compared with oral administration. Rectal administration greater compared with oral		Sodium caprate > sodium laurate > sodium caprylate > sodium oleate.
Resveratrol	Preferred and only viable route Except for the topical application			Low water solubility which affects its absorption. To increase its solubility, ethanol or organic solvents may be used Dose-dependent
Lycorine			No significant difference between the two administration routes (IP, iv)-The concentration in plasma was undetectable, which indicated that lycorine cleared quickly from the body	
Emodin	Not the best method because of poor intestinal absorption, fast elimination, and low bioavailability			Gender-dependent
Aescin	Film-coated tablet with sustained-release allowed a high bioavailability			
Reserpine	The oral route is rapidly absorbed, reaching its peak concentration level after approximately 2 hours			
G-RB1[213]	The low oral bioavailability of ginsenoside- RB1 and rapid reduction of ginsenoside-Rg1 in blood indicated that formula modification is			

	necessary			
CELASTROL	To greatly improve absorption of celastrol when use celastrol-containing Thunder God Vine (TGV) tablets are orally administered.			Gender-dependent

UNDER PEER REVIEW

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