Review Article

Reconsidering the Role of Phytochemicals against Covid 19 in Light of their Pharmacological Profiles and Pharmaceutical Technology

ABSTRACT

Many publications discussed the potential role of phytochemicals; in the management of COVID-19. Most described the potency and mechanisms of antiviral activity of certain compounds against coronaviruses. Other publications explored the potential efficacy of some natural compounds in the management of lung injury and other complications. However, limited publications deal with pre-clinical or clinical studies to demonstrate the efficacy and safety of these phytochemicals. A gap in knowledge regarding the pharmacology of most compounds was realized. Moreover, limited studies demonstrated the role of pharmaceutical technology to enhance the bioavailability or development of lung delivery formulations of these compounds. Some compounds showed favorablepharmacology profiles that suggest them as candidatesfor more pre-clinical and clinical investigations. These include eucalyptol (1, 8-cineole) and cinnamaldehyde. Pharmaceutical technology and novel delivery system such as inhalation could enhance the pharmacokinetics (PK) characteristics of phytochemicals.

Key words: phytochemicals; COVID-19; SARS-CoV-2; eugenol;eucalyptol(1,8-cineole); nanotechnology;viral pneumonia.

Abbreviations and glossary of terms

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.

Intoduction

1. COVID 19

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 confirmed, with more than 3.92 million confirmed deaths(Roser, Ritchie et al. 2021). More details are available in many reviews(Chakraborty and Maity 2020, Yang, Yu et al. 2020, Singh, Pritam et al. 2021).Tremendous effort has been given to the development of diagnostic tests, vaccines, and repurposing of drugs for optimal management of COVID-19(Wang, Hozumi et al. 2020).

2. Potential role of phytochemicals

This narrative review was based on PubMed search, English, using advanced drug search, of relevant terms, phytochemicals, natural compounds, Sars-cov 2, Covid-19. Initially, about 900 relevant articles were found, of which about 350 articleswere selected and summarized to highlight the potential value, the gap in knowledge in pharmacokinetics (PK) and detailed safety studies.

2.1 Overview of the potential role of phytochemicals in the management of COVID 19

A comprehensive web-based resource for natural products (about 200 compounds) was launched in 2020 (Monticolo, Palomba et al. 2020). Several review articles included an extensive search for medicinal plant extracts, compounds that have been identified and proven to affect the coronavirus. These reviews summarized the IC50, selectivity, mechanisms of action and structure of specified compounds including polyphenols(Annunziata, Sanduzzi Zamparelli et al. 2020, El-Missiry, Fekri et al. 2020, Paraiso, Revel et al. 2020). Flavonoids(Russo, Moccia et al. 2020, Solnier and Fladerer 2020)of which myricetin and scutellarin(Keum and Jeong 2012) were highlighted. Alkaloids (Kim, Min et al. 2019, Wink 2020)particularly lycorine(Li, Chen et al. 2005, Jin, Min et al. 2020) was of considerable interest, other alkaloids include tetrandrine, tangchinoline,cepharanthine(Kim, Min et al.)andreserpine(Wu, Jan et al. 2004). Sterols(Hisham Shady, Youssif et al. 2020),terpenoids(Wen, Kuo et al. 2007)(Chang, Yen et al. 2012),stilbenoid, resveratrol(Lin, Ho et al. 2017),triterpene glycoside (saponin) glycyrrhizin (Hoever, Baltina et al. 2005), and saponin (Aescin)(Wu, Jan et al. 2004). Tannins (tannic acid), 3-isotheaflavin-3-gallate, theaflavin-3,3′-digallate (Chen, Lin et al. 2005), and essential oils(Boukhatem and Setzer 2020, Senthil Kumar, Gokila Vani et al. 2020, Wilkin, Al-Yozbaki et al. 2020).

Many publications provided an overview of the utility of phytochemicals against COVID-19(Islam, Sarkar et al. 2020, Khalifa, Yosri et al. 2020, Boozari and Hosseinzadeh 2021).Some provided a detailed description of a specified compound(s) e.g., curcumin(Zahedipour, Hosseini et al.),valinomycin (Zhang, Ma et al. 2020),tanshinones(Park, Kim et al. 2012),resveratrol (Giordo, Zinellu et al. 2021) and glycyrrhizin (Cinatl, Morgenstern et al. 2003); or plant e.g. *Nigella sativa*(Islam, Hossain et al.).A non-comprehensive list was provided in tables 1-3. Structures of some compounds are presented in figure 1.

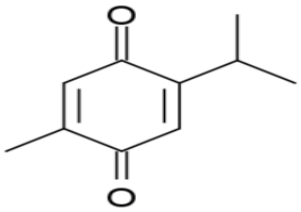
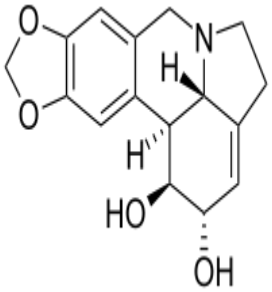
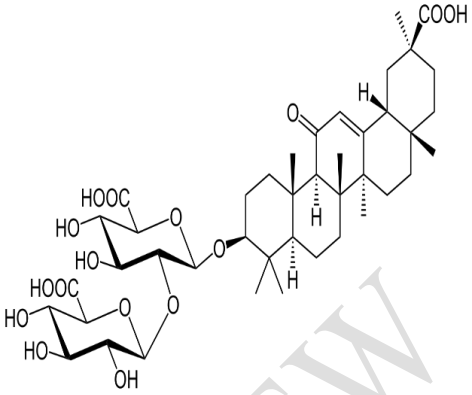
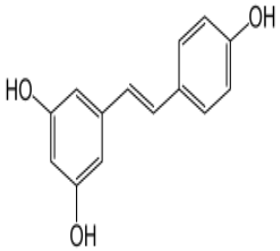
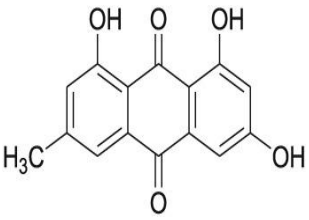
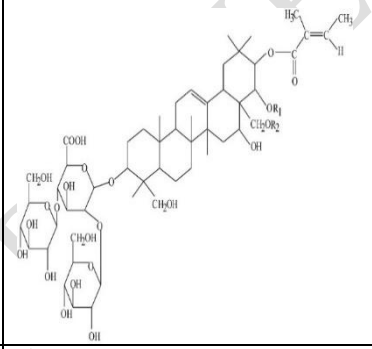
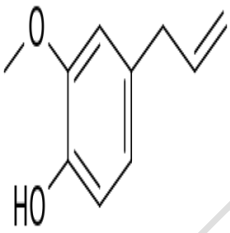
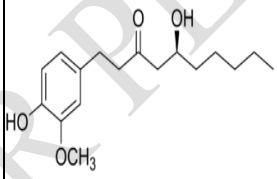
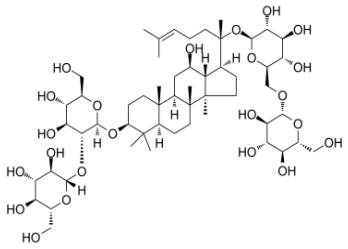
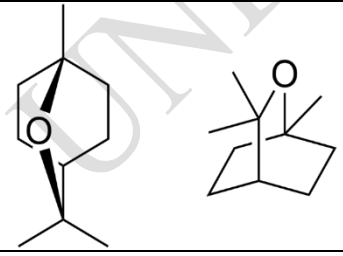
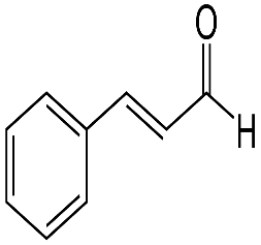
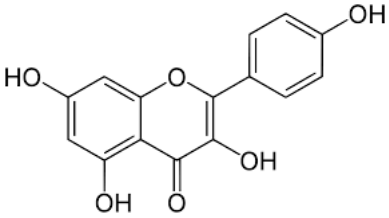
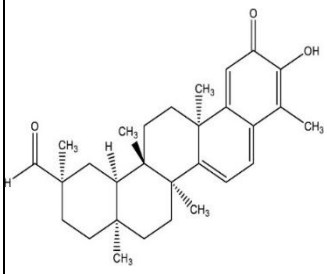
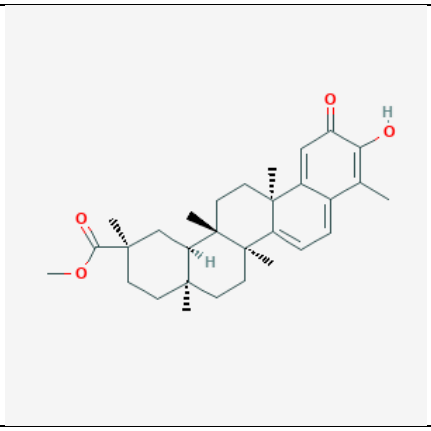
		
Thymoquinone	**Lycorine (LYC)**	**Glycyrrhizin**
		
Resveratrol	**Emodin**	**Aescin (Esc) (N-3)**
		
Eugenol	**Ginger**	**Ginsenoside-Rb1**
		
Eucalyptol	**Cinnamaldehyde**	**Kaempferol**

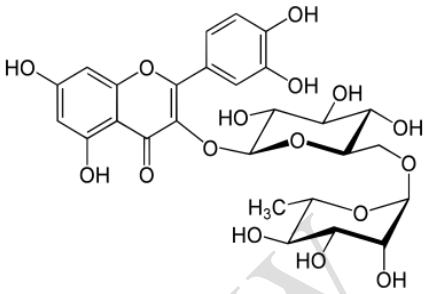
Figure 1: Structure of selected phytochemicals of potential role in management of COVID 19



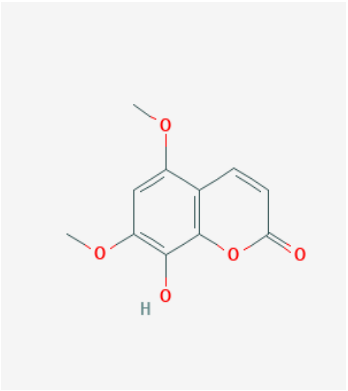
Celastrol



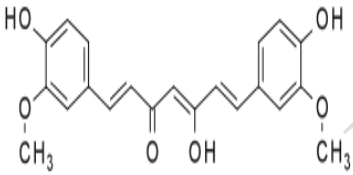
Pristimerin



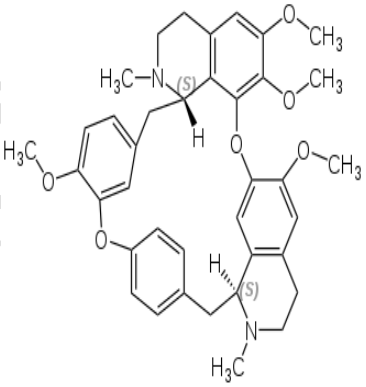
Rutin



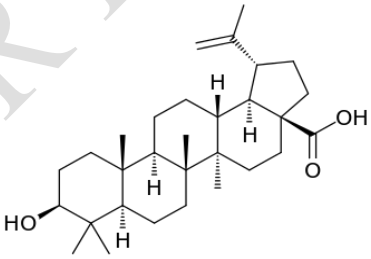
Leptodactylone,



Curcumin



Tetrandrine



Betulinic acid

Figure 1: Structure of selected phytochemicals of potential role in management of COVID 19

Table 1: Compounds suggested to interact with any of these targets of SARS COV- 2 Spike protein, 3CLpro or PLpro(Monticolo, Palomba et al. 2020).		
Compound	Class/ source	mechanism
Betulinic acid	Pentacyclic triterpenoid	3CLpro
Dihomo-γ-linolenic acid	ω−6 fatty acid.	3CLpro
Dihydrotanshinone	*Salvia miltiorrhiza*	Spike protein
TanshinoneIIa	*Salvia miltiorrhiza*	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 (Orhan and Senol Deniz 2020)

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
Broussochalcone B	Flavonoid	IC_{50} = 57.8 μM	SARS-CoV
Papyriflavonol A	Flavonoid	IC_{50} = 103.6μM	SARS-CoV
Terrestrimine	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 (Orhan and Senol Deniz 2020)

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} = 9.9μM	SARS-CoV
Iguesterin	Triterpene	IC_{50} = 2.6μM	SARS-CoV
Pristimererin	Triterpene	IC_{50} = 5.5μM	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
FRIL Lectin	Lectin	EC_{50} = 6.25 μg/ml	SARS-COV-2
APA Lectin	Lectin	EC_{50} = 0.45 μg/ml	SARS-CoV
UDA Lectin	Lectin	EC_{50} = 1.3 μg/ml	SARS-CoV

Other compounds are not listed above.

Resveratrol, EmodinAescin, Ginsenoside-Rb1, Leptodactylone,Celastrol, Tetrandrine, Cepharanthine, S-aikosaponinB_2, Quercetin-3-b-galactoside, Chalcones, Theaflavin, Myricetin, Scutellarein(Ho, Wu et al. 2007, Kim, Min et al. 2019, Fan, Wang et al. 2020, Lung, Lin et al. 2020, Zhang, Zhang et al. 2020, Pasquereau, Nehme et al. 2021, Zhang, Yang et al. 2021), thymoquinone and others from Islamic medicine.

Essential oils

Essential oils with potential antiviral and immunomodulating activity,8-cineole (eucalyptol), allyl sulfide, farnesene, farnesol, nerolidol; eugenol,menthol,carvacrol, cinnamaldehyde(Barboza, da Silva Maia Bezerra Filho et al. 2018, Huang, Liang et al. 2019, Silva, Figueiredo et al. 2020, Thuy, My et al. 2020).

2.2 Brief pharmacological Profile of selectedphytochemicals, focusing on their safety profile, pharmacokinetic (PK) and pharmaceutical approaches to improve.

2.2.1. Thymoquinone

It is a quinone compound found in the plant *Nigella sativa*. It has a broad pharmacological activity, and a good safety profile (Imran, Rauf et al. 2018). Its potential role in the management of Covid -19 was suggested based on its potential antiviral activity and ability to attenuate lung injury and inflammation (Isik, Kati et al. 2005, Al-Gabri, Qaid et al. 2019, Çolak, Kalemci et al. 2020, Sommer, Försterling et al. 2020). Thymoquinone has poor oral bioavailability[(Pathan, Jain et al. 2011)]and is likely due to its low solubility in water. Pharmaceutical formulations and nano delivery systems were suggested to improve its bioavailability and distribution(Goyal, Prajapati et al. 2017, Ansar, Latifah et al. 2020, Rathore, Rathbone et al. 2020)

2.2.2. Lycorine

Lycorine is a *phenanthridine Amaryllidaceae*alkaloid isolated from the bulbs of *Lycoris radiata* (L'Hér.) herb. It has broad pharmacological activity(Cao, Yang et al. 2013), it has potent activity against SARS-CoV with an EC50 value of 15.7 ± 1.2 nM. and selective index (SI) > 900(Li, Chen et al. 2005). 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 (Zhang, Zhang et al. 2020).

An animal study showed a very high volume of distribution but a short half-life(Ren, Zhao et al. 2014). Pre-clinical investigations are needed to determine other PK parameters such as protein binding and metabolism.

2.2.3. Glycyrrhizin

It is triterpene glycoside (saponin), which is also known as glycyrrhizinic acid isolated from *Glycyrrhiza glabra*. It has several pharmacological activities (Pastorino, Cornara et al. 2018). The compound or its active metabolite expresses antiviral effects against SARS-CoV in cell culture(Chen, Chan et al. 2004). *In vitro* studies demonstrated that glycyrrhizinic potently neutralizes SARS-CoV-2 by inhibiting the viral main protease (Mpro)(van de Sand, Bormann et al. 2020). It exhibited anti-inflammatory potential by several mechanisms including suppression of several proinflammatory mediators (Yang, Yuan et al. 2017).

Its low bioavailability, low volume of distribution suggest that it is not likely to achieve an

effective antiviral concentration of glycyrrhizinic 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.

2.2.4. Aescin(escin)

It's a blend of triterpene saponins extracted from the seeds of the *Aesculus Hippocastanum* (horse chestnut tree).It has a high molecularweight (M Wt.)(Yoshikawa, Murakami et al. 1998).It possessesantiviral and immunomodulatory activities(Gallelli, Zhang et al. 2020).It has been widely used in the clinical treatment of traumatic oedema, and chronic venous insufficiency(Gallelli 2019),escin was demonstrated to inhibit acute inflammation is similar to corticosteroids(Wu, Jan et al. 2004). The EC 50 for escin against SARS-CoVwas 6 µM(Wu, Jan et al. 2004). 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(Gallelli 2019). Injection formulation was registered in China and Italy for clinical trials to treat patients with COVID-19 pneumonia(López-Alcalde, Yan et al. 2020).

Escinis not absorbed orally (bioavailability< 0.3%);likely due to extensive first-pass metabolism(Wu, Zhang et al. 2012). EscinIaPK features were studied in rats following IV injection at dosages ranging from 0.5 to 2.0 mg/kg. The half-life of escinIa was about 7-12 hr., Vd l/Kg 3-6 L/Kg(Wu, Zhang et al. 2012). PK data in humans not available, calculated EC50 = 7 µg/ ml. against SRAS-COV, but efficacy against SARS-COV 2 was not studied.

2.2.5. Resveratrol

Resveratrol, a polyphenol compound (3,5,4'-trihydroxystilbene) found in grapes, mulberry and peanuts, possesses antioxidant, antitumor, antiviral and free radical scavenging properties(Marinella 2017).

Among the seven drugs tested against HCoV-229E *invitro*, resveratrol demonstrated a favourable antiviral effect superior to two tested drugs (EC50) = 4.6 µM) and lopinavir/ritonavir (EC50 = 8.8 µM), and Chloroquine (EC50 = 5 µM). Resveratrol has also the best selectivity index (SI) of 45.65 (Pasquereau, Nehme et al. 2021). The study documented its ability to attenuate lung injury in a variety of animal models and multiple mechanisms were suggested(Baur and Sinclair 2006). A meta-analysis of clinical trials documented its ability to reduce biomarkers of inflammation, TNF-α, and C-reactive protein(Koushki, Dashatan et al.).

Resveratrol has poor oral bioavailability due to extensive metabolism 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 administrationare not likely to achieve an effective antiviral level(Baur and Sinclair 2006). However, the optimized pharmaceutical formulation may solve this limitation e.g., nanotechnology-based formulations andliposomes(Huang, Liang et al. 2019, Lin, Hu et al. 2020).Clinical studies showedfavorable safety outcomes of resveratrol. A good safety profile was assured with doses up to 500 mg/d for 60 days (Movahed, Raj et al. 2020). Most reported adverse effects are mild GIT symptoms such as diarrhea(Cottart, Nivet-Antoine V Fau - Beaudeux et al.).However, an advanced delivery system is needed to improve its PK profile.

2.2.6. Emodin

Emodin (6-methyl-1,3,8-trihydroxyanthraquinone) is found in many plants such asChinese rhubarb (Rheum palmatum)(Agrawal, Tsay et al. 2017);it has many effective preventive and therapeutic effects (Cui, Chen et al.). It was demonstrated to blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction, 200 μMlikely block viral entry into host cells (Ho, Wu et al. 2007). It is one of the top 16 network-predicted re-purposed drugs against SARS-COV and is suggested among drug combinations(toremifene plus emodin)(Zhou, Hou et al. 2020). It is included among traditional Chinese medicine against viral infections (Runfeng, Yunlong et al. 2020). Its ability to attenuate lung injury is well documented in an animal model(Dong, Zhang et al. 2019).

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(Dong, Fu et al. 2016).Relatively it has low potency against SARS-COV (Basu 2020), suggest it is very difficult to achieve an effective level in the lung tissues.

2.2.7. Ginsenoside-Rb1

G-Rb1 appears to be most abundant in *Panax quinquefolius* (American Ginseng).Ginsenosides possesses a variety of potential health effects(Popovich, Yeo et al. 2012). The ability of ginseng to attenuate experimentally induced lung injury are well documented, several mechanisms were discussed(Jiang, Zhou et al. 2015). Molecular docking analysis indicated that ginsenosides have the potential to inhibit SARS-CoV-2 Mpro receptor(Garg, Anand et al.)

Genesiondis have very low bioavailability after oral administration(Tan, Xiong et al. 2013). Several studies documented the feasibility of enhancing its bioavailability by adopting several approaches(Zeng, Pan et al. 2013, Tam, Truong et al. 2018).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 adverse effects were seen(Carabin, Burdock et al. 2000).

2.2.8. Eugenol

Eugenol is a phenolic molecule (methoxy phenols, m. wt. 164.2) found in several plants such as cinnamon, clove,Tulsi.The potential value of clove and eugenol against COVID-19 was suggested based on their antiviral, anti-inflammatory, and antithrombotic effects(Vicidomini, Roviello et al. 2021). Docking analysis indicated the possible interaction of α-pinene and eugenol with SARS-CoV spike protein(Saxena, Kumar et al. 2021). The ability of eugenol to attenuate experimentally acute induced lung injury was documented(Zhang, Yang et al. 2021). It is likely mediated by the inhibition of lipoxygenase and cyclooxygenase pathways(das Chagas Pereira de Andrade and Mendes 2020).

In mice, eugenol was ready absorbed after oral administration. The mean plasma half-life was about14 hrs.suggesting a potential accumulation of the drug following repeated administrations(Guénette, Ross et al. 2007).A good safety profile was demonstrated in animal toxicity studies (Dhara and Tripathi 2020). It is generally recognized as safe by the food and drug administration(FDA)(Meeting and Organization 2013). However, local hypersensitivity reaction was reported in dental practice (Sarrami, Pemberton et al. 2002).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.

2.2.9. Gingerol

Gingerol, or [6] - gingerol, is a phenolic compound found in fresh ginger(*Zingiber officinale*).Pre-clinical *in vitro* and animal models documented a broad spectrum of therapeutic values(Butt and Sultan 2011), 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(Akinyemi, Thomé et al. 2016), inhibition of lipopolysaccharide (LPS)-induced inflammatory responses in macrophages(Villalvilla, da Silva et al. 2014), the potential of the

anti-inflammatory effect of some drugs such as paracetamol(Montserrat-de la Paz, Garcia-Gimenez et al. 2018).Other studies documented the therapeutic benefits in the management of allergic asthma and allergic rhinitis(Kardan, Rafiei et al. 2019, Yocum, Hwang et al. 2020).

Pharmacokinetic (PK) studies showed that, in general, is well absorbed orally and has good tissue distribution (Li, Cui et al. 2019, Simon, Darcsi et al. 2020). A good safety profile was reported in clinical trials(Wang, Zhang et al. 2014),several pharmaceuticalnanotechnology approaches were suggested to enhance its systemic availability or distribution(Wang, Wei et al. 2018, Wei, Yang et al. 2018).

2.2.10. 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 (Gilles, Zhao et al. 2010),it has low toxicity (LD50 for rats 2.5 g/kg)(Carabin, Burdock et al. 2000). It showed the ability to attenuate ALI in an animal model by different mechanisms(Gondim, Serra et al. 2019, Reis, Orak et al. 2021). A comprehensive review of the ability of essential oil to suppress several respiratory viruses was studied by Wani et al.(Wani, Yadav et al. 2021).

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(Bastos, Brito et al. 2009).Furthermore, investigations have shown that inhaling cineole has analgesic and anti-inflammatory properties, suggesting that it could be utilized to treat COPD and asthma(Juergens, Worth et al. 2020). Sharma et al. (Sharma and Kaur 2020)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(Sadlon and Lamson 2010).

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.

2.2.11. Cinnamaldehyde

Cinnamaldehydeisan active ingredient in the bark ofcinnamon trees and other species of the genus *Cinnamomum*. The essential oil of cinnamon bark contains> 90% cinnamaldehyde (predominantlythe Trans E- isomer) synthetic compound is also available.According to docking experiments, cinnamaldehyde may prevent SARC-CoV-2 from attaching to its target receptors (Kulkarni, Nagarajan et al. 2020). Cinnamaldehyde's preventive benefits in the animal model of ALI have been demonstrated(Almoiliqy, Wen et al. 2020). Different mechanisms were demonstrated, for example,LPS in the ALImodel; including neutrophils, macrophages, and total cell number in bronchoalveolar lavage fluid is inhibited. It reduced the levels of inflammatory cytokines such TNF-, IL-6, IL-13, and IL-1(Huang and Wang 2017).

Cinnamaldehyde is approved by the FDA for use within allergenic epicutaneous patch tests(Zhu, Liu et al. 2017). It has had a low potential for toxicity but weak sensitization reactions in animals and human skin allergy were reported(Isaac-Renton, Li et al. 2015). It is metabolized to cinnamyl alcohol and methyl cinnamate and cinnamic acid, these compounds are potentially toxic(Zhu, Liu et al. 2017). In acute studies, these materials have a low to moderate order of oral toxicity (LD50 values of 1.5–39 g/kg body weight)(Panel, Belsito et al. 2007).

About 52% of cinnamaldehyde isabsorbed 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(Panel, Belsito et al. 2007). Novel intravenous submicrometeremulsion showed good tissue distribution and enhanced antitumor efficacy without significant toxicity in an animal model of cancer (Zhao, Yuan et al. 2015).

2.2.12. 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 (Alam, Khan et al. 2020).Several studies suggested KMF has superior efficacy compared to many other natural compounds against SARS-COV-2(Khan, Heng et al. 2021, Mehmood, Khan et al. 2021). KMF shares structural similarities with other flavonoids such as myricetinanddihydromyricetin, which showed strong inhibitory activity against the 3-

chymotrypsin like protease(3CLpro) of SARS-COV-2 (Dai, Zhang et al. 2020). KMF was shown to inhibit MERS 3CLpro (IC50 = 35.3 μM) and SARS 3CLpro (IC50 = 116.3 μM)(Jo, Kim et al. 2020). Molecular docking documented strong interaction of KMF with SARs-CoV-2 Mpro 3CLpro(Khan, Ali et al. 2020). This finding was confirmed by another docking study, which also documented an inhibition rate of about 90 % at a concentration of 62.5 μM (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 SARSCoV2 antiviral treatment(Khan, Heng et al. 2021).

The ability of KMF to attenuate the experimentally induced lung injury are well documented, various mechanisms were suggested(Qian, Chen et al. 2019, Yang, Wei et al. 2021). KMF is expected to show low bioavailability, therefore several studies suggested the utility of pharmaceutic approaches such as phospholipid complexes; solid dispersion, self-emulsifying formulation to enhance its bioavailability(Chen, Sun et al. 2010), nanoformulations were also investigated to improve PK characteristics of KMF (Du, Chen et al. 2019). On the other hand, KMF was found to enhance the bioavailability of some drugs after oral administration(Jackson, Anderson et al. 2020).

2.2.13. 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 and buckwheat species (Jiang, Burczynski et al. 2007). Several computations and *in vitro* testing suggesting its activity against SARS-COV 2(Ibrahim, Mohamed et al. 2021, Rizzuti, Grande et al. 2021). 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(da Silva, da Silva et al. 2020). Moreover, it demonstrated a good ability to attenuate experimentally induced ALI(Huang, Horng et al. 2016), and potent thrombolytic activity(Dar and Tabassum 2012).

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(Barrington, Williamson et al. 2009). Intravenous or intranasal administration was suggested to improve the delivery of ruin (da Silva, da Silva et al.

2020).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(Imani, Maleki et al. 2021).

2.2.14. Leptodactylone

It is a coumarin isolated from *Leptodactylon* and *Linanthus* species, it is also isolated from *Boenninghauseniasessilicarpa*(Yang, Tian et al. 2007). *In vitro* studywas applied inVero-E6 cells infected by SARS-CoV and measuring the cell-protective effects (CPE) by fluorescence microscope. revealed that Lept produced 60 % protection of the infected cells (EC %) at 100 micro mols (Dean, Costa et al. 1978),pharmacokinetic and safety data of Leptodactyloneare not available.

2.2.15. Celastrol

It is a pentacyclic triterpenoid (belong to triterpene quinine methides) extracted from *Tripterygium wilfordii* (TW)(Salminen, Lehtonen et al. 2010),it has broad pharmacological activities(Ng, Chan et al. 2019). Celastrol inhibits SARS-COV 2 Mpro 3CLpro and acts as a superoxide radical scavenger, according to docking and other relevant studies(Caruso, Singh et al. 2020). Moreover, it showed promising *in vivo* results in animal models for inflammatory pulmonary diseases(Habtemariam, Nabavi et al. 2020).

In Rats the pure compound showed poor bioavailability which improved after using a related tablet form (Zhang, Li et al. 2012). Several studies showed the utility of pharmaceutical techniques to enhance its PK characteristics (Qi, Qin et al. 2014, Freag, Saleh et al. 2018). However, liver and kidney induced toxicity was demonstrated in animal studies(Wu, Chen et al. 2018),more studies are needed to clarify the safety concern.

2.2.16. Tetrandrine (TET)

It is a bis-benzylisoquinoline alkaloida calcium channel blocker. It is isolated from the plant *Stephania tetrandra*,it has immunomodulatory effects. It was found to be beneficial against inflammation, and lung cancer in clinical trials, with a favorable safety profile. It was also suggested that it was effective against the 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(Xu, Kusano et al. 2020).

It was suggested to act against the coronavirus by antagonism of the two-pore channel 2 (TPC2)(Heister and Poston 2020). 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 (Kim, Min et al. 2019). It showed promising effects in the management of silicosis, in one of these studies it was given by inhalation to ameliorate lung fibrosis(Su, Liang et al. 2020).
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(Heister and Poston 2020).

2.2.17. Pristimerin (Pris)

Pristimerin, a quinonoid triterpene, is a biological component isolated from the Chinese herbal plant Tripterygium wilfordii Hook, Celastraceae, and it has been claimed that pristimerin has anti-fungal, anti-oxidant, anti-bacterial, and antiviral characteristics [(Kim, Park et al. 2013, enzolifescience 2021). SARS COV IC50 = 5.5 0.7 M has been observed to be inhibited by it. According to several studies, pristimerin and its biological counterpart URB602 are monoglyceride lipase inhibitors, which could help us better understand how monoglyceride lipase works(Gastaldi, Marino et al. 2019). The creation of proteasomes was suppressed, NF-B activity and cyclin D1 expression were downregulated, and Bax, caspase, and PARP-1 were activated as part of pristimerin's anticancer activities.(Yang, Landis-Piwowar et al. 2008).
Pristimerin concentrations reached a maximum of 243.66 20.18 ng/mL after intravenous injection of 1 mg/kg, whereas pristimerin was poorly absorbed and reached Cmax 46.8 3.94 ng/mL at roughly 2.0 h after oral administration of the same dose. It took 1.84 hours to complete the half-life. By the oral route, pristimerin's absolute bioavailability was 28.4 percent, and its bioavailability was poor.The findings revealed that pristimerin has limited bioavailability, is

difficult to absorb in the intestine, and is primarily processed by phase I enzymes (Dong, Xu et al. 2015).

2.2.17. 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(Saeedi-Boroujeni, Mahmoudian-Sani et al. 2021, Thimmulappa, Mudnakudu-Nagaraju et al. 2021). Curcumin could potentially block ACE2 to prevent COVID19 entrance into host cells, according to in silico docking study(Utomo and Meiyanto 2020),it alsohas a potential inhibitory effect on COVID-19 Mpro (Khaerunnisa, Kurniawan et al. 2020).An *in vitro* study showed that treatment with cationic carbon dots based on curcumin can suppress coronavirus reproduction 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(Ting, Dong et al. 2018).Curcuminhas 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(Dai, Gu et al. 2018).

Curcumin has anti-inflammatory and anti-fibrotic effects by several mechanisms(Avasarala, Zhang et al. 2013). Furthermore, In experimental models of lung fibrosis, curcumin has been demonstrated to decrease collagen formation(Xu, Deng et al. 2007).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 (Titto, Ankit et al. 2020).

Curcumin has poor bioavailability and as such, it is not likely to show good tissue distribution. In the case of enhancing bioavailability or parenteral administration also due to its ability to interact with many proteins, potential adverse effects should be considered (Nelson, Dahlin et al. 2017). Some clinical trials suggested its good safety profile (oral administration) (Ryan, Heckler et al. 2013). However, It is considered unsafe for pregnant women; can cause GIT side effects, and there are some reports of liver injury (Balaji and Chempakam 2010, Luber, Rentsch et al. 2019)

2.2.18. Betulinic acid (BTA) and its analogue

BTA is lupine-type pentacyclic triterpenoid saponin (3β-hydroxy-lup-20) M Wt.approximately

457. It is found in the bark of several natural plants, primarily Betula. Its anti-inflammatory, anti-angiogenic, and immunomodulatory properties, as well as its anti-human immunodeficiency virus effects, have all been demonstrated. The majority of studies focused on its anticancer effects and postulated underlying mechanisms(Zhang, Hu et al. 2016)(Hordyjewska, Ostapiuk et al. 2019).

BTA was discovered to be a strong inhibitor of (SARS-CoV) *in vitro*(Wen, Kuo et al. 2007). Molecular modelling analysis indicated that betulinic acid interacts with coronavirus (SARS-CoV) 3CL protease(Pillaiyar, Manickam et al. 2016). Several studies suggested BTA ability to attribute experimentally induced lung injury by several mechanisms(Nader and Baraka 2012, Lingaraju, Pathak et al. 2015).

Betulinic acid has very low water solubility that causes low bioavailability,some derivatives were suggested to improve its bioavailability and retain antitumor activity(Gauthier, Legault et al. 2006). Other studies utilized pharmaceutical techniques such as liposomes, nanosuspension, nanoencapsulation analogue(Dutta, Paul et al. 2019, Wang, Hozumi et al. 2020).In an animal experiment, to test its potential anticancer activity which involves intraperitoneal administration of 10 mg/kg/day, a good safety profile was documented (Zeng, Yu et al. 2018).

Conclusion:

Many natural substances have been suggested to have anti-SARS-COV-2 action in vitro. However, preclinical research is sparse, and only a few substances have shown promising pharmacology profiles, for example good bioavailability (Table3)indicating that they could be candidates for clinical trials. The pharmacokinetics (PK) features of these substances could be improved with new pharmaceutical technologies and delivery systems.

Table 3: Bioavailability of phytochemicals)Li, Weihong et al. 2007, Jo, Shrestha et al. 2016, Yang, Zhai et al. 2018, Semwal, Chauhan et al. 2020, Gurjar and Pal 2021, Lima, Andrade et al. 2021(				
plasma concentration of phytochemicals	**Oral**	**Nasal/ Rectal**	**Intravenously (IV)/ Intraperitoneal 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	Oral route is rapidly absorbed, reaching its peak concentration level after approximately 2 hours			

RB1(Jo, Shrestha et al. 2016)	The low oral bioavailability of RB1 and rapid reduction of Rg1 in blood indicated that formula modification is necessary			
CELASTROL	To greatly improved absorption of celastrol when use celastrol-containing TGV tablets are orally administered.			Gender-dependent

NOTE:

The study highlights the efficacy of "traditional chinesse medicine" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable.

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