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Covid-19 treatment by plant compounds

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Abstract

The COVID-19 pandemic is a global public health epidemic, with significant mortality and morbidity, including critical care, putting a strain on health care services. In the city of Wuhan, China, a novel coronavirus called SARS-CoV-2 appeared at the end of 2019, causing an outbreak of unusual viral pneumonia. A type of coronavirus disease belonging to the family Coronaviridae is COVID-19. Moreover, the disease's symptoms include fever, dry cough, tiredness. It is possible to foresee numerous options to monitor or avoid emerging 2019-nCoV infections, including small-molecule drugs, interferon therapies, and Vaccines. Novel interventions may take a long time.

Keywords: Phytochemicals against; Herbal Medicines; Severe Acute Respiratory Syndrome; COVID-19; MERS-CoV; SARS-CoV.

1 Introduction

Serious mortality has been caused by a new coronavirus associated with a respiratory infectious illness. Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is the name of the virus. In numerous countries containing Saudi Arabia, this new MERS-CoV first was viewed [1]. In Wuhan, China, a recent coronavirus with the ability to transmit the infection from human to human that inducementating an exclusively earnest disease was reported around the end of December 2019 [2]. The name of the virus was SARS-CoV-2 and Coronavirus Disease 2019 (abbreviated "COVID-19") was named for the disease it causes. Most people infected with COVID-19 will meliorate without needing particular therapy and will experiment with light to medium respiratory disease. Older people especially those with underlying medical conditions for instance cancer, chronic respiratory disease, cardiovascular disease, and diabetes are most might progress in earnest diseases (WHO, 2020a)[3-6]. Pneumonia affected by extreme hot respiratory syndrome infection with coronavirus 2 (SARS-CoV-2) occurred in December 2019, in Wuhan City, Hubei Province, China. COVID-19 demonstrates a diversity of clinical symptoms that typically include fever, dry cough, and tiredness, often with pulmonary involvement. SARS-CoV-2 is extremely infectious and most people are vulnerable to infection within the population at large.

2 Life cycle and genome structure of coronavirus

COVID-19 structure is consists of RNA inside a capsid that contain a matrix protein and is a pleomorphic or spherical enveloped particle-containing nucleoprotein-associated single-stranded (positive-sense)[5, 7, 8].

Figure 1 shows that the spherical envelope contains hem agglutinin-esterase protein (HE) or club-shaped glycoprotein-projections.

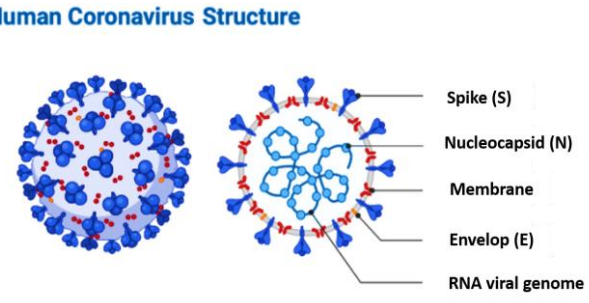

Figure 1. Human coronavirus structure [https://app.biorender.com].

3 Antiviral Activity of Herbal Medicines Coronaviruses and Phytochemicals against

For this purpose, highly useful sources may be medicinal plants, culinary spices, herbs, and aromatic herbal teas used in ethnobotanical therapy. During the SARS epidemic of 2003 [9], The effectiveness and productivity of herbal therapy and phytomedicine have been shown to prevent viral infections. Therefore, the usage of medicinal plants and herbs to struggle SARS-CoV-2 infections is promoted by numerous countries, containing Algeria [6, 9-18].

Scientists and Researchers have been impellent efforting to discover various molecules, antiviral extracts, and medicine against SARS-CoV, that first recognized in early 2003, following the prevalence of SARS-CoV. This prompted researchers to screen over 200 aromatic herbs, culinary spices, and medicinal plants against this SARS-CoV strain for it is antiviral properties[19]. Numerous groups began searching for anti-coronavirus agents after the outbreak of SARS, as well as certain phytochemical extracts and natural combinations that exist in traditional herbal medicines [12, 20-22]. Various studies documenting the inhibitory impact of

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isolated compounds or medicinal plants on various human coronavirus strains are accessible in Table 1.

Amongst mentioned items, four extracts represented mild to strong SARS-CoV inhibition impacts that include, Pyrrosia lingua (fern), *Lycoris radiata* (red spider lily) (Figure 2a), *Artemisia annua* (sweet wormwood) (Figure 2b), and *Lindera aggregata*, a member of the laurel family, which is an aromatic evergreen shrub. These extracts showed the antiviral effects, from low to high concentrations of the extract that were dose-dependent and diverse depending on the herbal extract considered. Exactly, *L. Radiata* displayed the best antiviral activity against the strain of the virus [21]. These consequences are dependable with the results achieved by two other research teams, which have described that an energetic composite i.e. glycyrrhizin, emanates in the roots of licorice (Figure 3a), by preventing viral replication, has an anti-SARS-CoV effect [20, 23]. In the additional research, glycyrrhizin (Glycyrrhiza glabra, Fabaceae family) (Figure 3b) also demonstrated antiviral attributes, in vitro antiviral activity on 10 separate clinical strains of SARS-CoV.

Baicalin (Figure 4a), was investigated under identical conditions in this study and also showed antiviral probable against SARS-CoV, that Baicalin was a former of the Baikal skullcap (*Scuttelaria baicalensis*) plant (Figure 4b) [10]. In previous publications, Baicalin has also been shown to prevent in vitro HIV-1 virus replication [14, 24]. In humans, the oral level of these molecules does not exceed a blood serum dose equal to the in vitro dose measured, and it should be remembered that in vitro outcomes should not equate with clinical efficacy in vivo.

Lycorine (Figure 5) has also established a strong antiviral impact against SARS-CoV and is a poisonous crystalline alkaloid found in many species of *Amaryllidaceae*, for instance, the narcissus, the surprise lily (Lycoris), and the cultivated lily of the bush (*Clivia miniata*). Several previous investigations recommend that lycorine has been reported to have an inhibitory action on the Poliomyelitis virus [25] and Herpes simplex virus (HSV, type I) [24] and seems to have broad antiviral properties.

Japanese honeysuckle (*Lonicera japonica Thunb*.) (Figure 6), the widely known Korean ginseng (Panax ginseng), and Eucalyptus tree (Figure 6), the last one via its active secondary metabolite ginsenoside-Rb1), are other culinary spices, plants, and medicinal herbs that have been known to have antiviral attributes against SARS-CoV[22].

Table 1. The antivirals against different strains of coronavirus (Cov) for Acute Respiratory Syndrome Severe, SARS, with isolated pure compounds or different medicinal plants[25].

HCoV-NL63 HCoV-299E HCoV-OC43	Griffithsin (*Griffithsia* sp.)	[26]
HCoV-NL63	*Sambucus formosana*	[27]
	Strobilanthes cusia leaf	[18]
SARS-CoV PLpro	*Psoralea corylifolia*	[28]
	Broussonetia papyrifera	[29]
SARS-CoV CLpro	*Torreya nucifera*	[30]
	Salvia miltiorrhiza	[31]
SARS-CoV 3CLpro	*Houttuynia cordata*	[32]
	Rheum palmatum	[33]
SARS-CoV helicase non-structural protein 13 (nsP13)	*Scutettaria baicalensis*	[34]
SARS-CoV PUMC01 F5	*Cinnamomum* sp.	[35]
SARS-CoV FFM1	*Laurus nobilis* Essential oil *fGentiana scabra*	[20]
	Glycyrrhetinic acid and glycyrrhizin found in: *Glycyrrhiza radix*	[36]
SARS-CoV BJ01	*Galla chinensis*	[37]
HCoV-229E	Saikosaponins (*Bupleurum* spp., *Heteromorpha* spp., *Scrophularia scorodonia)*	[11]
	Pelargonium sidoides	[38]
	Calophyllum blancoi	[39]
	Mulberry (Morus rubra, *Morus alba* var. *rosa*, *Morus alba* var. alba)	[40]
10 strains of SARS-CoV in fRhK4 cell line	Baicalin (*Scutellaria baicalensis)* Glycyrrhizin (*Glycyrrhiza uralensis)*	[10]
SARS-CoV (Hong Kong strain)	*Taxillus chinensis* *Cassia tora* *Dioscorea batatas*	[41]
Bovine coronavirus (BCV)	*Verbascum Thapsus*	[17]

	Cardamine angulata *Rosa nutkana* *Amelanchier alnifolia*	
SARS-CoV	*Panax ginseng* *Eucalyptus* spp. *Lonicera japonica*	[21]
	Boenninghausenia sessilicarpa	[42]
	Lindera aggregata Isatis indigotica *Pyrrosia lingua* *Artemisia annua*	[16]
	Lycoris radiata	[17]

Figure 2. Aromatic plants tested against SARS-CoV: (**a**) *Pyrrosia lingua* [25]; (**b**) *Artemisia annua* [25].

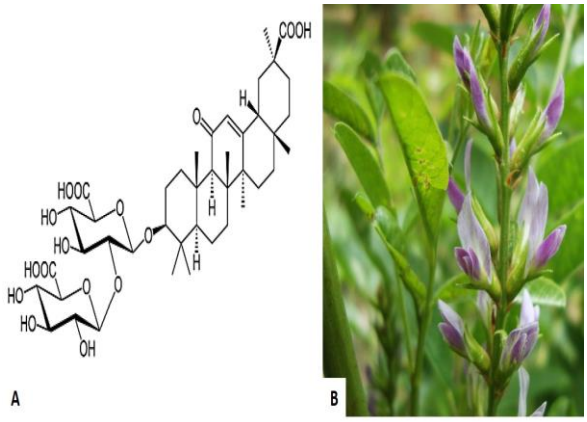

Figure 3. Structure of (**a**) glycyrrhizic acid (glycyrrhizin; glycyrrhizinic acid) [43]; (**b**) *Glycyrrhiza glabra* [25].

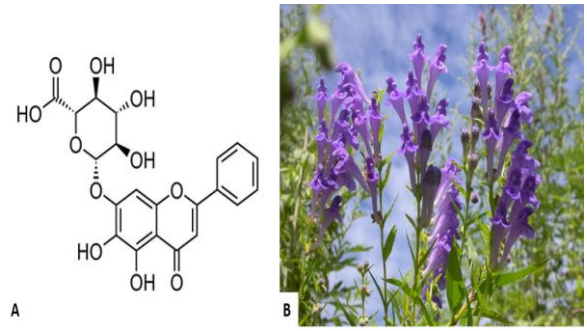

Figure 4. (**a**) Baicalin structural formula: baicalin is a flavone (flavonoid) found in several species of the genus *Scutellaria*, including (**b**) *Scutellaria baicalensis* root [24, 25].

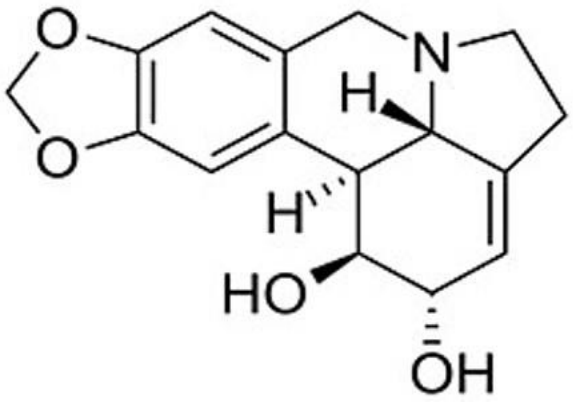

Figure 5. Lycorine chemical structure [25] (other names: narcissine, galanthidine, amaryllis) [25].

Figure 6. (**a**) Flowers of honeysuckle (*Lonicera* japonica Thunb). (**b**) Korean ginseng (*Panax ginseng*) [25].

One hundred medicinal herbs and aromatic from British Columbia were assessed against seven viruses for an antiviral effect [17]. In the doses used, the antiviral properties of twelve phytochemical extracts were shown. The most successful against the enteric coronavirus was the phytochemical extracts of Nootka or wild rose (Rosa nutkana) and Saskatoon or Pacific serviceberry (*Amelanchier alnifolia*) (Figure 7). A branch tip extract of red elderberry (Sambucus racemosa) and a root extract of tall cinquefoil (*Potentilla arguta*) (Figure 8) was completely blocked by the respiratory syncytial virus (RSV) (Figure 9). For testing the antiviral properties of herbal medicines Bioflavonoids have been examined [44]. The black tea flavonoid theaflavin (Figure 10) was a famous antioxidant

with the capability to scavenge free radicals and was able to neutralize bovine coronavirus infections. [45].

Figure 7. (**a**) Nookta Rose (*Rosa nutkana*) [25]. (**b**) Potentilla arguta [25]. (**C**) *Sambucus racemosa* (red elderberry) [25].

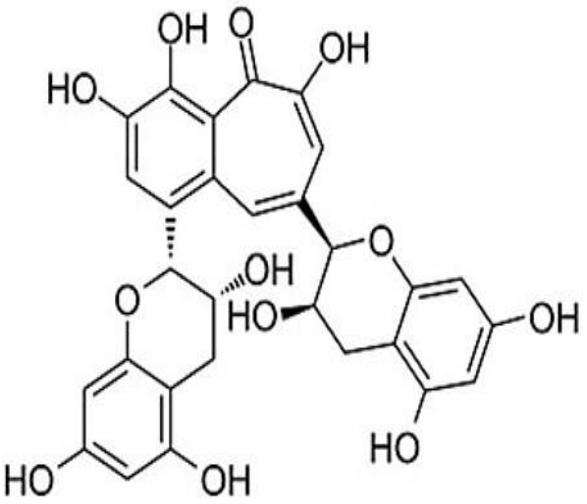

Figure 8. Theaflavin chemical structure [25, 46].

4 Way of Antiviral Action

Numerous studies and research of pure molecules and plant extracts with numerous coronavirus strains have been carried out. The main objectives were proteins involved in the conductance of proteases and ion channels and coronaviral replication [47]. Many researchers have found out that plant formulations prohibit in vitro and vivio viral replication [48, 49].

above-mentioned reports and other studies indicate that components of medicinal plants and many phytochemical extracts have antiviral attributes against coronaviruses [17], Their key mode of action tends to be the inhibition of viral replication [50]. Antiviral molecules do not need duplication to inactivate a virus and they behave are like an antiseptic or disinfectant [51]. Mutations created in the viral genome in the course of replication perhaps cause resistance to antiviral compounds [52].

The *Saikosaponins* (a, b_2, c, and d) (Figure 9), Naturally derived triterpene glycosides isolated from herbal medicinal products, for instance, Figwort (Scrophularia scorodonia, a member of the Scrophulariaceae family), parsley tree (Heteromorpha spp., a member of the Apiaceae family) and Chinese thoroughwax (*Bupleurum spp*., a member of the *Apiaceae* family) has antiviral activity against HCoV-22E9, a human-infected CoV species, and *anima scorodonia* [11, 53]. Such natural molecules containing viral attachment and penetration, after co-challenge with the virus, effectively deter and suppress the early process of infection by HCoV-229E.

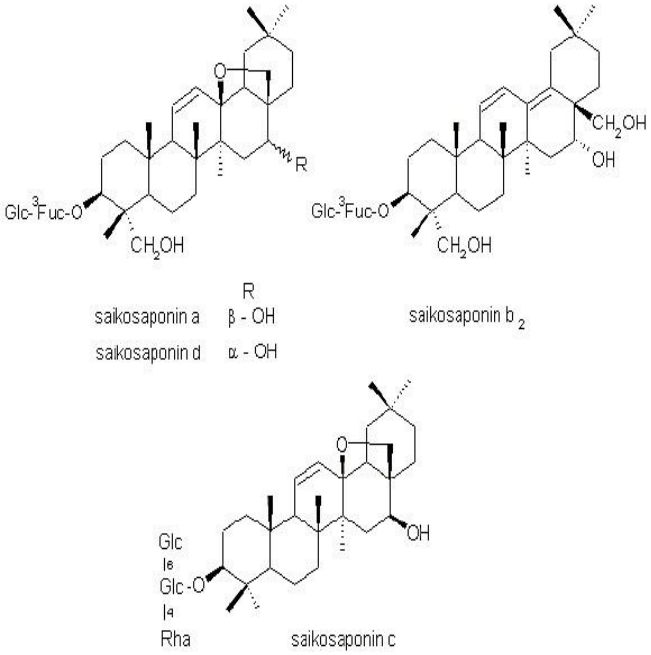

Figure 9. Chemical structures of saikosaponins a, c, and d [15, 25].

Natural SARS-CoV enzyme antagonists, such as nsP13 helicase and 3CL Myricetin-containing protease (Figure 10) (a flavonoid polyphenolic molecule with antioxidant effects detected in vegetables and fruits) and *scutellarein* (Figure 11) (a flavonoid found in the flowers, stems, and roots of *Scutellaria lateriflora*, a perennial member of the further Scutellaria species, and species *Lamiaceae*) were defined, dyer woad (Isatis indigotica) and (*Asplenium Belanger*) (Figure 12) and Japanese nutmeg-yew (*Torreya nucifera*) (Figure 12) [16, 30, 34].

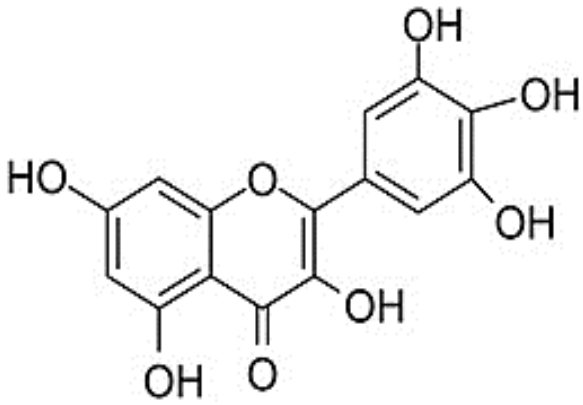

Figure 10. Chemical structure of Myricetin. Myricetin is a plant-based natural flavonoid with a wide variety of beneficial biological activities, containing, antioxidants, anti-inflammatory activities, and cancer [25].

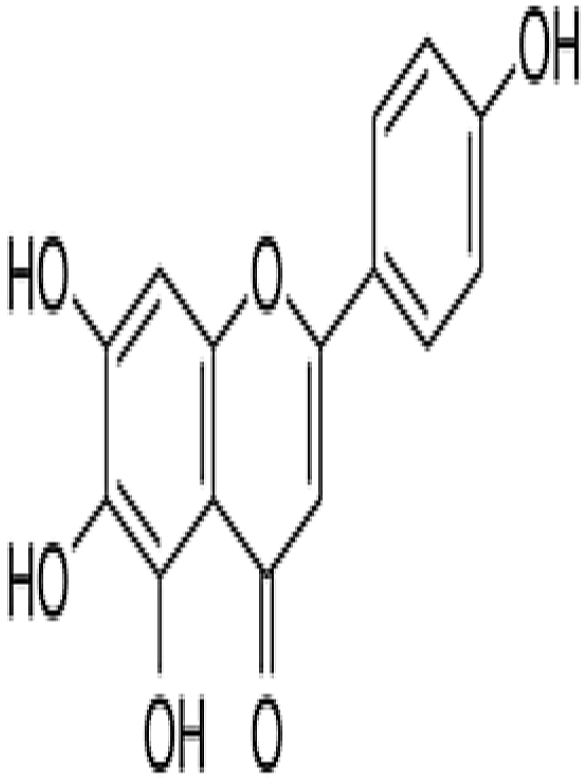

Figure 11. Scutellarein chemical structure [25].

Figure 12. (**a**) *Isatis indigotica* Fort. (Fam. Brassicaceae) and (**b**) Japanese nutmeg-yew (*Torreya nucifera*) [25].

Numerous natural anti-CoV phytomedicines contain aqueous fish mint extract (*Houttuynia or data*) (Figure 13), Several anti-SARS-CoV antiviral pathways have been shown to mediate, for instance, Viral RNA-dependent RNA polymerase inhibition and viral 3CL protease activity suppression [30].

Figure 13. *Houttuynia cordata* [25].

Herbal extracts have been used to ameliorate many diseases as conventional medicines. Various plant extracts were found to inhibit the replication of viruses [54]. While the antibacterial and antifungal properties of aromatic herbs, medicinal plants, and volatile oils are established, there is currently insufficient scientific evidence to determine the non-toxic and efficient methods of using them as antiviral treatments. The best choices for effective antiviral chemotherapy are specific compounds that work on different viral biosynthetic pathways. They suppress different developments in the viral replication cycle, and thus little to no viral progeny is produced. Small doses of these medications that do not harm the host cell can function. The replication of viruses would deter them, thereby therapeutic the infected cells. Unfortunately, resistance to these specific drugs can evolve by replicating viruses. on the other side, viral drugs bind solubilize structural viral glycoproteins with the virus's enveloped membrane shell and [11, 30, 32]. Numerous therapeutic agents are the basis of the complex metabolism of natural bio-actives and have contributed to the production of novel antivirals. Herbal antiviral drugs have been understudied to pesticides. Some experimental studies, however, have started to more precisely test their efficacy [25]. Antiviral activity against such coronaviruses have been demonstrated by medicinal plants and their isolated components [17], Suppression of viral replication is mainly the mechanism of action (Table 2) of these traditional supplements [11, 16, 21, 37, 50].

Table 2. Directory of isolated active compounds or medicinal plants inhibiting Coronaviruses [25].

(Phytochemicals or Compounds)	Name	Antiviral Mechanism	IC50 or EC50 value	References
Rosa nutkana	Wild Rose or nootka Rose	Mechanisms of reduction or inhibition of the activity of enteric coronavirus	-	[17]
Medicinal Plants *Amelanchier alnifolia*	Western serviceberry or pacific serviceberry or saskatoon			
Luteolin		Blocking the viral entry of SARS pseudo-type/ HIV-luc virus.	9.02 µM	[37]
Lycoris radiata	Red spider lily	Reduction or inhibition of penetration and viral attachment.	2.4 ± 0.2 µg/mL	[20]
Artemisia annua	Sweet wormwood		34.5 ± 2.6 µg/mL	
Pyrrosia lingua	Tongue Fern		43.2 ± 14.1 µg/mL	
Lindera aggregata	Spicewood		88.2 ± 7.7 µg/mL	
Isatis indigotica (Beta-sitosterol)	Dyer's woad or Chinese Woad	Inhibition of 3CL-like protease and nsP13 helicase.	1.210 µM	**[16]**
Curcumin		Inhibition of 3CL protease.	40 µM	[55]
Astragalus membranaceus	Chinese astragalus or mongolian milkvetch or	Immunomodulatory effects by the proportion of CD4+ lymphocytes and increasing the number of lymphocytes.	-	[56]
Black tea (Theaflavin)		Inhibition of 3C-like protease of SARS-CoV.	9.5 µM	[57]
Bupleurum marginatum	Margined Chinese Thoroughwax	Interfering with early stages of viral replication	-	[11]
Saikosaponins B2		Inhibition of penetration steps of HCoV-22E9 and viral attachment.	1.7 ± 0.1 µM/L	[11]
Rheum officinale	Chinese rhubarb	Inhibition of the interaction between SARS-CoV S	1 to 10 µg/mL	[58]
Polygonum multiflorum	Tuber fleecerflower	Angiotensin-converting enzyme 2 (ACE2) and protein.		

Houttuynia cordata	Chameleon-plant or Fish mint	Inhibition of RNA-dependent RNA polymerase (RdRp) and 3CL-like protease and viral polymerase.	-	**[32] [59]**
Torreya nucifera (Amentoflavone)	Japanese torreya or Japanese nutmeg-yew	Inhibition of 3CL protease and nsP13 helicase.	8.3 µM	[30]
Glycyrrhiza glabra (Licorice Root)	Sweetwood or Liquorice	Effect in the lungs by a glycoside known as LicoA.	-	[60]
Verbascum Thapsus (Verbascoside)	Common mullein or great Mullein.	Active ingredients decrease inflammation during respiratory infection.	-	[61]
Hypericum perforatum	Perforate St John's wort or common Saint John's wort	Inhibition of mRNA expression in Avian coronavirus infectious bronchitis virus (IBV).	-	[62]
Herbal extracts (*Gentiana scabra*, Cibotium barometz, Taxillus chinensis, Cassia tora and *Dioscorea batatas*, *Cassia tora*)		Inhibition of 3CL-like protease.	39 µg/mL and 44 µg/mL (two extracts of Cibotium barometz)	**[41]**
Sambucus nigra	Common elder or Elderberry, blue elder	Inhibition of chicken coronavirus strain	-	[63]
Ruscus aculeatus	Knee holly or piaranthus ,Butcher's broom	Anti-inflammatory and anti-thrombotic properties. Decreases of cerebral ischemia-induced blood–brain barrier dysfunction. Protection of lungs from inflammatory injury	-	[64]
Psoralea corylifolia (Bavachinin)	Babchi	Inhibitions of papain-like protease (PLpro).	38.4 ±2.4 µM	[28]
Myricetin		3CL protease inhibition of SARS-CoV.	-	[34]
Lycorine		Inhibition of cell division of different strains of coronaviruses (HCoV-OC43, HCoV-NL63, MERS-CoV, and MHV-A59).	0.15–0.31µM.	**[65]**
Sambucus formosana	Blue elder, *common* elder or elderberry	Inhibition of chicken coronavirus strain and coronavirus NL63 by interfering with the viral envelopes, rendering them non-infectious.	-	[27]

5 Classes of essential oils

Essential oils can be classified based on the number of carbon chain formed from basic isoprene units (monoterpenes: C_{10}, sesquiterpenes: C_{15}, and diterpenes: C_{20}). Essential oils include the following classes of compounds;

- Hydrocarbons (Instances contain: αsabinene, p-menthane, α-pinene, β-pinene, Limonene, myrcene, p-cymene, fenchane, myrcene, α–phellandrene, thujane, azulene, farnesene, cadinene, and sabinene).
- Esters (Instances contain: geraniol acetate, eugenol acetate, linalyl acetate, and bornyl acetate).
- Oxides (Instances contain: sclareol oxide, linalool oxide, bisabolone oxide, and ascaridole).
- Lactones (Instances contain: alantrolactone, bergaptene, costuslactone, dihydronepetalactone, nepetalactone, citroptene, pinepetalactone, aesculatine, and psoralen).
- Alcohols (Instances contain: borneol, menthol, linalool, santalol, nerol, citronellol, and geraniol).
- Phenols (Instances contain: eugenol, thymol, carvacrol, and chavicol).
- Aldehydes (Instances contain: cumin aldehyde, citronellal, citral, myrtenal, cinnamaldehyde, and benzaldehyde).
- Ketones (Instances contain: pulegone, camphor, menthone, carvone, fenchone, thujone, and verbenone)

Instances of some classes of essential oils constituents, monoterpene hydrocarbon and oxygenated monoterpenes, sesquiterpene hydrocarbon, and oxygenated sesquiterpenes are specified in Figures 14, 15, and 16, respectively [66-68].

6 Therapeutic benefits of essential oils

Essential oils can provide aromatic herbs, spices, and some dietary supplements for the body. Essential oils, for example, citrus peel and orange, cherry, spearmint, black pepper, caraway, and lemongrass, are available from a lot of diverse dietary sources. Consequently, human exposure to essential oils is widespread by diet or environment. In certain situations, essential oils may be absorbed from the food matrix or as pure products and cross the blood-brain barrier rapidly. This later property is explained by the lipophilic character of volatile compounds and their small scale. The action of essential oils starts with three potential ways of entering the human body, As well as direct absorption into the skin tissue through inhalation, ingestion, or diffusion [69-72].

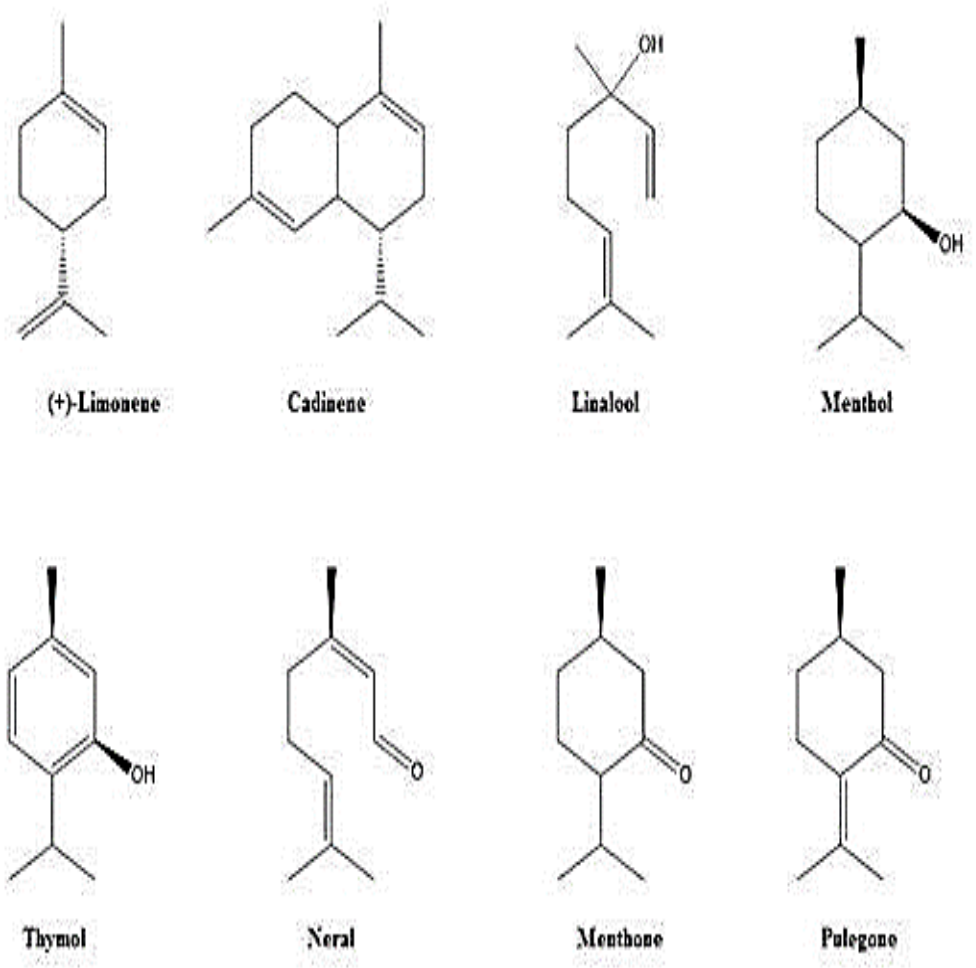

Figure 14. Instances of important oil constituent [66].

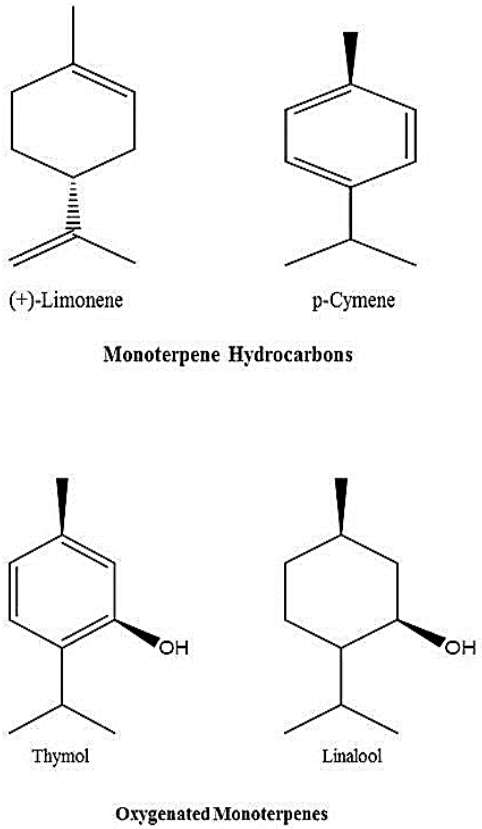

Figure 15. Groups of vital oil (Monoterpene hydrocarbons and Oxygenated monoterpenes) [66].

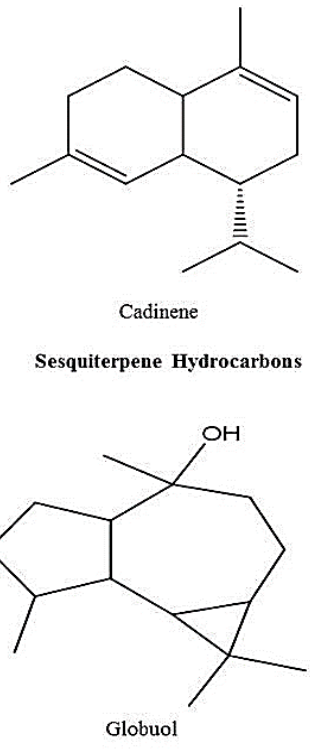

Figure 16. Groups of vital oils (Sesquiterpene hydrocarbons and Oxygenated Sesquiterpene) [66].

7 Conclusion

There is no specific treatment for COVID-19 at present. Given the high rate of human transmission of this virus and it is pandemics, to find a way to specific treatment or prevention, it is significant to create the basis of its replication, structure, and pathogenicity. Due to the spread of the disease at an unprecedented pace around the globe, the outbreak of COVID-19 has threatened almost all industries. Notably, COVID-19 is an RNA virus that poses a public health threat. The pandemic responsible for the ongoing global health crisis has quickly become a novel coronavirus disease (COVID-19), transmitted from humans to humans. Presently, it is significant to monitor the cause of infection, The use of existing drugs and means to proactively monitor the development of the disease is to cut off the route of transmission. We should also aim to develop specific medicines and promote vaccine research and development.

Competing interests

The authors declare that no conflict of interest would prejudice the impartiality of this scientific work.

Authors' contribution

All authors of this study have a complete contribution to data collection, data analyses, and manuscript writing.

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