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REVIEW ARTICLE

Herbal medicine as an alternative method to treat and prevent COVID-19

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ABSTRACT

The current outbreak of serious respiratory syndrome (COVID-19) has resulted from a novel coronavirus (SARS-CoV-2) infection. This infectious disease was classified as a pandemic by the World Health Organization (WHO) because it threatens public health and life worldwide. Recently, restrictions in many countries are applied to detect the infected individuals, isolate them, and attempt to find appropriate treatments that can help decrease the disease's severe symptoms. Regardless of the conducted efforts, the number of reported cases of coronavirus infections is still growing up. Yet, no medication or vaccine was approved to prevent and treat people from this coronavirus, though many research and medication companies are still developing medicines. This review aims to summarize the possible herbs and plants as natural herbal medicine along with western medicine, which could assist treat or protect people from COVID-19. Compounds of andrographolide, quercetin, baicalin, curcumin, glycyrrhizic acid, emodin, patchouli alcohol, luteolin, and myricetin are found in different plants and were found to be good health remedies. Understanding the infection rules, clarifying the pathogenic mechanisms, and detecting the appropriate medication treatment could improve the development of the essential treatment and prevention methods. Since the finally-approved drug for this virus is still absent, and a sharp increase in infection numbers is taking place, it becomes urgent to present possible alternatives, such as the Chinese herbal medicines, in an attempt to cure SARS-CoV-2 infection.

Keywords COVID19, medicinal plants, nature herbal medicine, plants extract, traditional Chinese medicine, treatment methods

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INTRODUCTION

In late 2019, a pneumonia sickness of an unknown source has started in Wuhan city/China and spread rapidly to the rest of the world.[1] A series of studies were conducted

in China on samples collected from patients with symptoms, and an unknown betacoronavirus was detected.[2] The discovered coronavirus, identified as SARS-CoV-2, led to an epidemic disease; commonly called COVID-19, which was defined as a transmitted infection among people,[3,4] and classified as a pandemic by the WHO.[5] In the middle of March 2020, more than 178,700 confirmed cases were reported in around 140 countries, where the majority located in China, the source of the virus, and followed by Spain, Iran, Italy, and South Korea.[6] The National Health Commission of China listed COVID-19's diagnosis and treatment within the epidemic diseases treated by Traditional Chinese Medicine (TCM). Although the disease's conditions, symptoms, and severity could differ depending on multiple parameters, such as local climate, patient's immunity, physical conditions, and the virus itself, the TCM treatment guideline was recommended from many regions based on the sickness variation. The sharp increase in the number of COVID-19 cases raised the panic of this pandemic, which promoted the efforts to find a rapid solution. This situation made it necessary to study Chinese herbal medicines activity against coronavirus. These plants could be employed in treating the COVID-19 and find alternative treatments because they contain small molecular compounds that have a therapeutic impact on the virus.[7]

In this review, we summarized the medical impact of selected herbs from Chinese herbal medicine that could treat SARS-CoV-2 by targeting its proteins. Furthermore, we anticipated the relationship between the effective compounds depending on the molecular structure and their impact on the corona virus's molecular targets. The compounds included are emodin, quercetin, luteolin, curcumin, glycyrrhizic acid, andrographolide, patchouli alcohol, myricetin baicalin, and phenolic compounds. These compounds could be found in different plants; for instance, Aloe vera, Rheum palmatum. In comparison, quercetin is found in onions, green tea, and apples.

TRADITIONAL CHINESE HERBAL MEDICINE THERAPY

The Chinese herbal medication is a mixture of different herbs made by an herbalist based on the individual patient's status and conditions. The diagnosis follows the Chinese diagnostic patterns (palpation, listening, smelling, inspection, and inquiry). Antiviral activities were reported for many Chinese herbal prescriptions, such as Yinhua Pinggan granule, San Wu Huangqin Decoction (SWHD), and Lianhua Qingwen Capsule, which might assist in preventing the spread and propagation of the virus. Moreover, they could be able to recover and heal lungs' damage that could occur by coronaviruses.[8–10]

In the current coronavirus outbreak, traditional Chinese herbal medicine was found as a successful method of treatment to prevent and cure COVID-19.[11–13] In addition, this kind of medicine could be integrated with western medicine to reduce adverse occasions and other complications induced by an antibiotic, glucocorticoid, and antiviral remediations.[14,15] After the respiratory syndrome outbreak, the National Administration of Traditional Chinese Medicine gathered a team of experts to set a traditional Chinese herbal medicine treatment program. On January 24^{th}, 2020, the first recovered patient was dis-

charged from a hospital in Beijing after being treated with traditional Chinese herbal medicine.[16] Later, another recovery case was reported after treating with traditional Chinese herbal medicine; this refers to the wide window of traditional Chinese herbal medicine to treat patients with the COVID-19.[17] On January 27^{th}, 2020, the National Health Commission of the People's Republic of China (PRC) with other organizations published "Diagnosis and Treatment of Pneumonia Caused by Novel Coronavirus Infection (Trial Version 4). This issue contained the updated traditional Chinese herbal medicine treatment program and recommended the health organizations and committees to consider the combination of Chinese herbs with western medicine.[18] Despite the confirmed activity of traditional Chinese herbal medicine in treating COVID-19's patients, there are still doubts about its effectiveness.

Thereby, our goal in this study was to review the related studies regarding traditional Chinese herbal medicine to treat COVID-19 patients to provide practical evidence. Reports showed that about 14-16% of COVID-19 patients suffered from severe conditions as dyspnea, where 5% needed special treatment.[19] However, the mortality rate of COVID-19 was about half of the patients who went through critical conditions. The National Health Commission and National Administration of Traditional Chinese Medicine of the PRC established a clinical guideline to manage the COVID-19 pandemic (NHC-NATCM-China guidelines).[20] In this work, traditional Chinese herbal medicines were suggested as treatment methods for serious COVID-19's cases. Recommending these herbs was presented in a general agreement of experts, which encouraged researchers worldwide to study these herbs in much more details.

MEDICINAL PLANTS

For several years, medicinal plants have been used in different indigenous health schemes and traditional medicines for treating diseases.[21] Naturally occurring herbal medicine provides a wide variety of natural products, which can be used as an ancillary guide to unlocking many mysteries behind human illnesses.[22,23] According to a report by the WHO, 80% of people in developing countries rely on conventional plants for health needs.[23–25] With the enhanced resistance of microorganisms (bacteria, viruses, and parasites) to traditional anti-microbial therapy, alternative therapies are being re-explored at a growing rate, particularly from herbal sources.[25] Assessing the possible antiviral activity of various natural resources has gained remarkable attention with the emergence and re-emergence of new viruses, concerning the availability of advancing technological resources.[21,23,26] A variety of herbs have been investigated, and their effects against viral infections have been identified.[21] Amidst the mounting global concerns about the COVID-19 outbreak, understanding the natural products with antiviral properties is essential for providing an alternative management option for COVID-19.

The use of natural products and phytomedicine continues to grow fast around the world, with many people nowadays reverting to such remedies in different national healthcare set-

tings for the treatment of various health challenges.[23] Herbal phytoconstituents effectively reduced infectious conditions, where they were the only treatments available before antibiotics were introduced. In particular, herbal medicinal products provide a rich tool for the production of novel antivirals. The use of these plants dates back to the beginning of civilization.[27,28] Traditional Chinese medicine includes treatments of herbal and acupuncture, where those aim to prevent and treat diseases by enhancing the immunity of the body.[29,30] Chinese medicine needs experience and knowledge; here, no adverse reactions could be identified if Chinese herbs are properly used,[30,31] Seven coronaviruses have been detected with an ability to spread among humans; three of them are harmful, namely, SARS (severe acute respiratory syndrome, China, 2002), MERS (Middle East respiratory syndrome, Saudi Arabia, 2012), and SARS-CoV-2 (COVID-19, 2019). These viruses are belonging to the coronaviridae family of the coronavirus genus. The genome sequence analysis concluded that SARS-CoV-2 belongs to the beta type genus, where this type also contains the Bat SARS-like coronavirus, SARS, and MERS. Furthermore, based on the nucleic acid structure similarity, COVID-19 is a betacoronavirus. This mini-review article aims to survey and introduce important medicinal herbs and plants with antiviral activities against SARS and Covid-19.

ANDROGRAPHOLIDE

The andrographolide is a labdane diterpenoid that is mainly isolated from the Andrographis paniculate (green chiretta) herbaceous plant extract. This component was utilized in different medical functions due to its remarkable biological activity, such as immunity regulation, anti-hyperglycemia, anti-bacteria, anti-virus, anti-parasite, and anti-tumor.[32–34] Previous reports showed that andrographolide could treat multiple viruses such as influenza A virus (IAV),[35] human immunodeficiency virus (HIV),[36] Enterovirus D68 (EV-D68),[37] dengue virus (DENV),[38,39] and Chikungunya virus (CHIKV)[40] due to its wide range of antiviral properties. Recently, Enmozhi et al. found that andrographolide could be a good inhibitor for SARS-CoV-2 through *in silico* studies by influencing the viral 3-chymotrypsin-like cysteine protease ($3CL^{pro}$).[41] In general, andrographolide is highly abundant and has low cost and cytotoxicity; though, its strong antiviral activity against different types of viruses needs to be further studied.

QUERCETIN

It is a flavonoid compound that could commonly found in fruits and vegetables. In addition to its dietary property, quercetin owns multiple biological activities, including its anti-functions against inflammations, oxidants, viruses, allergies, cancer, and mood deterioration, similar to vasoprotective medication.[42–44] Previous studies showed that quercetin has antiviral activity against a group of viruses, including IAV,[44] Hepatitis

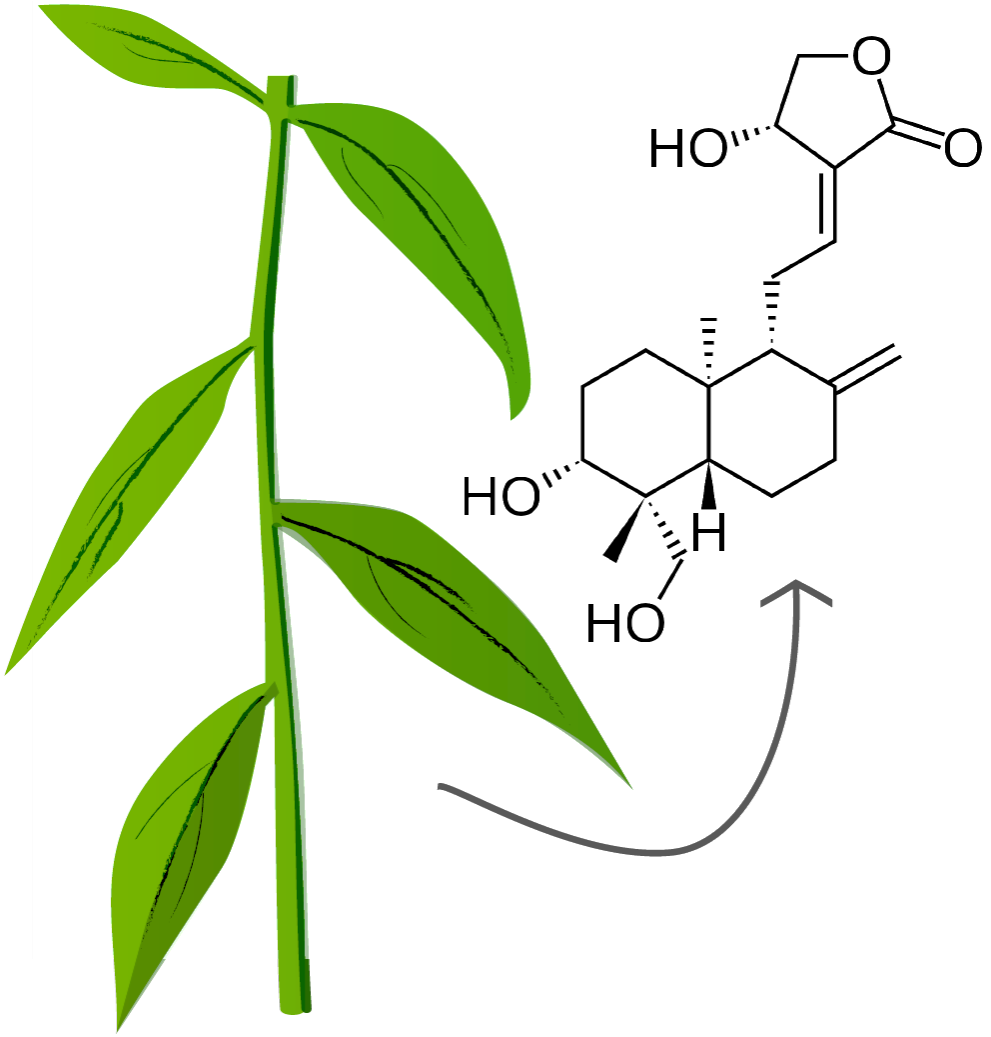

Figure 1 Andrographis paniculata and andrographolide structure

C Virus (HCV),[45] Enterovirus 71 (EV-71),[46] SARS-CoV, etc.[47,48] Regarding the SARS viruses, quercetin showed a relatively high inhibition rate and half-maximal inhibitory concentration (IC_{50}) values of 82% and 73 μM, respectively, against SARS-CoV $3CL^{pro}$ in Pichia pastoris fungus.[47]

BAICALIN

It is another medicinal component found in Scutellaria baicalensis Georgi (Chinese name: Huang Qin) and has a wide window of curative applications as sensitizer and anti-apoptosis.[49,50] Chen et al. reported the antiviral activity of baicalin versus SARS type viruses, with an effective concentration to reduce the virus forming unit by 50% (EC_{50}) value of 12.5 μg/ml within two days. The activity was reduced as the incubation time con-

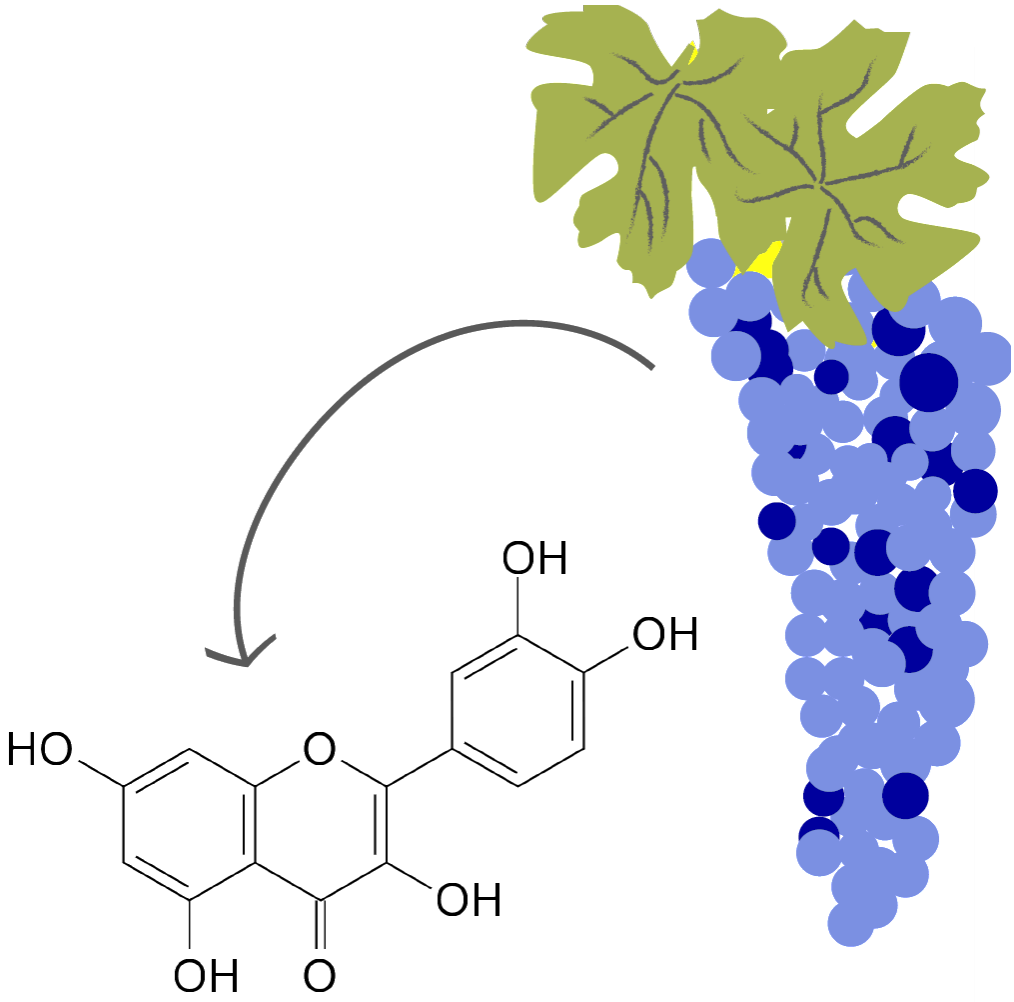

Figure 2 Quercetin is found in many fruits and vegetables

tinued more than two days.[51] The similarity between the current COVID-19 virus (SARS-CoV-2) and SARS-CoV is anticipated to obtain an analogous antiviral effect from baicalin on the recent virus. Furthermore, Deng et al. utilized UV spectrophotometry to identify angiotensin-converting enzyme inhibition, where baicalin was found to be a good *in vitro* inhibitor angiotensin-converting enzyme (ACE), with an IC_{50} value of 2.24 mM.[52] Considering the low toxicity of baicalin, its usage as a drug or treatment agent could be promising against COVID-19.

CURCUMIN

Its International Union of Pure and Applied Chemistry (IUPAC) name is (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). It is an anti-cancer, antioxidant,

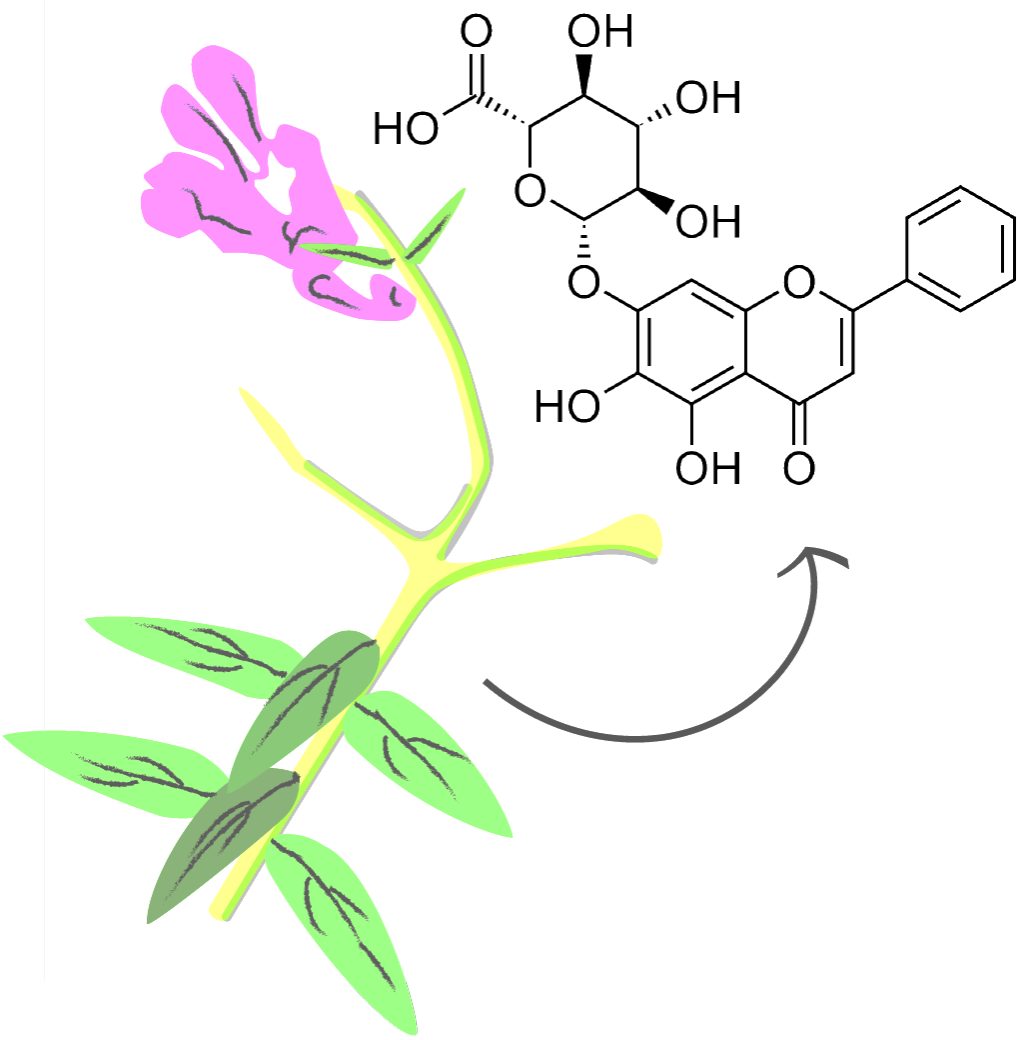

Figure 3 Scutellaria baicalensis Georgi and baicalin structure

anti-inflammatory, and amphipathic molecule that contains a polar center and a lipophilic methine segment surrounding it.[53] The β-dicarbonyl group in curcumin structure promoted the H-bond donating and accepting, where this group functions as a phenylic hydroxyl moiety and methoxy group. Also, curcumin can be used as a Michael reaction acceptor due to its affinity to multivalent metals and non-metals, which leads to a high polymerization around CC.[54]

Here, two polyphenols, Catechin and Curcumin, were reported through computational approaches, which have a dual binding affinity. Catechin binds to viral S-protein and ACE2 with a binding energy of -10.5 Kcal/mol and -8.9 Kcal/mol, respectively. As a result, it binds with a greater affinity than that of curcumin, which are -7.9 Kcal/mol and - 7.8 Kcal/mol for S-protein and ACE2, respectively. While curcumin gets bound directly to the receptor-binding domain (RBD) of viral S-protein, catechin binds to the proximity of S-protein's RBD sequence. A molecular simulation study demonstrated that curcumin directly binds with

the RBD site of S-protein during 40-100ns. In contrast, catechin binds with S-protein near the RBD site and causes fluctuation in amino acid present in the RBD and its proximity. In conclusion, this computational study predicted the possible use of the above two polyphenols for therapeutic/preventive intervention.[55]

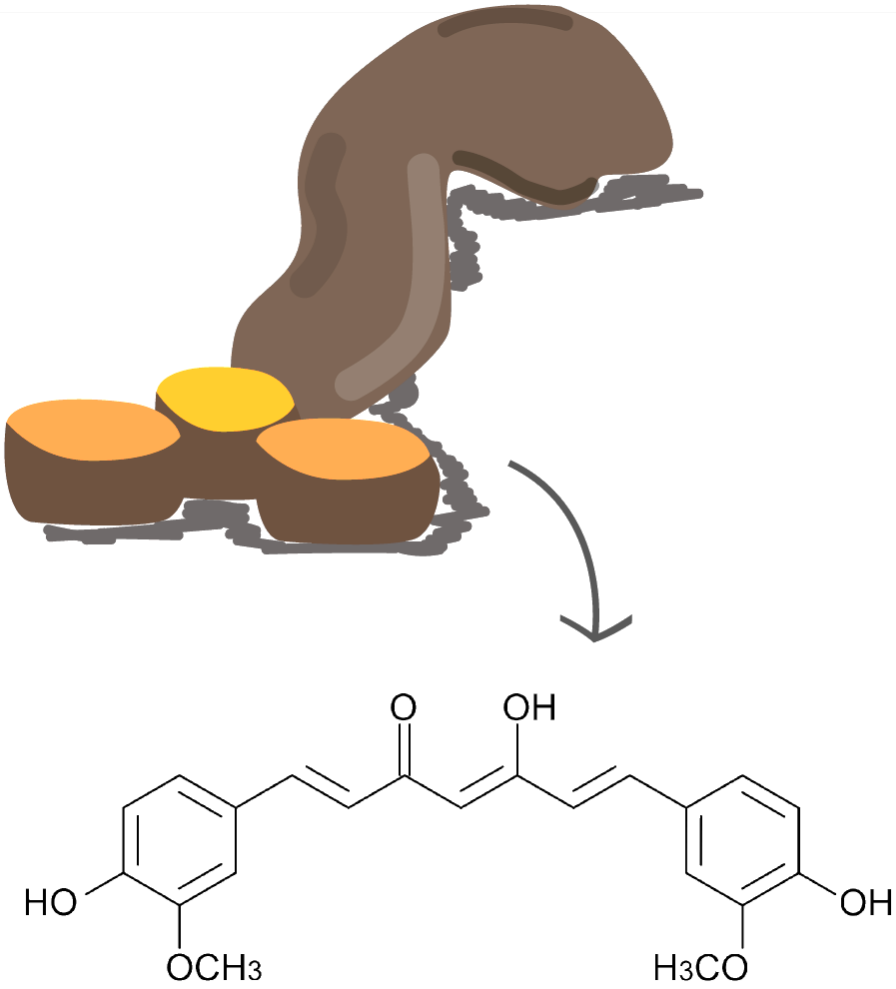

Figure 4 Curcumin and its structure

GLYCYRRHIZIC ACID

It is a component obtained from the traditional Chinese medicine plant licorice (Chinese name: Gan Cao). Glycyrrhiza uralensis (Chinese liquorice) possesses many active compounds, including thymol and carvacrol, which were found to affect the viral and bacterial infections.[56] Many studies showed that licorice and its ingredients could prevent lung infections and damage, making it an excellent herbal candidate to treat SARS viruses.[57]

Cinatl et al. investigated the impact of a group of conventional antiviral drugs, namely ribavirin, mycophenolic acid, glycyrrhizic acid, 6-azouridine, and pyrazofurin on SARS-CoV. Findings showed that glycyrrhizic acid had the highest inhibitory effect among others, to decrease the viral adsorption and penetration.[58] Hoever et al. also showed the high glycyrrhizic acid anti-SARS-CoV efficiency; this could indicate the glycyrrhizic acid promising application in treating COVID-19 patients. This could be explained as SARS-CoV-2 and SARS-CoV are similar in structure, though they were sub-classed to different groups.[59] Furthermore, glycyrrhizic acid has a significant role in preventing immune hyperactivation and cytokine storm immune response.[60] Thereby, it is rational to recommend studying this component against SARS-CoV-2 infection intensely.

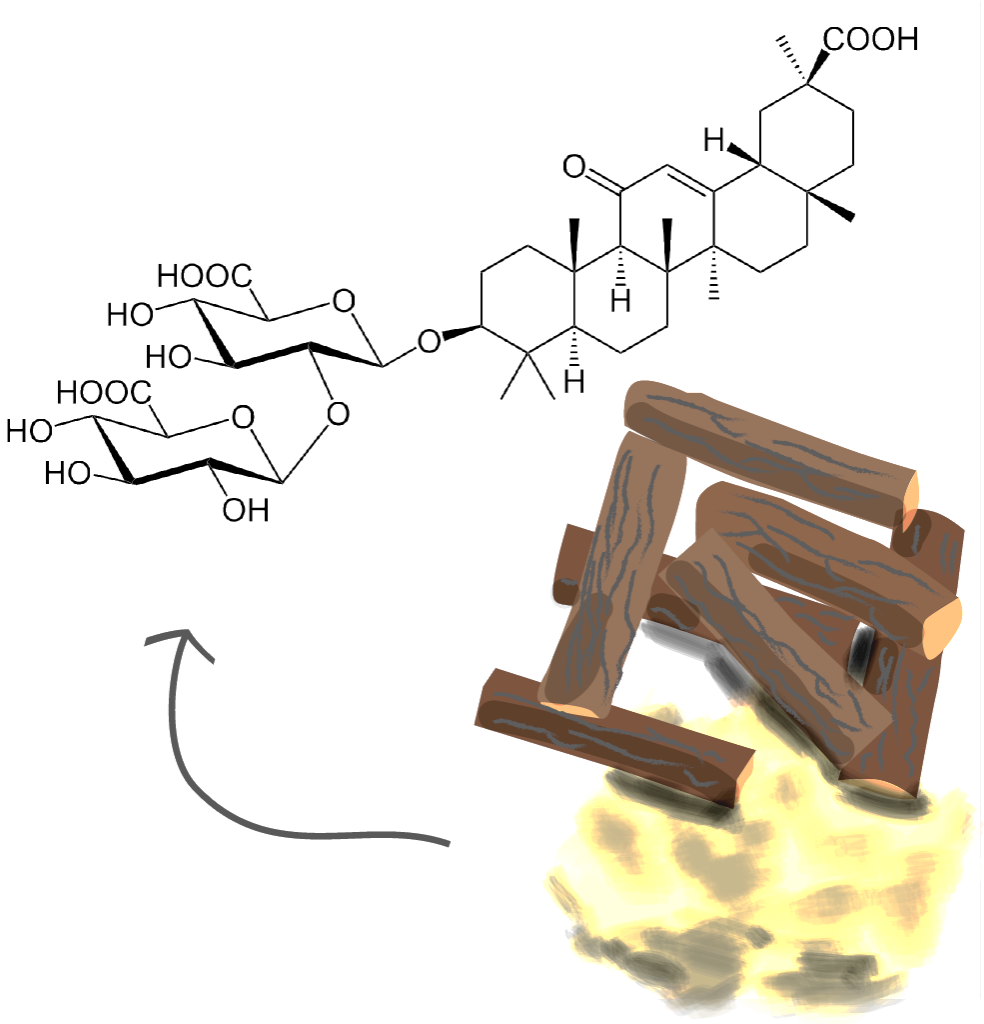

Figure 5 Licorice and glycyrrhizic acid structure

EMODIN

Its IUPAC name is 1,3,8-trihydroxy-6-methylanthraquinone and can be naturally found in anthraquinone derivatives and some Chinese herbs species, such as Aloe vera, Rheum palmatum, Polygonum cuspidatum, Cassia obtusifolia, and Polygonum multiflorum. The mentioned plants have a long history in traditional medicines in several areas worldwide, particularly in eastern Asia. Yet, their pharmaceutical advantages and cure ability are still investigated by many researchers. Previous reviews have summarized the anti-cancerogenic and anti-inflammatory properties of emodin. However, in recent years, an increasing number of studies (based on the Scopus database) discuss emodin's anti-tumor and anti-inflammatory effects. Emodin was also reported owing multiple pharmaceutical functions, like anti-osteoporotic, antiviral, anti-bacterial, anti-allergic, anti-diabetic, immunosuppressive, neuroprotective and hepatoprotective activities.[61] Emodin, the major component in Rheum and Polygonum genus, is anticipated to prevent binding S protein of SARS-CoV with the ACE2 and the infectivity of S protein-pseudo typed retrovirus with Vero E6 cells. The above mentioned approaches suggest that emodin is an interesting anti-SARS-CoV compound and could be considered a good candidate to treat the novel SARS-CoV.[62]

PATCHOULI ALCOHOL

Patchouli alcohol (PA), also called Patchoulol, is a tricyclic sesquiterpene ingredient obtained from the traditional Chinese medicine plant patchouli. This herb owns a wide window of pharmacological and biological applications, including antiviral, anti-tumor, anti-inflammatory, antioxidant, and immunomodulatory.[63] Also, it *in vitro* influenced the anti-influenza A virus (IAV) and H1N1 (swine flu) virus to a remarkable degree.[64]

LUTEOLIN

Luteolin (3′,4′,5′,7′-tetrahydroxyflavone) is one of the flavonoids group that naturally exists in a massive number of plants and has multiple pharmaceutical functions, such as anti-diabetic, anti-inflammatory, anti-bacterial, anti-cancerogenic, antiviral, antioxidant, anti-proliferative, and heart protective.[65] This component is obtained from Chinese medicine herbs available almost everywhere and at a low price.[66] Hence, Luteolin is suggested as a potential therapy to treat COVID-19 pandemic.

MYRICETIN

Myricetin is a common plant-derived flavonoid and has many types of nutrition. Moreover, it commonly enters the ingredients of different foods and beverages. Likewise,

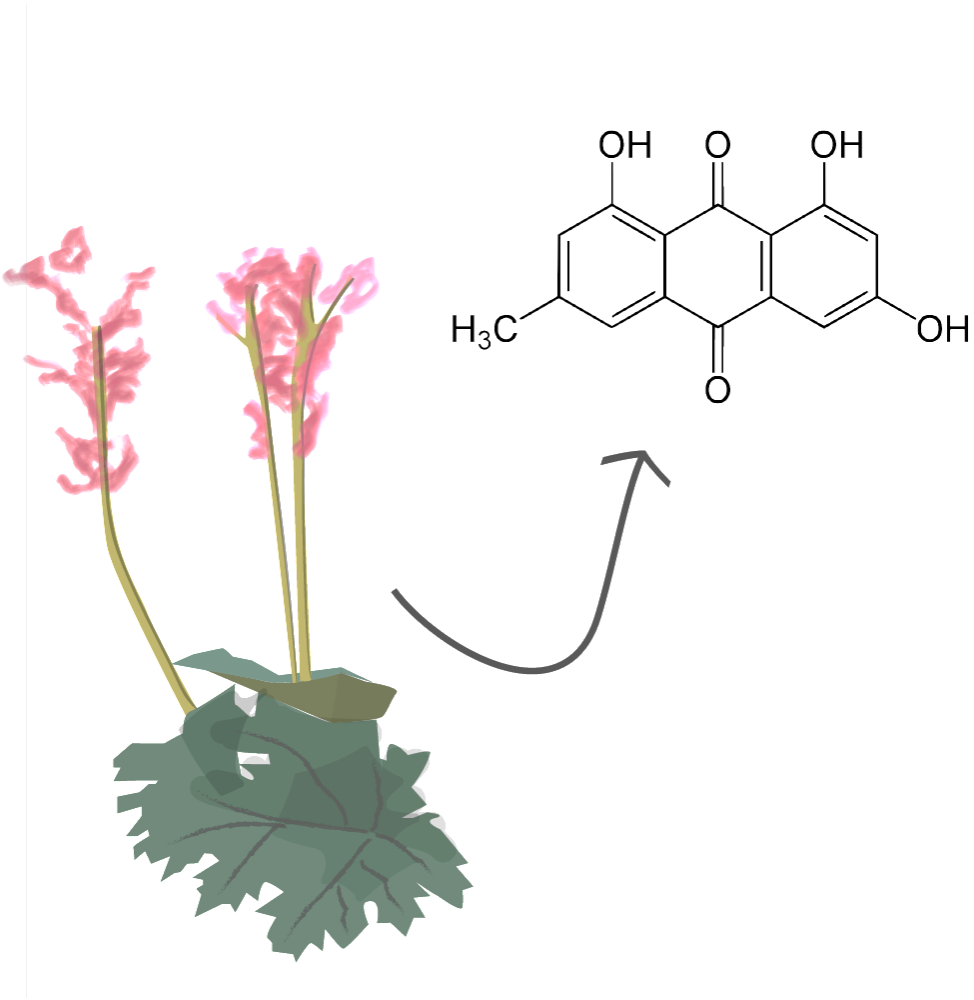

Figure 6 Rheum palmatum and emodine structure

Myricetin's previous plants and herbs show a wide window of potentials and roles as anti-inflammatory, anti-cancer, anti-diabetic, and antioxidant. This component has a long history that dates back to more than a century. The first isolation was from Myrica nagi Thumb (Myricaceae) in the late 1800s in India and was finally obtained as pale-colored crystals.[67] Yu. et al. reported that myricetin *in vitro* inhibited SARS-CoV's helicase protein by influencing the ATPase action, but not the unwinding activity of nonstructural protein 13 (nsP13). Furthermore, it was observed that myricetin and scutellarein had no cytotoxicity versus normal breast epithelial MCF10A cells. It can be suggested that the naturally-existing flavonoids, including myricetin, might serve as a SARS-CoV 2 inhibitor.[68]

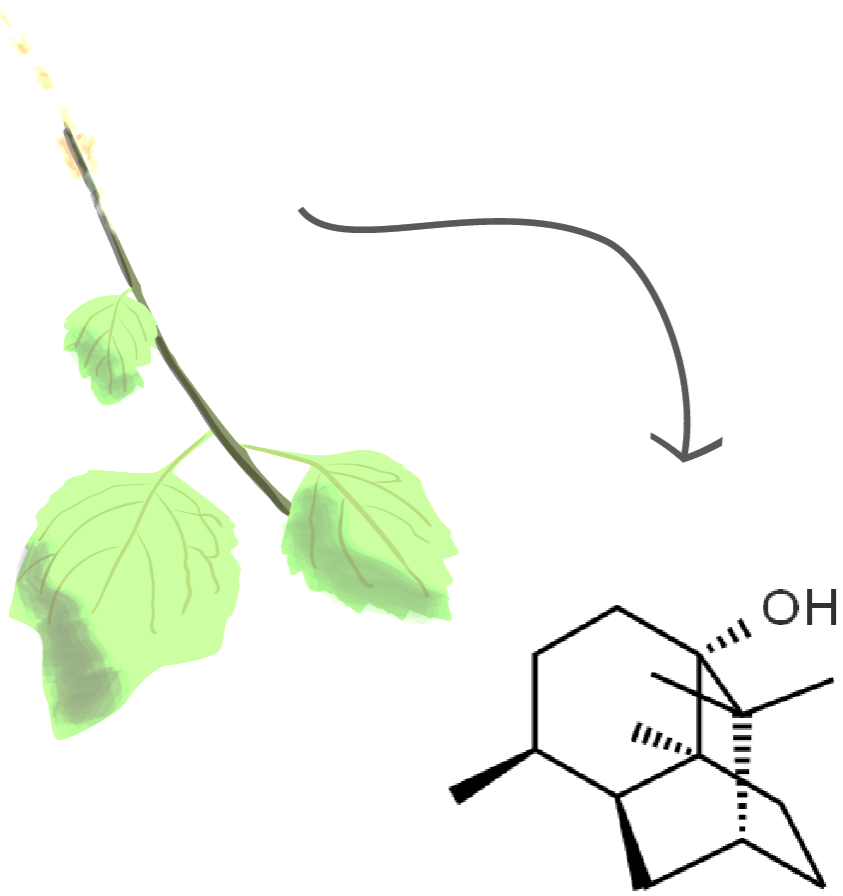

Figure 7 Patchouli and Patchouli alcohol (PA)

CONCLUSIONS

COVID-19 caused an enormous threat to global health and safety worldwide. It became crucial for governments, hospitals, researchers, companies, and even individuals to gather and control the pandemic outbreak and decrease the mortality rate as much as possible. So far, it is still ambiguous to comprehend the virus's specific mechanism; thus, no specific medication or vaccine has been developed. Nevertheless, it is still crucial to detect and control the source of disease, cut the chain of infection, and utilize the available drugs to decrease and treat the disease's symptoms. There is a need to directed the efforts to develop specific medications, push forward to discover a vaccine, follow strategies to decrease the morbidity duration and mortality rate, and protect people's lives. This study aimed to demonstrate the most promising compounds from traditional Chinese herbal medicine

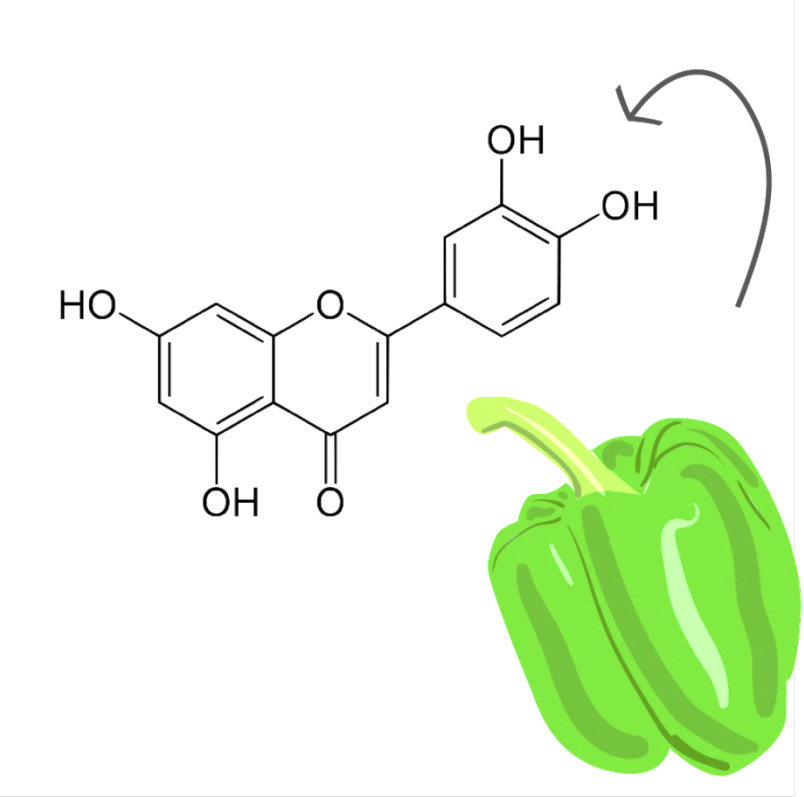

Figure 8 Luteolin structure; and pepper as an example of the plants that it exists in.

applied to similar types of viruses and showed high inhibitory activity. These plants are anticipated to function as antiviral drugs to treat the current SARS-CoV-2 virus based on *in vitro* and *in vivo* studies. Components of andrographolide, quercetin, baicalin, curcumin, glycyrrhizic acid, emodin, patchouli alcohol, luteolin, and myricetin were found to have a good medical history. Computer simulation and molecular docking exhibited good binding ability for these monomers with the SARS-CoV-2 virus and host targets so that they could block the virus-host binding sites. The abundance, low price, and low toxicity of the traditional Chinese medicine herbs that contain many useful ingredients encourage their use as potential drugs for COVID-19.

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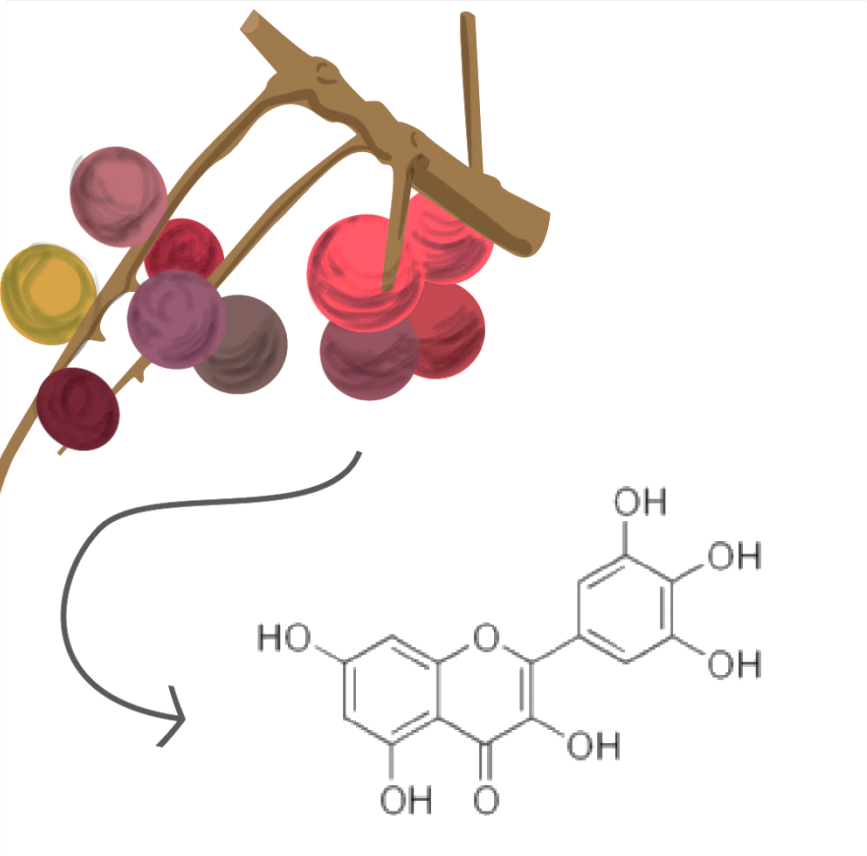

Figure 9 Myrica nagi Thunb and myricetin structure

DECLARATIONS

Authors' contributions

All authors have equally contributed to this review.

Conflict of interest

The authors declare no conflict of interest.

Ethical approvals

Not required.

Data availability

Not applicable.

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