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# Phytomedicine and the COVID-19 pandemic

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## 1. Introduction

Recent epidemic outbreak of novel human coronavirus baptized “SARS-CoV-2” (similar to previous virial strains MERS-CoV and SARS-CoV) induced in China, and no single country is an exception from COVID-19 disease (Antonelli, Donelli, Maggini, & Firenzuoli, 2020; Li & De Clercq, 2020). Till date, no vaccination and cure against SARS-CoV-2 exist, while the current therapeutic options are limited (Li & De Clercq, 2020). With the continuously expanding terrible pandemic of COVID-19 infection, globally increasing numbers of COVID-19 patients and contacts progressively jump to heavy burdens beyond capabilities. Developing and poor countries are under severe humanity disasters; even the economies of developed nations have collapsed. As worldwide health authorities and hospitals are currently overloaded, home treatment of contacts and mild COVID-19 cases have become a fact necessitating some evidence-based suggested measures in addition to some health advices (Antonelli et al., 2020; El Sayed et al., 2020).

Coronaviruses cause acute respiratory and CNS diseases in many animals including humans (Kim et al., 2008). These were first reported by Tyrrell and Bynoe in 1966 who isolated and cultivated these viruses from patients with common cold symptoms. They are a family of enveloped viruses having a large, positive-sense single-stranded 27–32 kb genomic RNA and a helical nucleocapsid (Kim et al., 2010). The genomic RNA encodes seven to eight genes. Their genome (RNA) is packed together with nucleocapsid (N) protein and three envelope proteins, namely, E (envelope), M (membrane), and S (spike). The term “coronaviruses” was used for these viruses, which was based on their spherical morphology with solar corona-like surface projections (corona in Latin means

crown) (Kim et al., 2008; Rathinavel, Palanisamy, Palanisamy, Subramanian, & Thangaswamy, 2020; Velavan & Meyer, 2020). Coronaviruses are animal viruses and belong to Coronaviridae family. These are further divided into alpha, beta, gamma, and delta subfamilies. The alpha and beta are provenanced from mammals, especially from bats. Among seven human-infecting subtypes, betacoronaviruses are responsible for severe fatalities (Velavan & Meyer, 2020; Yang et al., 2010). SARS-CoV-2 appears to be mutated form of SARS-CoV. It is a newly isolated coronavirus and belongs to B lineage of betacoronaviruses. It relates closely to SARS-CoV of Chinese chrysanthemum-headed bat origin (Benvenuto et al., 2020; Sun, Lu, Xu, Sun, & Pan, 2020).

The phytotherapy-based research and phytotherapeutic medicines can virtually probe and invent potential cures and remedies for viral infections like SARS, MERS, and CoV. Yet the horizon of phytomedicines needed to be explored. Globally, vast genera of plant and herb have been illustrated with clinical trials and have showed potential to cure based on their immune system boosting capacity against coronavirus diseases. Phytomedicines with strong preventive and immunity boosting and therapeutic effects with various mechanisms have been studied well in China. Cinchona bark which is pharmacological derivatives of chloroquine has already showed promising results in clinical trials. Mainly the laboratory studies have provided evidences for phytomedicines and plant extracts (Liu, Zhang, He, & Li, 2012). From various clinical studies of databases, Liu et al. (2012) concluded the methodology of various clinical trials remained questionable, yet the phytomedicines demonstrated promising potential to boost the human immune system, overall patient health, and lessening of COVID-19 and SARS symptoms. Therefore, in this chapter, a brief description of the potential phytomedicines and latest research in phytotherapy against coronavirus have been illustrated to provide researchers in the field with some vital hints to be used for planning future studies. An ideal anti-COVID-19 medication must be safe conferring three basic therapeutic effects, that is, enhancing the antiviral immunity, tissue protection/repair, and exerting potent antiviral effects.

## 2. The origin of COVID-19 pandemic

After its emergence in the end of 2019, the outbreak of COVID-19 soon became pandemic of great concern. The disease emerged as unexplained pneumonia cases in Wuhan, China, in December 2019 and declared as PHEIC (Public Health Emergency of International Concern) by WHO in January 2020. This is the sixth public health emergency of international concern after H1N1, polio, Ebola in West Africa, and Zika and Ebola in the Democratic Republic of Congo that occurred in 2009, 2014, 2014, 2016, and 2019, respectively. The disease was formally named as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) by the International Committee on Taxonomy of Viruses. Now in middle of 2020, SARS-CoV-2 has been declared a clinical threat to general public worldwide (Lai, Shih, Ko, Tang, & Hsueh, 2020; Sun et al., 2020; Velavan & Meyer, 2020).

According to WHO report, SARS-CoV-2 was detected in samples collected from Huanan Seafood Market in China. Recent studies based on evolutionary analyses suggest that it is more likely that SARS-CoV-2 was novel and was independently introduced from animals to humans (Chen, Xiong, Bao, & Shi, 2020). The presence of bats and live animals in Huanan Seafood Market and findings based on genomic analyses further strengthen this idea that the virus might have transmitted through bat droppings as contamination (Velavan & Meyer, 2020). It is yet to be confirmed if a specific animal species is carrier of this virus. According to one study, SARS-CoV-2 was found to be a chimeric virus between bat and an unknown origin (Li et al., 2020). This study supports the theory that the transmission chain of SARS-CoV-2 started from bats to humans whereas human-to-human transmission more likely occurs through respiratory tract droplets (Lai et al., 2020; Velavan & Meyer, 2020). Comparative studies of SARS-CoV-2 genes with other animals suggest that snakes are most likely wildlife repository for this novel virus (Sun et al., 2020).

### 3. Pathogenesis of SARS-CoV-2

Recent reports show that COVID-19 may progress as both symptomatic and asymptomatic infections. The initial clinical sign in former case is pneumonia. The common symptoms include upper nasal tract infections such as high fever, headaches, nasal congestion, coughs, sore throat, fatigue, muscular pain, vomiting, and diarrhea. Among these symptoms, high fever (~88%) and coughs (~67%) are most common, whereas diarrhea (3.7%) and vomiting (5%) are rare signs. On progression of disease the patients were reported to develop dyspnea, hemoptysis, lymphocytopenia, leukopenia, myocarditis, and increased levels of aspartate aminotransferase and inflammation markers, that is, proinflammatory cytokines and C-reactive proteins. Abnormalities can be seen in computed chest tomography (CT) images of patients as ground glass-like and patchy consolidation areas in infected patients' bilateral lungs (Sun et al., 2020; Velavan & Meyer, 2020). The mean incubation period of 5 days was observed for SARS-CoV-2 before onset of disease. In the case of symptomatic infections, clinical signs usually appear in a period of less than a week followed by appearance of pneumonia in second or third week of infection (Guan et al., 2020; Li et al., 2020).

Receptor recognition by viruses is the first and essential step of viral infections of host cells. Knowledge about the receptor recognition mechanisms of coronaviruses is critical for understanding of their pathogenesis and for developing novel prevention or cure for the disease caused by them. It has been known that the receptor-binding domain (RBD) of coronaviruses recognizes a variety of host protein receptors including angiotensin-converting enzyme 2 (ACE2), aminopeptidase N (APN) (also known as CD13), dipeptidyl peptidase 4 (DPP4), carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), and cellular serine protease TMPRSS2. SARS-CoV  $\beta$ -

coronavirus indeed utilizes ACE2 and TMPRSS2 to enter into the host cells. In the light of the fact that the novel SARS-CoV-2 genome has high similarity with SARS-CoV  $\beta$ -coronavirus and that the most amino acid residues essential for ACE2 binding by SARS-CoV RBD were conserved in SARS-CoV-2 RBD, it was logical to predict that ACE2 and TMPRSS2 could also facilitate the entry of novel SARS-CoV-2 into the host cells. This prediction was indeed found true, and this so far has been a breakthrough to understand, develop, and establish options for prevention and treatment of COVID-19.

The fatality of COVID-19 is associated with damage to alveolar cells, which triggers a series of systemic reactions resulting in patient's death. SARS-CoV-2 infects lungs through entering alveolar epithelial cells by receptor-mediated endocytosis. Here, ACE2 (angiotensin-converting enzyme 2) serves as entry receptor for the virus. This is same as for other SARS coronaviruses (Ho, Wu, Chen, Li, & Hsiang, 2007; Zhou et al., 2020). In the case of SARS-CoV, SARS-CoV spike (S) protein binds to cellular receptors and mediates fusion of host and viral membranes. This protein also carries virus-neutralizing epitopes that neutralize antibodies in host. Pathogenesis of SARS-CoV is highly affected by gene mutations of this protein (Ho et al., 2007). ACE2 is expressed in type I and II alveolar epithelial cells in normal human lungs being more expressed (83%) in type II cells. Studies show that ACE2 is expressed more in men as compared with women, whereas in terms of ethnicity Asians have higher expression levels of ACE2 in their alveolar epithelial cells. Hence, Asian males appear more susceptible to SARS-CoV-2 infection. Binding of SARS-CoV-2 to ACE2 receptor triggers more expression of ACE2, which causes damage to alveoli, and this ultimately leads to death if not treated (Sun et al., 2020; Zhao et al., 2020). There is 10–20 times stronger receptor-binding ability for SARS-CoV-2 than SARS-CoV (Wrapp et al., 2020).

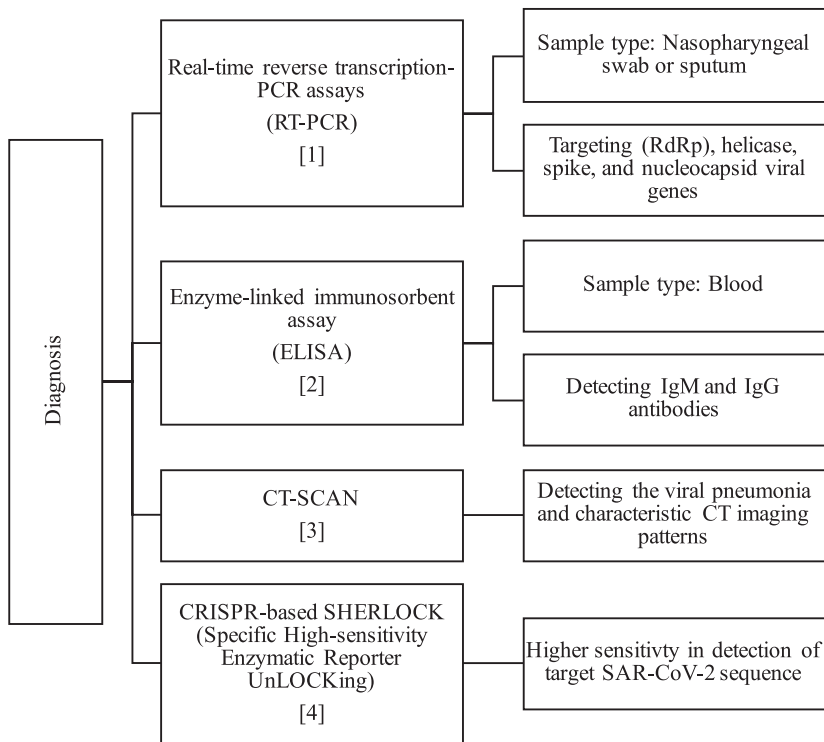
## **4. Options for the treatment of Covid-19 infection: Is there room for phytomedicine?**

### **4.1 The need for proper diagnosis**

The first line of control of SARS-CoV2 infection and decisive factor in the initiation of course of its treatment is the proper diagnosis, particularly distinction from general cold infections. Generally, sputum examination and other diagnostic tests are conducted to confirm signs of early infections (Chhikara, Rathi, Singh, & Poonam, 2020). Fig. 1 enlists the up till date reliable laboratory tests for the diagnosis of SARS-CoV-2 infections.

### **4.2 Current and probable options for the treatment of COVID-19**

The infection caused by SARS-CoV-2 is a novel and deadly respiratory condition; the existing antiviral drugs and vaccines have only been partially



**FIG. 1** Types and principles of diagnostic tests applicable for the detection of COVID-19. [1] Ai et al. (2020) and Chan et al. (2020); [2] Liu et al. (2020); [3] Shi et al. (2020); [4] Zhang, Abudayyeh, and Gootenberg (2020).

successful, and till date, no specified therapeutics have been elucidated. The only urgent management strategies include oxygen therapy, fluid management with conservative protocol in intensive care units, and the use of broad-spectrum antibiotics for treating secondary microbial infections (Huang et al., 2020). The World Health Organization (WHO) has made an urgent call for the development of vaccine, diagnostic tests for asymptomatic, and drugs for the cure. Currently the prevention of the outbreak is the utmost priority for protection (Cucinotta & Vanelli, 2020). Based on current information on mechanism and disease cycle from similar kind of viral infections, various therapeutic targets were identified to develop effective treatments against this novel virus.

#### 4.2.1 Entry inhibitors

The SARS-CoV-2 virus infection begins when its crown-like projections made up of glycoprotein form a complex with the angiotensin-converting enzyme 2 receptors of the host cells from the respiratory system. A variety of heterocyclic molecules with the ability to make complexes might result in the development of entry inhibitor drugs (Yuan et al., 2017).

#### 4.2.2 *Replication inhibitors*

Coronavirus genomes encode a protein RNA-dependent RNA polymerase (RdRp) that aids in replication of viral RNA using host machinery. RNA polymerase inhibitor-based drug such as remdesivir and DNA synthesis inhibitors such as lamivudine and tenofovir disoproxil have potential to inhibit its replication in infected cells. Protease inhibitors that interrupt protein translation such as lopinavir/ritonavir have also showed promising results (Sheahan et al., 2020). The proteins which have no structural frames such as 3CLpro (chymotrypsin-like protease) and PLP (papain-like protease) are crucial to complete coronavirus replication in the host cell. So, inhibitors of 3CLpro such as flavonoids and cinanserin (Chen et al., 2005; Jo, Kim, Shin, & Kim, 2020) and inhibitors of PLP such as diarylheptanoids (Park et al., 2012) also have prospective applications in the treatment of COVID-19 outbreak.

#### 4.2.3 *Heterocyclic drugs*

Antimalarial drugs such as chloroquine inhibit glycosylation in many viruses, leading to alteration of newly synthesized proteins. These drugs have been proven effective against infections caused by SARS-CoV-19 in many studies. Other such drugs proved effective include galidesivir, garunavir, and umifenovir. Neuraminidase inhibitors (oseltamivir), vinylsulfone, and protease inhibitors have also showed potential anticoronaviral activity. Nanodrug delivery systems have been used in formulation with newly developed drugs to improve efficacy in targeting the drug (Liu, Liu, et al., 2020; Liu, Morse, Lalonde, & Xu, 2020).

#### 4.2.4 *Biological therapeutics: Antibodies and plasma therapy*

Biological therapeutics using antibodies is another possibility for the cure of this infectious disease. Immune targeting of epitope of human monoclonal antibody (CR3022) and B- and T-cell epitopes of spike and nucleocapsid proteins of SARS-CoV-2 can be explored for the protection against SARS-CoV-2 (Shanmugaraj, Siri wattananon, Wangkanont, & Phoolcharoen, 2020). Moreover, to conduct clinical trials for plasma therapy, various convalescent patients donated the plasma against SARS-CoV-2. It exhibited positive results for the treatment of acute and severe SARS-CoV-2 infections (Chen et al., 2020).

#### 4.2.5 *Vaccines*

It is imperative to design a vaccine for reducing SARS-CoV-2 infectious severity and viral transmissions, thereby controlling the outbreak. To treat SARS-CoV and MERS-CoV, in the recent years, several vaccination attempts following weakened virus, inactivated virus, recombinant DNA, vectors, protein vaccines, and subunit vaccines were tested in animals (Graham, Donaldson, & Baric, 2013). Such attempts to treat SARS-CoV-2 are also in progress, but it requires several months to years for the development of such cure.



#### 4.2.6 Herbal drugs

Various herbal formulations including traditional Chinese medicine, traditional Indian ayurvedic medicine, and other herbal medicines have been used to mitigate symptoms associated with the outbreak. No clinical trials yet confirm the efficacy of these herbal extracts; however, phytochemicals have shown promising results based on their mode of actions inside the human body (Zhang, 2020).

### 5. Prospective phytomedicines for COVID-19 and their possible mode of action

The emergence of infectious diseases caused by novel viral strains that are resistant to common antiviral drugs is a major worldwide issue. Interestingly, herbal medicines, also known as phytomedicines derived from traditional Chinese, Japanese, Indian, and European herbal medicine systems, are promising candidates for the discovery and development of novel antiviral drugs (Reichling & Schnitzler, 2011). Therefore, in the recent years, a huge number of experiments confirming the antiviral efficacies of medicinal plant extracts and secondary metabolites (i.e., such as flavonoids, naphthodianthrones, and anthraquinones) have been conducted (Abad, Guerra, Bermejo, Irurzun, & Carrasco, 2000; El-Toumy et al., 2018; Jabborova, Davranov, & Egamberdieva, 2019; Mateeva et al., 2017; Moshawih, Cheema, Ahmad, Zakaria, & Hakim, 2017; Simões et al., 1999; Sokmen et al., 2005; Vijayan, Raghu, Ashok, Dhanaraj, & Suresh, 2004). Particularly, in the last two decades, a number of medicinal plant extracts and/or related physiologically active ingredients have been reported to exhibit antiviral activities. Some of the phytochemicals proven effective against the viruses or symptoms related to what shown by COVID-19 along with mode of action are discussed in this section.

Chinese traditional medicine (TCM) is highly recommended by the government of China for the eradication of SARS-CoV-2 (Yang, Islam, Wang, Li, & Chen, 2020). It was reported that following medicinal plants and their derived formulations have been used in 23 provinces of China and proved effective for the treatment of COVID-19. These include *Agastache rugosa*, *Astragalus membranaceus*, *Radix platycodonis*, *Atractylodis Rhizoma*, *Cyrtomium fortunei*, *Lonicerae Japonicae*, *Glycyrrhiza uralensis*, *Fructus Forsythiae*, *Saposhnikoviae divaricata*, and *Rhizoma Atractylodis* (Luo et al., 2020). Although most of the treatments were found to lack proper statistical designs, effectiveness of these trials could be questioned. However, some TCM formulations and their possible mode of actions against novel coronavirus are listed in Table 1.

In addition to these formulations, many herbal extracts have been proposed as supplement to treat symptoms of COVID-19. For example, *Tinospora cordifolia* extract having immunomodulatory effect against human immunodeficiency virus is effective to treat related symptoms (Kalikar et al., 2008). Similarly, herbal



**TABLE 1** Phytochemicals identified and extracted from Chinese medicinal herbs and their mode of action against treatment of COVID-19.

Phytochemicals	Chinese herbs	Mode of action	Reference
Phenolic compounds in plant extract	<i>Isatis indigotica</i>	Inhibition of the cleavage activity of SARS-3CLpro enzyme	<a href="#">Lin et al. (2005)</a>
Phenolic compounds in plant extract	<i>Houttuynia cordata</i>	Inhibition of viral RNA-dependent RNA polymerase activity (RdRp)	<a href="#">Lau et al. (2008)</a>
Isobavachalcone, herbacetin, helichrysetin, quercetin, 3- $\beta$ -D-glucoside	Multiple herbs	Inhibition of cleavage activity of MERS-3CLpro enzyme	<a href="#">Jo, Kim, Kim, Shin, and Kim (2019)</a>
Glycyrrhizin	<i>Glycyrrhizae radix</i>	Inhibition of viral attachment and penetration	<a href="#">Wolkerstorfer, Kurz, Bachhofner, and Szolar (2009)</a>
Flavonoids such as rhoifolin, pectolinarin, epigallocatechin gallate, gallic acid, quercetin, and herbacetin	<i>Litchi chinensis</i> and <i>Rheum palmatum</i> (Chinese rhubarb)	Inhibition of SARS-3CLpro activity	<a href="#">Xu, Xie, Hao, Jiang, and Wei (2011)</a> and <a href="#">Jo et al. (2020)</a>
Baicalin	<i>Scutellaria baicalensis</i>	Inhibition of angiotensin-converting enzyme (ACE)	<a href="#">Deng, Aluko, Jin, Zhang, and Yuan (2012)</a>

extracts of *Anthemis hyalina*, *Nigella sativa*, and *Citrus sinensis* decreased the coronavirus replication and downregulated TRP genes that maybe involved in the survival of coronavirus in epithelial cells in a study conducted by [Ulasli et al. \(2014\)](#). Likewise, medicinal plants such as *Heteromorpha* spp. and *Scrophularia scorodonia* possess various phytochemicals, for example, saikosaponins, a derivative of triterpene-oleanane found abundantly across many angiosperm families ([Li et al., 2018](#)). It is reported to possess medicinal functions such as modulation of immune function, antiinflammation, antihepatoma, and antimicrobial effects; therefore it has been shown to be active against measles, herpes simplex, influenza, varicella zoster, and human immunodeficiency viruses and related symptoms ([Bermejo et al., 2002](#); [Chiang, Ng, Liu, Shieh, &](#)

Lin, 2003). A study conducted by Cheng, Ng, Chiang, and Lin (2006) indicated that saikosaponin B<sub>2</sub> has potent antiviral property against infection caused by human coronavirus 229E and possible mode of action includes inhibitory effect on attachment, penetration, and replication of the novel coronavirus. Similarly, *Zingiber officinale*-derived phytochemical 6-gingerol showed promising anticoronaviral properties due to its high binding affinity against multiple SARS-CoV-2 targets, namely, RNA-binding protein, proteases, and spike proteins (Rathinavel et al., 2020).

## 6. Plant secondary metabolites and antiviral drugs

Plants produce a vast array of organic compounds that are differentially scattered among numerous taxa of the plant kingdom and are not primarily concerned with growth and development, known as plant secondary metabolites (Tiwari & Rana, 2015). These natural plant constituents or phytochemicals attribute characteristic medicinal properties to the plants. Extensive biological investigations have revealed a broad spectrum of pharmacological and physiological activities such as antiinflammatory, antioxidant, and anticancerous that led to its use in the formulation of promising drugs for the treatment of different diseases (Zhang et al., 2015). Many of these bioactive compounds are known to inhibit coronaviruses including MERS-CoV, SARS-CoV-1, and SARS-CoV-2 based on their potential to destroy proteases of coronavirus structural proteins and polymerases essential for its replication machinery (Khaerunnisa, Kurniawan, Awaluddin, Suhartati, & Soetjipto, 2020). Some of anticoronaviral activities and their respective mode of actions are discussed under this section. Plant secondary metabolites are mainly classified as alkaloids, phenolic compounds, and terpenoids.

### 6.1 Alkaloids

Alkaloids are a class of naturally occurring plant secondary metabolites primarily containing amine-type structure with basic nitrogen atom. Due to unique structural properties, many of alkaloids can be referred to as DNA intercalators such as berberine, emetine, and sanguinarine. The DNA intercalators can inhibit the transcription, replication, and translation of genetic material, in addition to its ability to stabilize the structure. Therefore these alkaloids have the potential to inhibit coronavirus replication and development within the host cell (Velu, Palanichamy, & Rajan, 2018). Many quinoline and isoquinoline alkaloids such as quinine, skimmianine, dictamine, cinchonine, and  $\beta$ -carboline have proved effective in treatment of many viruses including SARS-CoV-1. Chloroquine, a derivative of alkaloid quinine, has been clinically proved effective in treating SARS-CoV-2 infections (Wink, 2020). Moreover, colchicine, an alkaloid derived from the seeds of *Colchicum autumnale*, is under clinical trial for its strong antiinflammatory property in treatment of COVID-19 patients due to inhibition of NLRP3 inflammasomes and reduced activation of interleukin (Deftereos

et al., 2020). Therefore it is assumed that medicinal plants producing alkaloids may be promising candidates in developing the treatment for COVID-19.

## 6.2 Terpenoids

Terpenoids such as monoterpenes and sesquiterpenes, the derivatives of isopentenyl diphosphate (IPP), are the most abundant class of plant secondary metabolites (Ashour, Wink, & Gershenzon, 2018). These contain pharmacological properties that play important ecological roles such as plant protection against insect predators, herbivores, and microbial pathogens; therefore they are important candidates for medicine and biotechnology (Cheng et al., 2007). Numerous studies confirmed that terpenoids can inhibit the protease activity of viruses by interfering with related amino acids. Intriguingly, terpenoid-based drugs such as thymoquinone, forskolin, ginkgolide A, menthol, salvinatorin A, citral, noscapine, bilobalide, and beta-selinene have been identified as potent inhibitors of viral proteases by binding with aspartate, asparagine, and phenylalanine amino acid sites (Shaghghi, 2020). Similarly, an important eucalyptus oil component known as eucalyptol (1,8 cineole) has been proved effective against main-protease (Mpro) during in silico studies; therefore, it may be regarded as a potent candidate for the treatment of COVID-19 among many other related terpenoids (Sharma & Kaur, 2020). In addition to that, it has been reported that various diterpenoids, triterpenoids, and essential oils having salicylaldehyde and trans-myrtanol derived from a wide range of medicinal plants are promising candidates as fumigates for the protection against COVID-19 (Nikhat & Fazil, 2020).

## 6.3 Polyphenols and flavonoids

Polyphenolic compounds such as phenolic acids, stilbenes, and lignans are the important natural substances found in many plants, and due to strong antioxidant potential, they have several pharmacological applications (Ma et al., 2011; Yáñez et al., 2013). Flavonoids are the major class of polyphenols that are widely found in vegetables and fruits. They have been used in numerous formulations for the treatment of diseases such as atherosclerosis, Alzheimer, and cancer owing to the biological properties such as antiinflammatory, antioxidant, anticancer, and antimutagenic (Leyva-López, Gutierrez-Grijalva, Ambriz-Perez, & Heredia, 2016; Rengasamy et al., 2019). Some of the flavonoids are reported to possess antiviral ability. In particular, apigenin, luteolin, quercetin, kaempferol, daidzein, amentoflavone, epigallocatechin, puerarin, and epigallocatechin gallate were reported to inhibit the proteolytic activity of chymotrypsin-like protease (3CLpro) of SARS-CoV (Jo et al., 2020; Nguyen et al., 2012; Ryu et al., 2010). Moreover, other polyphenols including both flavonoids and nonflavonoids have been reported to target spike (S) glycoproteins of SARS-CoV-2, which are, therefore, proven effective in destroying the structure of novel coronavirus. It was reported that polyphenols such as curcumin, kaemp-

ferol, and pterostilbene specifically target and bind to S1 domain of these proteins. Other polyphenolic compounds, particularly quercetin, apigenin, luteolin, genistein, resveratrol, isorhamnetin, and fisetin, were reported to interact and target the S2 domain of SARS-CoV-2 spike proteins (Pandey et al., 2020). The angiotensin-converting enzyme (ACE) receptors in humans are the potential receptors for SARS-CoV-2. Therefore research into finding the potential binders and inhibitors to the ACE receptors can open up new insights in COVID-19 therapy. Polyphenols, specially caffeic acid, flavonoids, chrysin, myricetin, rutin, hesperetin, pinocembrin, galangin, luteolin, and phenethyl ester, were reported to possess inhibition properties against ACE receptors and therefore are promising phytochemicals for the treatment of SARS-CoV-2 infection based on in silico and molecular docking studies (Güler, Tatar, Yildiz, Belduz, & Kolayli, 2020). Furthermore, many in-vitro and in-vivo studies will be helpful in the development of drugs based on these phytochemicals, which are more effective, safer, and inexpensive than other alternatives.

## 7. Conclusion

Since 1940, around 400 new infectious pathogens have been identified, and the production of vaccines has proven successful in the past, but in the case of COVID-19, no cure exists yet. COVID-19 infection has presented a grave threat to the global health and economy. It has claimed more than 258,000 deaths worldwide till date. Globally, researchers are in race to find a cure. Strict epidemiological measures have been implemented initially like the largest quarantine in history. However, there are attempts to find a chemical drug; several clinical trials have confirmed that medicinal plant extracts in combination with other drugs have shown promising results. Plant secondary metabolites or phytochemicals are products of plant metabolism that are involved in defense mechanisms against insect and pathogenic attack. Numerous bioactive compounds, broadly classified as alkaloids, polyphenols, and terpenoids, have been proved effective against novel coronaviruses in numerous in silico, in vivo, in vitro, and clinical trials carried out all over the world, that is, chloroquine derived from plant has already shown promising results. Primary mode of action for phytochemicals includes the entry inhibition of these viruses by binding with the specific receptor sites in targeted cells and/or halting the replication process of these viruses by destroying viral polymerases and proteases essential to perform important task in viral replication. Phytomedicines have also proven to boost up immunity against novel coronavirus. However, clinical trials confirming the effectivity of any drug on COVID-19 are absent. Yet the phytomedicines with immunity boosting properties seem potential candidates. Further investigations are needed to identify and test all possible targets.

## References

- Abad, M. J., Guerra, J. A., Bermejo, P., Irurzun, A., & Carrasco, L. (2000). Search for antiviral activity in higher plant extracts. *Phytotherapy Research*, 14(8), 604–607.
- Ai, T., Yang, Z., Hou, H., Zhan, C., Chen, C., Lv, W., et al. (2020). Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: A report of 1014 cases. *Radiology*, 296, E32–E40. <https://doi.org/10.1148/radiol.2020200642>.
- Antonelli, M., Donelli, D., Maggini, V., & Firenzuoli, F. (2020). Phytotherapeutic compounds against coronaviruses: Possible streams for future research. *Phytotherapy Research*, 34(7), 1469–1470. <https://doi.org/10.1002/ptr.6712>.
- Ashour, M., Wink, M., & Gershenzon, J. (2018). Biochemistry of terpenoids: Monoterpenes, sesquiterpenes and diterpenes. *Annual Plant Reviews Online*, 258–303.
- Benvenuto, D., Giovanetti, M., Ciccozzi, A., Spoto, S., Angeletti, S., & Ciccozzi, M. (2020). The 2019-new coronavirus epidemic: Evidence for virus evolution. *Journal of Medical Virology*, 92(4), 455–459.
- Bermejo, P., Abad, M. J., Díaz, A. M., Fernández, L., De Santos, J., Sanchez, S., et al. (2002). Antiviral activity of seven iridoids, three saikosaponins and one phenylpropanoid glycoside extracted from *Bupleurum rigidum* and *Scrophularia scorodonia*. *Planta Medica*, 68(02), 106–110.
- Chan, J. F. W., Yip, C. C. Y., To, K. K. W., Tang, T. H. C., Wong, S. C. Y., Leung, K. H., et al. (2020). Improved molecular diagnosis of COVID-19 by the novel, highly sensitive and specific COVID-19-RdRp/HeI real-time reverse transcription-PCR assay validated in vitro and with clinical specimens. *Journal of Clinical Microbiology*, 58(5).
- Chen, L., Gui, C., Luo, X., Yang, Q., Günther, S., Scandella, E., et al. (2005). Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro. *Journal of Virology*, 79(11), 7095–7103.
- Chen, L., Xiong, J., Bao, L., & Shi, Y. (2020). Convalescent plasma as a potential therapy for COVID-19. *The Lancet Infectious Diseases*, 20(4), 398–400.
- Cheng, A. X., Lou, Y. G., Mao, Y. B., Lu, S., Wang, L. J., & Chen, X. Y. (2007). Plant terpenoids: Biosynthesis and ecological functions. *Journal of Integrative Plant Biology*, 49(2), 179–186.
- Cheng, P. W., Ng, L. T., Chiang, L. C., & Lin, C. C. (2006). Antiviral effects of saikosaponins on human coronavirus 229E in vitro. *Clinical and Experimental Pharmacology and Physiology*, 33(7), 612–616.
- Chhikara, B. S., Rath, B., Singh, J., & Poonam, F. N. U. (2020). Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics. *Chemical Biology Letters*, 7(1), 63–72.
- Chiang, L. C., Ng, L. T., Liu, L. T., Shieh, D. E., & Lin, C. C. (2003). Cytotoxicity and anti-hepatitis B virus activities of saikosaponins from *Bupleurum* species. *Planta Medica*, 69(08), 705–709.
- Cucinotta, D., & Vanelli, M. (2020). WHO declares COVID-19 a pandemic. *Acta Bio-Medica: Atenei Parmensis*, 91(1), 157–160.
- Deftereos, S., Giannopoulos, G., Vrachatis, D. A., Siasos, G., Giotaki, S. G., Cleman, M., et al. (2020). Colchicine as a potent anti-inflammatory treatment in COVID-19: Can we teach an old dog new tricks? *European Heart Journal-Cardiovascular Pharmacotherapy*. <https://doi.org/10.1093/ehjcvp/pvaa033>.
- Deng, Y. F., Aluko, R. E., Jin, Q., Zhang, Y., & Yuan, L. J. (2012). Inhibitory activities of baicalin against renin and angiotensin-converting enzyme. *Pharmaceutical Biology*, 50(4), 401–406.
- El Sayed, S. M., Almaramhy, H. H., Aljehani, Y. T., Okashah, A. M., El-Anzi, M. E., AlHarbi, M. B., et al. (2020). The evidence-based TaibUVID nutritional treatment for minimizing COVID-19

- fatalities and morbidity and eradicating COVID-19 pandemic: A novel approach for better outcomes (a treatment protocol). *American Journal of Public Health Research*, 8(2), 54–60.
- El-Toumy, S. A., Salib, J. Y., El-Kashak, W. A., Marty, C., Bedoux, G., & Bourgougnon, N. (2018). Antiviral effect of polyphenol rich plant extracts on herpes simplex virus type 1. *Food Science and Human Wellness*, 7(1), 91–101.
- Graham, R. L., Donaldson, E. F., & Baric, R. S. (2013). A decade after SARS: Strategies for controlling emerging coronaviruses. *Nature Reviews Microbiology*, 11(12), 836–848.
- Guan, W. J., Ni, Z. Y., Hu, Y., Liang, W. H., Ou, C. Q., He, J. X., ... Du, B. (2020). Clinical characteristics of 2019 novel coronavirus infection in China. *New England Journal of Medicine*, 382, 1708–1720. <https://doi.org/10.1056/NEJMoa2002032>.
- Güler, H. I., Tatar, G., Yildiz, O., Belduz, A. O., & Kolayli, S. (2020). An investigation of ethanolic propolis extracts: Their potential inhibitor properties against ACE-II receptors for COVID-19 treatment by molecular docking study. *ScienceOpen Preprints*. <https://doi.org/10.14293/S2199-1006.1.SOR-PP5BWN4.v1>.
- Ho, T. Y., Wu, S. L., Chen, J. C., Li, C. C., & Hsiang, C. Y. (2007). Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Research*, 74(2), 92–101.
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., et al. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506.
- Jabborova, D., Davranov, K., & Egamberdieva, D. (2019). Antibacterial, antifungal, and antiviral properties of medical plants. In *Medically important plant biomes: Source of secondary metabolites* (pp. 51–65). Singapore: Springer.
- Jo, S., Kim, H., Kim, S., Shin, D. H., & Kim, M. S. (2019). Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. *Chemical Biology & Drug Design*, 94(6), 2023–2030.
- Jo, S., Kim, S., Shin, D. H., & Kim, M. S. (2020). Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of Enzyme Inhibition and Medicinal Chemistry*, 35(1), 145–151.
- Kalikar, M. V., Thawani, V. R., Varadpande, U. K., Sontakke, S. D., Singh, R. P., & Khiyani, R. K. (2008). Immunomodulatory effect of *Tinospora cordifolia* extract in human immuno-deficiency virus positive patients. *Indian Journal of Pharmacology*, 40(3), 107.
- Khaerunnisa, S., Kurniawan, H., Awaluddin, R., Suhartati, S., & Soetjipto, S. (2020). Potential inhibitor of COVID-19 main protease (Mpro) from several medicinal plant compounds by molecular docking study. *Preprints*, 1–14. <https://doi.org/10.20944/preprints202003.0226.v1>.
- Kim, H. Y., Eo, E. Y., Park, H., Kim, Y. C., Park, S., Shin, H. J., & Kim, K. (2010). Medicinal herbal extracts of *Sophorae radix*, *Acanthopanax cortex*, *Sanguisorbae radix* and *Torilis fructus* inhibit coronavirus replication in vitro. *Antiviral Therapy*, 15(5), 697–709.
- Kim, H. Y., Shin, H. S., Park, H., Kim, Y. C., Yun, Y. G., Park, S., ... Kim, K. (2008). In vitro inhibition of coronavirus replications by the traditionally used medicinal herbal extracts, *Cimicifuga rhizoma*, *Melaleuca cortex*, *Coptidis rhizoma*, and *Phellodendron cortex*. *Journal of Clinical Virology*, 41(2), 122–128.
- Lai, C. C., Shih, T. P., Ko, W. C., Tang, H. J., & Hsueh, P. R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, 55(3), 105924.
- Lau, K. M., Lee, K. M., Koon, C. M., Cheung, C. S. F., Lau, C. P., Ho, H. M., et al. (2008). Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. *Journal of Ethnopharmacology*, 118(1), 79–85.
- Leyva-López, N., Gutierrez-Grijalva, E. P., Ambríz-Pérez, D. L., & Heredia, J. B. (2016). Flavonoids as cytokine modulators: A possible therapy for inflammation-related diseases. *International Journal of Molecular Sciences*, 17(6), 921.

- Li, G., & De Clercq, E. (2020). Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nature Reviews Drug Discovery*, 19, 149–150.
- Li, Q., Guan, X., Wu, P., Wang, X., Zhou, L., Tong, Y., ... Xing, X. (2020). Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *New England Journal of Medicine*, 382(13), 1199–1207. <https://doi.org/10.1056/NEJMoa2001316>.
- Li, X. Q., Song, Y. N., Wang, S. J., Rahman, K., Zhu, J. Y., & Zhang, H. (2018). Saikosaponins: A review of pharmacological effects. *Journal of Asian Natural Products Research*, 20(5), 399–411.
- Lin, C. W., Tsai, F. J., Tsai, C. H., Lai, C. C., Wan, L., Ho, T. Y., et al. (2005). Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds. *Antiviral Research*, 68(1), 36–42.
- Liu, W., Liu, L., Kou, G., Zheng, Y., Ding, Y., Ni, W., et al. (2020). Evaluation of nucleocapsid and spike protein-based ELISAs for detecting antibodies against SARS-CoV-2. *Journal of Clinical Microbiology*, 58(6), 1–7. <https://doi.org/10.1128/JCM.00461-20>.
- Liu, W., Morse, J. S., Lalonde, T., & Xu, S. (2020). Learning from the past: Possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem*, 21(5), 730–738. <https://doi.org/10.1002/cbic.202000047>.
- Liu, X., Zhang, M., He, L., & Li, Y. (2012). Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS). *Cochrane Database of Systematic Reviews*, 10, CD004882. <https://doi.org/10.1002/14651858.CD004882.pub3>.
- Luo, H., Tang, Q. L., Shang, Y. X., Liang, S. B., Yang, M., Robinson, N., et al. (2020). Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chinese Journal of Integrative Medicine*, 1–8.
- Ma, X., Wu, H., Liu, L., Yao, Q., Wang, S., Zhan, R., et al. (2011). Polyphenolic compounds and antioxidant properties in mango fruits. *Scientia Horticulturae*, 129(1), 102–107.
- Mateeva, N., Eyunni, S. V., Redda, K. K., Ononuju, U., Hansberry, T. D., II, Aikens, C., et al. (2017). Functional evaluation of synthetic flavonoids and chalcones for potential antiviral and anticancer properties. *Bioorganic & Medicinal Chemistry Letters*, 27(11), 2350–2356.
- Moshawih, S., Cheema, M. S., Ahmad, Z., Zakaria, Z. A., & Hakim, M. N. (2017). A comprehensive review on *Cosmos caudatus* (Ulam raja): Pharmacology, ethnopharmacology, and phytochemistry. *International Research Journal of Educational and Sciences*, 1(1), 14–31.
- Nguyen, T. T. H., Woo, H. J., Kang, H. K., Kim, Y. M., Kim, D. W., Ahn, S. A., et al. (2012). Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*. *Biotechnology Letters*, 34(5), 831–838.
- Nikhat, S., & Fazil, M. (2020). Overview of Covid-19; its prevention and management in the light of Unani medicine. *Science of the Total Environment*, 138859.
- Pandey, P., Rane, J. S., Chatterjee, A., Kumar, A., Khan, R., Prakash, A., & Ray, S. (2020). Targeting SARS-CoV-2 spike protein of COVID-19 with naturally occurring phytochemicals: An in silico study for drug development. *Journal of Biomolecular Structure and Dynamics*, 1–11.
- Park, J. Y., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, S. J., Kim, D., et al. (2012). Diarylheptanoids from *Alnus japonica* inhibit papain-like protease of severe acute respiratory syndrome coronavirus. *Biological and Pharmaceutical Bulletin*, 35(11), 2036–2042. <https://doi.org/10.1248/bpb.b12-00623>.
- Rathinavel, T., Palanisamy, M., Palanisamy, S., Subramanian, A., Thangaswamy, S., et al. (2020). Phytochemical 6-Gingerol – A promising drug of choice for COVID-19. *International Journal of Advanced Science and Engineering*, 6(4), 1482–1489. <https://doi.org/10.29294/IJASE.6.4.2020.1482-1489>.



- Reichling, J., & Schnitzler, P. (2011). Antiviral effects of essential oils used traditionally in Phytomedicine. In G. Bagetta, M. Cosentino, M. T. Corasaniti, & S. Sakurada (Eds.), *Herbal medicines: Development and validation of plant-derived medicines for human health* (p. 317). Taylor & Francis (Chapter 18).
- Rengasamy, K. R., Khan, H., Gowrishankar, S., Lagoa, R. J., Mahomoodally, F. M., Khan, Z., et al. (2019). The role of flavonoids in autoimmune diseases: Therapeutic updates. *Pharmacology & Therapeutics*, 194, 107–131.
- Ryu, Y. B., Jeong, H. J., Kim, J. H., Kim, Y. M., Park, J. Y., Kim, D., et al. (2010). Biflavonoids from *Torreya nucifera* displaying SARS-CoV 3CLpro inhibition. *Bioorganic & Medicinal Chemistry*, 18(22), 7940–7947.
- Shaghaghi, N. (2020). Molecular docking study of novel COVID-19 protease with low risk terpenoid compounds of plants. *ChemRxiv*. 10.
- Shannugaraj, B., Siri wattananon, K., Wangkanont, K., & Phoolcharoen, W. (2020). Perspectives on monoclonal antibody therapy as potential therapeutic intervention for coronavirus disease-19 (COVID-19). *Asian Pacific Journal of Allergy and Immunology*, 38(1), 10–18.
- Sharma, A. D., & Kaur, I. J. (2020). Eucalyptol (1,8 cineole) from eucalyptus essential oil a potential inhibitor of COVID 19 corona virus infection by molecular docking studies. *Preprints*, 1–8. <https://doi.org/10.20944/preprints202003.0455.v1>.
- Sheahan, T. P., Sims, A. C., Leist, S. R., Schäfer, A., Won, J., Brown, A. J., et al. (2020). Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nature Communications*, 11(1), 1–14.
- Shi, H., Han, X., Jiang, N., Cao, Y., Alwalid, O., Gu, J., et al. (2020). Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: A descriptive study. *The Lancet Infectious Diseases*, 20(4), 425–434. [https://doi.org/10.1016/S1473-3099\(20\)30086-4](https://doi.org/10.1016/S1473-3099(20)30086-4).
- Simões, C. M. O., Falkenberg, M., Mentz, L. A., Schenkel, E. P., Amoroso, M., & Girre, L. (1999). Antiviral activity of south Brazilian medicinal plant extracts. *Phytomedicine*, 6(3), 205–214.
- Sokmen, M., Angelova, M., Krumova, E., Pashova, S., Ivancheva, S., Sokmen, A., et al. (2005). In vitro antioxidant activity of polyphenol extracts with antiviral properties from *Geranium sanguineum* L. *Life Sciences*, 76(25), 2981–2993.
- Sun, P., Lu, X., Xu, C., Sun, W., & Pan, B. (2020). Understanding of COVID-19 based on current evidence. *Journal of Medical Virology*, 92(6), 548–551.
- Tiwari, R., & Rana, C. S. (2015). Plant secondary metabolites: A review. *International Journal of Engineering Research and General Science*, 3(5), 661–670.
- Ulasli, M., Gurses, S. A., Bayraktar, R., Yumrutas, O., Oztuzcu, S., Igci, M., et al. (2014). The effects of *Nigella sativa* (ns), *Anthemis hyalina* (Ah) and *Citrus sinensis* (Cs) extracts on the replication of coronavirus and the expression of TRP genes family. *Molecular Biology Reports*, 41(3), 1703–1711.
- Velavan, T. P., & Meyer, C. G. (2020). The COVID-19 epidemic. *Tropical Medicine & International Health*, 25(3), 278.
- Velu, G., Palanichamy, V., & Rajan, A. P. (2018). Phytochemical and pharmacological importance of plant secondary metabolites in modern medicine. In *Bioorganic phase in natural food: An overview* (pp. 135–156). Cham: Springer.
- Verma, S. (2020). In search of feasible interventions for the prevention and cure of novel Coronavirus disease 2019. *OSF Preprints*, 1–13. <https://doi.org/10.31219/osf.io/q6tsc>.
- Vijayan, P., Raghu, C., Ashok, G., Dhanaraj, S. A., & Suresh, B. (2004). Antiviral activity of medicinal plants of Nilgiris. *Indian Journal of Medical Research*, 120, 24–29.
- Wink, M. (2020). Potential of DNA intercalating alkaloids and other plant secondary metabolites against SARS-CoV-2 causing COVID-19. *Diversity*, 12(5), 175.

- Wolkerstorfer, A., Kurz, H., Bachhofner, N., & Szolar, O. H. (2009). Glycyrrhizin inhibits influenza a virus uptake into the cell. *Antiviral Research*, 83(2), 171–178.
- Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., ... McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, 367(6483), 1260–1263.
- Xu, X., Xie, H., Hao, J., Jiang, Y., & Wei, X. (2011). Flavonoid glycosides from the seeds of Litchi chinensis. *Journal of Agricultural and Food Chemistry*, 59(4), 1205–1209.
- Yáñez, J. A., Remsberg, C. M., Takemoto, J. K., Vega-Villa, K. R., Andrews, P. K., Sayre, C. L., et al. (2013). Polyphenols and flavonoids: An overview. In N. M. Davies, & J. A. Yáñez (Eds.), *Flavonoid pharmacokinetics. Methods of analysis, preclinical and clinical pharmacokinetics, safety and toxicology* (pp. 1–71). Hoboken, NJ: John Wiley & Sons, Inc.
- Yang, C. W., Lee, Y. Z., Kang, I. J., Barnard, D. L., Jan, J. T., Lin, D., ... Lee, S. J. (2010). Identification of phenanthroindolizines and phenanthroquinolizidines as novel potent anti-coronaviral agents for porcine enteropathogenic coronavirus transmissible gastroenteritis virus and human severe acute respiratory syndrome coronavirus. *Antiviral Research*, 88(2), 160–168.
- Yang, Y., Islam, M. S., Wang, J., Li, Y., & Chen, X. (2020). Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): A review and perspective. *International Journal of Biological Sciences*, 16(10), 1708.
- Yuan, Y., Cao, D., Zhang, Y., Ma, J., Qi, J., Wang, Q., ... Zhang, X. (2017). Cryo-EM structures of MERS-CoV and SARS-CoV spike glycoproteins reveal the dynamic receptor binding domains. *Nature Communications*, 8, 15092.
- Zhang, F., Abudayyeh, O. O., & Gootenberg, J. S. (2020). A protocol for detection of COVID-19 using CRISPR diagnostics. In *A protocol for detection of COVID-19 using CRISPR diagnostics* (p. 8).
- Zhang, K. (2020). Is traditional Chinese medicine useful in the treatment of COVID-19? *The American Journal of Emergency Medicine*. <https://doi.org/10.1016/j.ajem.2020.03.046>. In press.
- Zhang, Y. J., Gan, R. Y., Li, S., Zhou, Y., Li, A. N., Xu, D. P., et al. (2015). Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules*, 20(12), 21138–21156.
- Zhao, Y., Zhao, Z., Wang, Y., Zhou, Y., Ma, Y., Zuo, W., et al. (2020). Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. *American Journal of Respiratory and Critical Care Medicine*, 202(5), 756–759. <https://doi.org/10.1164/rccm.202001-0179LE>.
- Zhou, P., Yang, X. L., Wang, X. G., Hu, B., Zhang, L., Zhang, W., ... Chen, H. D. (2020). A pneumonia outbreak associated with a new coronavirus of probable bat origin. *nature*, 579(7798), 270–273.