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PATHOGENECITY OF CORONAVIRUS AND EFFECT OF NATURAL PRODUCTS FOR IMMUNOMODULATION

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ABSTRACT

Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that this is likely the zoonotic origin ofCOVID-19. Person-to-person transmission of COVID-19 infection led to the isolation of patients that were subsequently administered a variety of treatments. Extensive measures to reduce person-to-person transmission of COVID-19 have been implemented to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. In this review, we highlight the symptoms, epidemiology, transmission, pathogenesis, phylogenetic analysis and future directions to control the spread of this fatal disease.

KEYWORDS: Coronavirus; SARS-CoV-2; SARS-CoV; MERS-CoV; Pathogenesis; Immunomodulation; Anti-Corona Natural Medicine; Chinese Natural Medicine; In-silico Screening; Plasma Therapy Against Corona Patients.

INTRODUCTION

Coronavirus is one of the major pathogens that primarily target the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. These patients were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China. Early reports predicted the onset of a potential Coronavirus outbreak given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, named by WHO on Feb 11, 2020) which was deemed to be significantly larger than 1 (ranges from 2.24 to 3.58) .The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died. By January 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension, and cardiovascular disease. These patients were presumed to be infected in that hospital, likely due to nosocomial infection. It was concluded that the COVID-19 is not a super-hot spreading virus (spread by one patient to many others), but rather likely spread due to many patients getting infected at various locations throughout the hospital through unknown mechanisms. In addition, only patients that got clinically sick were tested, thus there were likely many more patients that were presumably infected. As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (COVID-19) were reported in 25 provinces (districts and cities) in China. The China National Health Com-mission reported the details of the first 17 deaths up to January 22, 2020. On January 25, 2020, a total of 1975 cases were confirmed to be infected with the COVID-19 in mainland China with a total of 56 deaths. Another report on January 24, 2020 estimated the cumulative incidence in China to be 5502 cases. As of January 30, 2020, 7734 cases have been confirmed in China and 90 other cases have also been reported from a number of countries that include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany. The case fatality rate was calculated to be 2.2% (170/7824). The first case of COVID-19 infection confirmed in the United States led to the description,

identification, diagnosis, clinical course, and management of this case. This includes the patient's initial mild symptoms at presentation and progression to pneumonia on day 9 of illness.[1] Further, the first case of human-to-human transmission of COVID-19 was reported in the US on January 30, 2020. The CDC has so far screened > 30,000 passengers arriving at US airports for the novel coronavirus. Following such initial screening, 443 individuals have been tested for coronavirus infection in 41 states in the USA. Only 15 (3.1%) were tested positive, 347 were negative and results on the remaining 81 are pending. A report published in Nature revealed that Chinese health authorities concluded that as of February 7, 2019, there have been 31,161 people who have contracted the infection in China, and more than 630 people have died of infection. At the time of preparing this manuscript, the World Health Organization (WHO) re-ported 51,174 confirmed cases including 15, 384 severe cases and 1666 death cases in China. Globally, the number of confirmed cases as of this writing (February 16, 2020) has reached 51,857 in 25 countries.

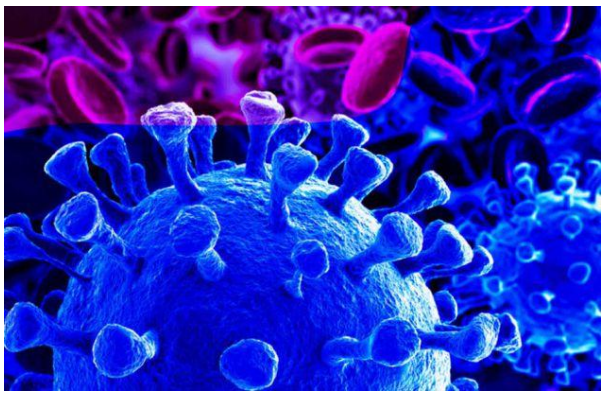


Figure-1: Corona virus cascade.

Virology of corona virus: Coronaviruses are enveloped viruses with a positive sense single-stranded RNA genome (26e32 kb). Four coronavirus genera (a,b,g,d) have been identified so far, with human corona viruses (HCoVs) detected in the A Coronavirus (HCoV-229E and NL63) and B Coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera. In late December 2019, patients presenting with cough, fever, and dyspnea with acute respiratory distress syndrome (ARDS) due to an unidentified microbial infection were reported in Wuhan, China. Virus genome sequencing of five patients with pneumonia hospitalized from December 18 to December 29, 2019, revealed the presence of a previously unknown b-CoV strain in all of them. This isolated novel b-CoV shows 88% identity to the sequence of two bat-derived severe acute respiratory syndromes (SARS)-like Coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21, and about 50% identity to the sequence of MERS-CoV. The novel b-CoV was then named "SARS-CoV-2" by the International Virus Classification Commission. The phylogenetic tree of SARS-like corona viruses complete genome sequences is CoV. The novel b-CoV was then named "SARS-CoV-2" by the International Virus Classification Commission. The phylogenetic tree of SARS-like coronaviruses complete genome sequences is (ORF1a/b), about two-thirds of viral RNA, are translated into two large polyproteins. In SARS-CoV and MERS-CoV, two polyproteins, pp1a and pp1ab, are processed into 16 non-structural proteins (nsp1-nsp16), which form the viral replicase transcriptase complex.[2]

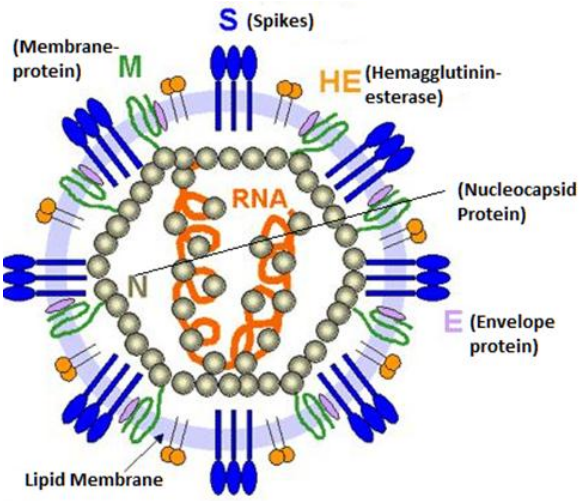


Figure-2: Spikes of corona.

Those nsps rearrange membranes originating from the rough endoplasmic reticulum (RER) into double-membrane vesicles where viral replication and transcription occur. The other ORFs of SARS-CoV-2 on the one-third of the genome encode four main structural proteins: spike (S), envelope (E), nucleocapsid (N) and membrane (M) proteins, as well as several accessory proteins with unknown functions which do not participate in viral replication. Several groups of scientists in China have all discovered that SARS-CoV-2, just like SARS-CoV, requires the angiotensin-converting enzyme 2 (ACE2) as a receptor to enter cells. The binding of the virus with host cell receptors is a significant determinant for the pathogenesis of infection. SARS-CoV most likely originated in bats and adapted to non-bat ACE2 variants as it crossed species to infect humans. Dipeptidyl peptidase 4 (DPP4, also known as CD26) was identified as a functional receptor for MERS-CoV, because the receptor-binding S1 domain of the MERS-CoV spike protein was copurified with DPP4 specifically from lysates of susceptible Huh-7 cells. MERS-CoV can bind DPP4 from multiple species, which promotes the transmission to humans and other species, and infection of cells from a large number of species. A better understanding of the relative effects of receptor binding and protease action will help predict whether specific zoonotic corona viruses infect humans and the possibility of adaptation.

Pathogenicity of corona virus

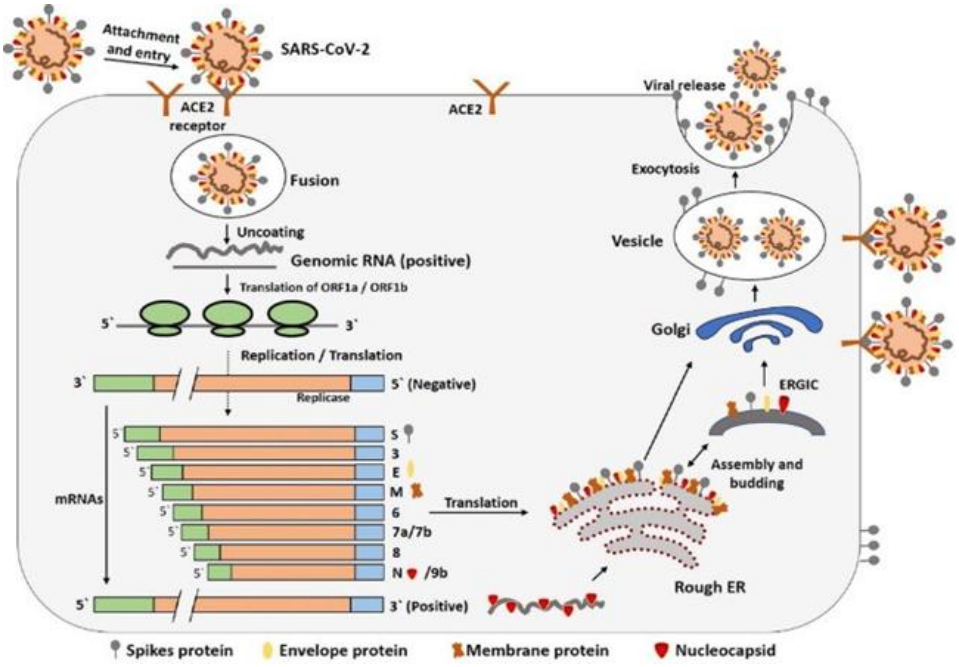


Figure 3: Pathogenicity.

Corona virus attachment and release: Patients with COVID-19 show clinical manifestations including fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia, which are similar to the symptoms of SARS-CoV and MERS-CoV infections. Hence, although the pathogenesis of COVID-19 is poorly understood, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a lot of information on the pathogenesis of SARS-CoV-2 infection to facilitate our recognition of COVID-19.[3]

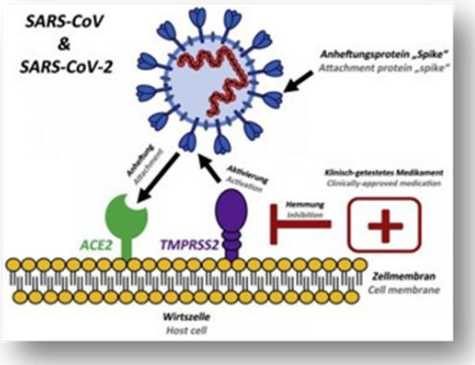


Figure 4: Corona virus replication.

1. Coronavirus Entry and Replication: Coronavirus S protein has been reported as a significant determinant of virus entry into host cells. The envelope spike glycoprotein binds to its cellular receptor, ACE2 for SARS-CoV and SARS-CoV-2, CD209L (a C-type lectin, also called L-SIGN) for SARS-CoV, DPP4 for MERS-CoV. The entry of SARS-CoV into cells was initially identified to be accomplished by direct membrane fusion between the virus and plasma membrane. Belouzard et al. found that a critical proteolytic cleavage event occurred at SARS-CoV S protein at position (S20) mediated the membrane fusion and viral infectivity. MERS-CoV also has evolved an abnormal two-step furin activation for membrane fusion. Besides membrane fusion, the clathrin-dependent and independent endocytosis mediated SARS-CoV entry too. After the virus enters the cells, the viral RNA genome is released into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate. The newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus.

2. Antigen Presentation in Coronavirus Infection: While the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC), which is a central part of the body's anti-viral immunity. Antigenic peptides are presented by major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) and then recognized by virus specific cytotoxic T lymphocytes (CTLs). Hence, the understanding of antigen presentation of SARS-CoV-2 will help our comprehension of COVID-19 pathogenesis. Unfortunately, there is still lack of any report about it, and we can only get some information from previous researches on SARS-CoV and MERS-CoV. The antigen presentation of SARS-CoV mainly depends on MHC I molecules, but MHC II also contributes to its

presentation. Previous research shows numerous HLA polymorphisms correlate to the susceptibility of SARS-CoV, such as HLA-B*4601, HLA-B*0703, HLA-DRB1*1202 and HLA-Cw*0801, whereas the HLA-DR0301, HLA-Cw1502 and HLA-A*0201 alleles are related to the protection from SARS infection. In MERS-CoV infection, MHC II molecules, such as HLA-DRB1*11:01 and HLA-DQB1*02:0, are associated with the susceptibility to MERS-CoV infection. Besides, gene polymorphisms of MBL (mannose-binding lectin) associated with antigen presentation is related to the risk of SARS-CoV infection. These researches will provide valuable clues for the prevention, treatment, and mechanism of COVID-19.

3. Humoral and cellular immunity: Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells. Similar to common acute viral infections, the antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG production. The SARS-specific IgM antibodies disappear at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role, and the SARS-specific IgG antibodies primarily are S-specific and N-specific antibodies. Comparing to humoral responses, there are more researches on the cellular immunity of coronavirus. The latest report shows the number of CD4þ and CD8þT cells in the peripheral blood of SARS-CoV-2-infected patients significantly is reduced, whereas its status is excessive activation, as evidenced by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions. Similarly, the acute phase response in patients with SARS-CoV is associated with severe decrease of CD4þT and CD8þT cells. Even if there is no antigen, CD4þ and CD8þ memory T cells can persist for four years in a part of SARS- CoV recovered individuals and can perform T cell proliferation, DTH response and production of IFN-g. Six years after SARS-CoV infection, specific T-cell memory responses to the SARS-CoV's peptide library could still be identified in 14 of 23 recovered SARS patients. The specific CD8þT cells also show a similar effect on MERS-CoV clearance in mice. These findings may provide valuable information for the rational design of vaccines againstSARS-CoV-2.

4. Cytokine storm in COVID-19: The report in Lancet shows ARDS is the main death cause of COVID-19. Of the 41 SARS- CoV-2-infected patients admitted in the early stages of the outbreak, six died from ARDS. ARDS is the common immune pathological event for SARS-CoV-2, SARS-CoV and MERS- CoV infections. One of the main mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18,IL-33, TNF-a, TGFb, etc.) and chemokines (CCL2, CCL3, CCL5,CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection. Similar to those with SARS-CoV, individuals with severe MERS-CoV infection show elevated levels of IL-6, IFN-a, and CCL5, CXCL8, CXCL-10 in serum compared to those with the mild-moderate disease. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally lead to death in severe cases ofSARS-CoV-2 infection, just like what occurs in SARS-CoV and MERS-CoV infection.[4]

5. Coronavirus Immune Evasion: To better survive in host cells, SARS-CoV and MERS-CoV use multiple strategies to avoid immune responses. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs). However, SARS-CoV and MERS-CoV can induce the production of double- membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their ds-RNA. IFN-I (IFN-a and IFN-b) has a protective effect on SARS- CoV and MERS-CoV infection, but the IFN-I pathway is inhibited in infected mice. Accessory protein 4a of MERS-CoV may block the induction of IFN at the level of MDA5 activation through direct interaction with double-stranded RNA. Besides, ORF4a, ORF4b, ORF5, and membrane proteins of MERS-CoV inhibit nuclear transport of IFN regulatory factor 3 (IRF3) and activation of IFN-b promoter. The antigen presentation can also be affected by the coronavirus. For example, gene expression related to antigen presentation is down-regulated after MERS-CoV infection. Therefore, destroying the immune evasion of SARS-CoV-2 is imperative in its treatment and specific drug development.

Effect of natural products for immunomodulation: Natural compounds have contributed enormously to immunomodulatory therapeutics. Since ancient times, natural medicines have constituted treatments with minimal side effects. There are thousands of natural compounds that are known to influence the immune system by either affecting the functions of immune cells or affecting antibody secretion to control the infection and to maintain immune homeostasis. The relevance of this research would be crucial to the search for better treatments, both to complement those that already exist and to develop new strategies for the prevention and treatment of immune-related diseases. Therefore, it is interesting to dissect the molecular mechanisms of the immunomodulatory effects of natural compounds and to discover novel promising candidates that can be used in the future immunotherapeutic strategies. Immunomodulation is a key issue in tissue homeostasis for the physiological stability of organisms. Consequently, it is important to search for immunoregulators, such as those derived from natural immunomodulators, with less severe side effects. This is the case for the work of Y.-H. Cheng et al. in which the authors demonstrate Th-1 selective immunomodulatory

activity for crude leaf extracts from Neolitsea spp., which contains phytochemicals meriting further research as potentials for development as selective immunomodulators. Additionally, M. O. Arruda et al. reported the modulatory activity of *Mentha piperita* (peppermint) leaf hydroalcoholic extract on macrophages, which are essential cells against bacterial infection, by attenuating their oxidative stress and improving their survival.

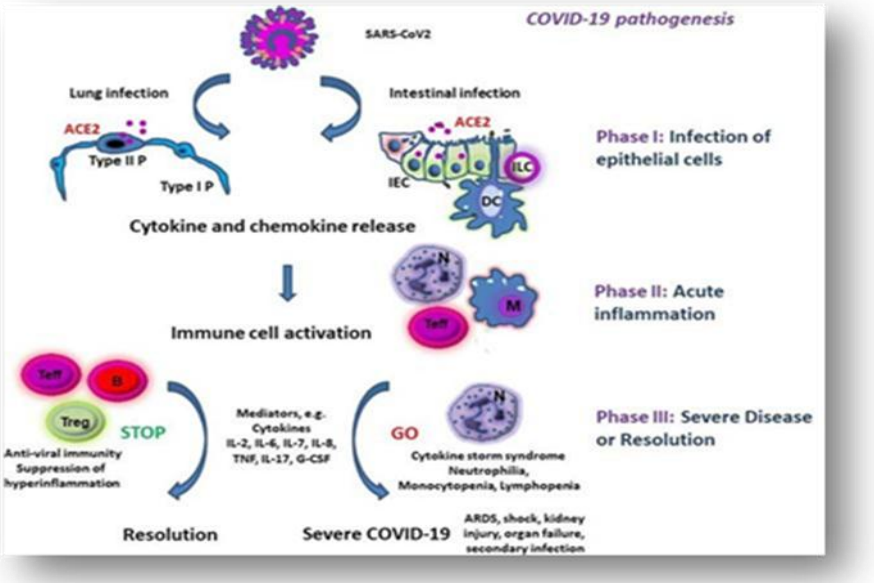


Figure-5: Immunomodulation.

Furthermore, S. Lewicki et al. explored the immunomodulatory properties of the *Rhodiola kirilowii* aqueous extract to stimulate innate immunity in an attempt to avoid, or to limit, the excessive use of antibiotics during pregnancy and lactation, which has been associated with a risk for immune system developmental disorders. Cytokines and chemokines regulate immune responses by signalling, through membrane receptors, whose signaling pathways can be evaded or mimicked by viruses.[5]

Natural products effective against corona virus: The antiviral activities from several Natural Products and Chinese Herbal medicines against coronavirus (CoV). These Chinese herbal medicines and purified natural products provide a rich resource for novel antiviral drug development, while *in-silico* screening and AI will enable more chemical combinations to be tested with fewer human trials, making drug development faster, cheaper, and safer. Although the WHO said: "To date, there is no specific medicine recommended to prevent or treat the novel corona virus", Chinese medicine (CM) approaches including oral administration of preventive herbal formulae, were always recommended for prevention and treatment of infectious diseases, even during the current outbreak of COVID-19.

Based on that information, 23 provinces in China issued CM programs for prevention of COVID-19 using the following herbs:

(a) *Radix astragali* (Huangqi), is a popular traditional Chinese medicine and its active compounds may help strengthen the immune system and reduce inflammation. Astragalus is sometimes also given as an injection or by IV in a hospital setting.
(b) *Radix glycyrrhizae* (Gancao) or liquorice root is one of the 50 fundamental herbs used in traditional Chinese medicine.
(c) *Radix saposhnikoviae* (Fangfeng), Saposhnikovia divaricata — known as fángfēng meaning "protect against the wind" in Chinese and siler in English — is the sole species in the genus Saposhnikovia (family Apiaceae), still frequently referenced under the obsolete genus name Ledebouriella in many online sources devoted to traditional Chinese medicine.
(d) *Rhizoma Atractylodis Macrocephalae* (Baizhu), it is praised as "the most important herb of tonifying and invigorating the spleen".
(e) *Lonicerae Japonicae Flos* (Jinyinhua), is one of the most commonly used traditional Chinese medicines, contains biologically active compounds such as caffeic acid derivatives, essential oil, flavonoids, iridoid glycosides and terpenoids, and has anti-inflammatory, antitumor, antioxidant, antiallergy, immunomodulating and antibacterial activity biological activities.
(f) *Fructus forsythia* (or called Lian qiao in mandarin) has long been known as the panacea for people who are particularly susceptible to skin infections and it has a broad-spectrum antimicrobial activity (*Staphylococcus aureus* and *Shigella*) and a certain inhibition on influenza

virus, leptospira, and other pathogens. It has also anti-inflammatory and antipyretic effects.

The conclusions were that based on historical records and human evidence of SARS and H1N1 influenza prevention, Chinese herbal formula could be an alternative approach for prevention of COVID-19 in high-risk population, but prospective and rigorous population studies are warranted to confirm the potential preventive effect of CM.

Moreover, it has been reported that saikosaponins (A, B2, C, and D) — which are naturally occurring triterpene glycosides — isolated from medicinal plants such as:
Bupleurum sp. (Bupleurum is a large genus of annual or perennial herbs or woody shrubs, with about 190 species, belonging to the family Apiaceae.
Heteromorpha sp. (Heteromorpha is a genus of plants within the family Apiaceae commonly known as the celery, carrot or parsley family, or simply as umbellifers)
Scrophularia scorodonia (the genus Scrophularia of the family Scrophulariaceae comprises about 200 species of herbaceous flowering plants commonly known as figworts).
All exert antiviral activity against HCoV-22E9—a species of CoV which infects humans and bats, and along with human coronavirus OC43 it is one of the viruses responsible for the common cold).

Conclusion: Saikosaponins (A, B2, C, and D) effectively prevented the early stage of HCoV-22E9 infection, including viral attachment and penetration.
It has also been reported that extracts from-
Lycoris radiate (known as the red spider lily, hell flower, red magic lily, or equinox flower, is a plant in the amaryllis family Amaryllidaceae, commonly known as the amaryllis family).

Artemisia annual (or Sweet wormwood belongs to the plant family of Asteraceae).

Pyrrosia lingua (is an epiphytic fern in the family Polypodiaceae).

Lindera aggregata (is a plant species belonging to the genus Lindera, and common names include spicewood, spicebush, and Benjamin bush) all display anti–SARS activity after a screening analysis using hundreds of Chinese medicinal herbs. Moreover, natural inhibitors against the SARS enzymes, such as the nsP13 helicase and 3CL protease, have been identified and include-

Myricetin (flavonoid polyphenolic compound with antioxidant properties found in vegetables, fruits, nuts, berries, tea and red wine).

Scutellarein (a flavone that can be found in *Scutellari lateriflora*, a hardy perennial herb of the mint family and other members of the genus Scutellaria, as well as *Asplenium belangeri*).

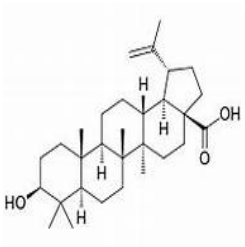
Phenolic compounds from: *Isatis indigotica* and *Torreya nucifera*. Other anti-CoV natural medicines include the water extract from *Houttuynia cordata* (also known as fish mint, fish leaf, rainbow plant, chameleon plant, heart leaf, fish wort, Chinese lizard tail, or bishop's weed, and is one of two species in the genus Houttuynia), which has been observed to exhibit several antiviral mechanisms against SARS, such as inhibiting the viral 3CL protease and blocking the viral RNA-dependent RNA polymerase activity.[6]

HUANGQI **FANGFENG** **BAIZHU**

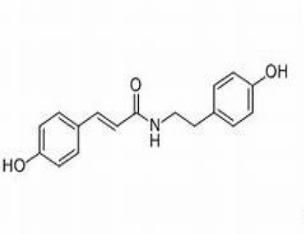
JIN YIN HUA **LIAN QIAO** **LYCORIS RADIATA**

Figure 6: Chinese medicine.

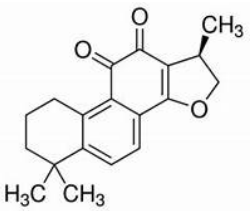
***In-silico* screening:** *In-silico* and biological processing, a series of small molecules from natural compounds have been screened searching for antiviral drugs. For that reason, in the first step of the process a literature search was conducted for natural compounds that had been biologically confirmed acting against SARS and MERS. The resulting compounds were cross-checked for listing in the Traditional Chinese Medicine Systems Pharmacology Database, and compounds meeting both requirements were subjected to absorption, distribution, metabolism and excretion (ADME) evaluation to verify that oral administration would be effective. Next, a docking analysis was used to test whether the compound had the potential for direct COVID-2019 protein interaction. In the second step the Chinese herbal database was searched to identify plants containing the selected compounds, and the plants containing 2 or more of these compounds identified in the screen were then checked against the catalogue for classic herbal usage.



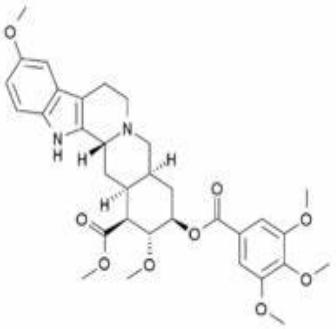
Betulinic acid



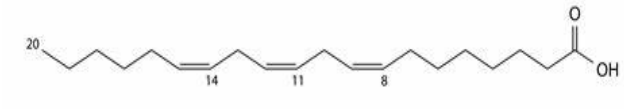
Coumaroyltyramine



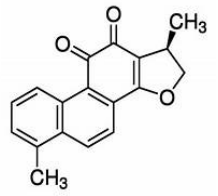
Cryptotanshinone



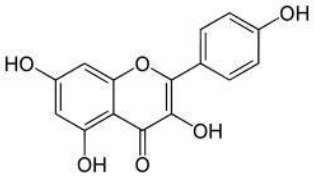
Desmethoxyreserpine



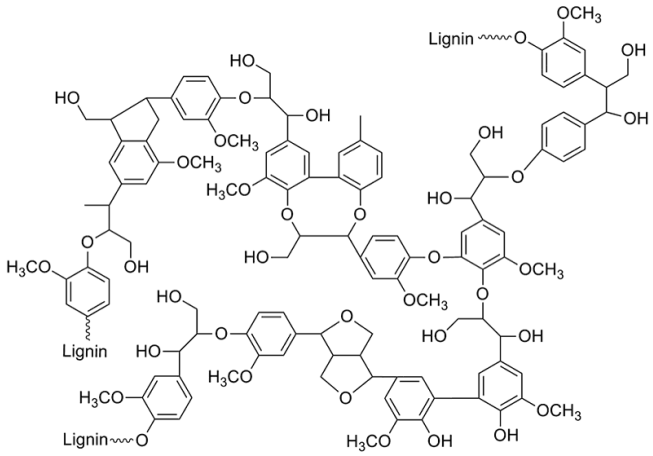
Dihomo-γ-linolenic acid



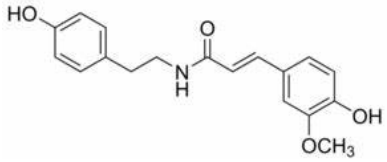
Dihydrotanshinone



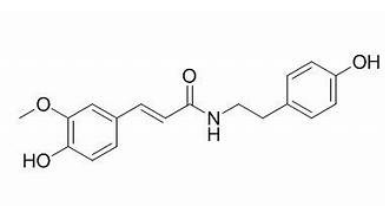
Kaempferol



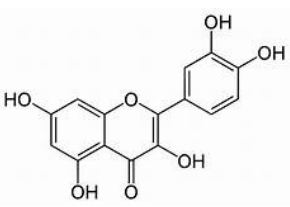
Lignan



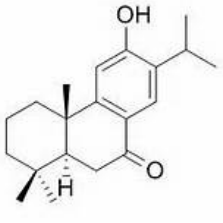
Moupinamide



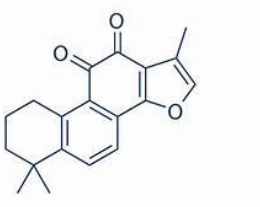
N-cis-feruloyltyramine



Quercetin



Sugiol



Tanshinone IIa

Figure 7: Natural products against corona.

Finally, network pharmacology analysis was used to predict the general *in-vivo* effects of each selected herb. In the end, 13 natural compounds (betulinic acid, coumaroyltyramine, cryptotanshinone, desmethoxyreserpine, dihomo-γ-linolenic acid, dihydrotanshinone, kaempferol, lignan, moupinamide, N-cis-feruloyltyramine, quercetin, sugiol, tanshinone IIa) that exist in traditional CM were found to have potential anti-COVID-2019 activity. Further, 125 Chinese herbs were found to contain 2 or more of these 13 compounds and of these 125 herbs, 26 were catalogued as treating viral respiratory infections. Network pharmacology analysis predicted that the general in vivo roles of these 26 herbal plants were related to regulating viral infection, immune/inflammation reactions and hypoxia response.[7]

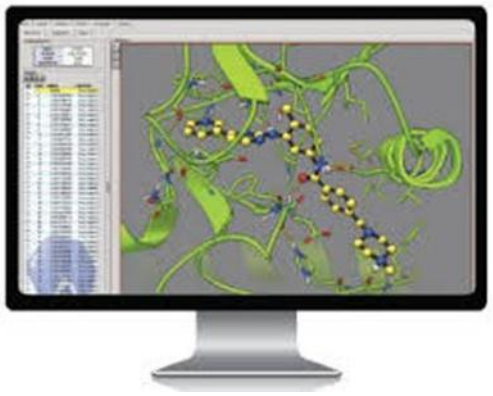
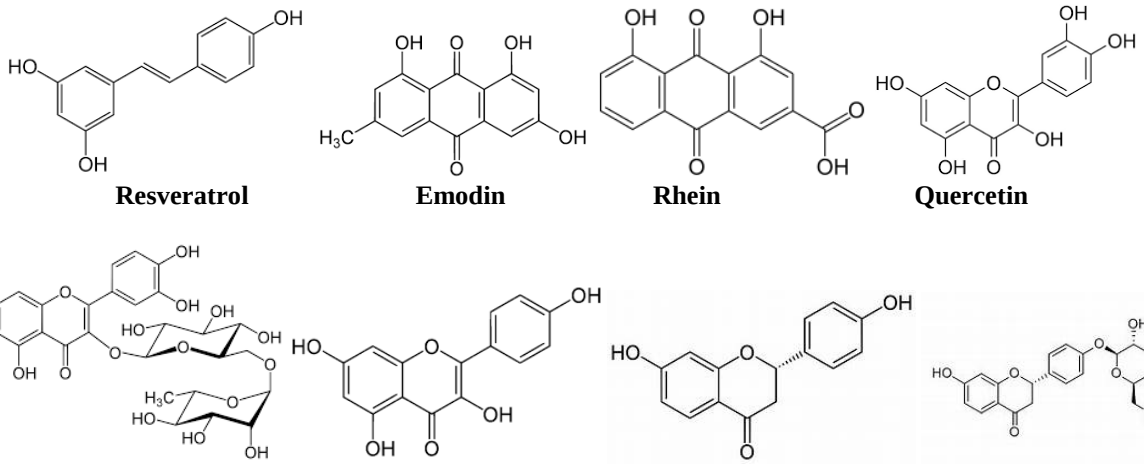


Figure 8: In-silico screening of natural products.



Resveratrol **Emodin** **Rhein** **Quercetin**

Rutin **Kaempferol** **Iquiritigenin** **Liquiritin**

Figure 9: Natural drugs.

Combined treatment of western medicines and Chinese natural products: In another interesting study, from Shanghai Public Health Clinical Center, it has been reported that four patients with mild or severe COVID-19 pneumonia have been cured or have significant improvement in their respiratory symptoms after treatment with combined lopinavir/ritonavir (Kaletra®: the two antiretroviral components lopinavir and ritonavir, are protease inhibitors designed to block HIV viral replication), arbidol (a broad-spectrum antiviral compound that blocks viral fusion), and Shufeng Jiedu Capsule (SFJC, a traditional Chinese medicine: resveratrol, emodin, rhein, quercetin, rutin, kaempferol, iquiritigenin and liquiritin) on the base of supportive care. SFJDC is a traditional Chinese medicine for treatment of influenza in China. The duration of the antiviral treatment was 6– 15 days and in addition, all patients were given antibiotic treatment and started on supplemental oxygen after admission to the hospital. All four patients in this study were recruited from January 21 to January 24, 2020 at Shanghai Public Health Clinical Centre, which is a designated hospital for COVID-19 pneumonia.[8]

So, two mild and two severe COVID-19 pneumonia patients were given combined Chinese and Western medicine treatment, and by February 4, 2020 three of them gained significant improvement in pneumonia associated symptoms, while the fourth patient with severe pneumonia was still using ventilators by the cutoff date for data collection. The efficacy of antiviral treatment including lopinavir/ritonavir, arbidol, and SFJDC warrants further verification in future studies. In this clinical study, 135 COVID-19 patients were all received antiviral therapy (135 received both Kaletra and interferon), while 59 received antibacterial therapy, and 36 received corticosteroids. In addition, many patients (124) received traditional CM. The Chinese herbals used to treat COVID-19 primarily included glycyrrhiza, ephedra, bitter almond, gypsum, reed root, amomum, and trichosanthes, and their primarily function was to clear heat, to relieve cough and to increase immunity. This study suggested that patients should receive Kaletra very early and should also be treated by a combination of western and CM, since Kaletra and traditional CM played an important role in the treatment of the viral pneumonia. Of course, further studies are required to explore the role of Kaletra and traditional Chinese Medicines in the treatment of COVID-19.

Convalescent Plasma Therapy Against In Coronavirus Patients

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which originated in Wuhan, China, has become a major concern all over the world. The pneumonia induced by the SARS-CoV-2 is named coronavirus disease 2019 (COVID-19). By Feb 22, 2020, this virus has affected more than 77 700 people worldwide and caused more than 2300 deaths. To date, no specific treatment has been proven to be effective for SARS-CoV-2 infection. Apart from supportive care, such as oxygen supply in mild cases and extracorporeal membrane oxygenation for the critically ill patients, specific drugs for this disease are still being researched. In the USA, the first patient infected with SARS-CoV-2 was treated by supportive care and intravenous remdesivir, before the patient recovered and was discharged. However, randomised clinical trials are needed to evaluate the safety and efficacy of remdesivir in the treatment of COVID-19. Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone. Moreover, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma. In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks. A protocol for the use of convalescent plasma in the treatment of Middle East respiratory syndrome coronavirus was established in 2015. In terms of patients with pandemic 2009 influenza A H1N1 (H1N1pdm09) virus infection, a prospective cohort study by Hung and colleagues showed a significant reduction in the relative risk of mortality (odds ratio 0·20 [95% CI 0·06–0·69], p=0·01) for patients treated with convalescent plasma. Additionally, in a subgroup analysis, viral load after convalescent plasma treatment was significantly lower on days 3, 5, and 7 after intensive care unit admission. No adverse events were observed. A multicentre, prospective, double-blind, randomised controlled trial by Hung and colleagues showed that using convalescent plasma from patients who recovered from the influenza A H1N1pdm09 virus infection to treat patients with severe influenza A H1N1 infection was associated with a lower viral load and reduced mortality within 5 days of symptom onset. A meta-analysis by Mair-Jenkins and colleagues showed that the mortality was reduced after receiving various doses of convalescent plasma in patients with severe acute respiratory infections, with no adverse events or complications after treatment. Another meta-analysis by Luke and colleagues identified eight studies involving 1703 patients with 1918 influenza pneumonia from 1918 to 1925 who received an infusion of influenza-convalescent human blood products, which showed a pooled absolute reduction of 21% (95% CI 15–27; p≤ 0.001) in the overall crude case-fatality rate at low risk of bias.[9]

One possible explanation for the efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viraemia. Schools and colleagues reported that 3BNC117-mediated immunotherapy, which is a broad neutralising antibody to HIV-1, enhances host humoral immunity to HIV-1. An *in-vivo* trial also showed that the effects of this antibody were not only limited to free viral clearance and blocking new infection, but also included acceleration of infected cell clearance. Viraemia peaks in the first week of infection in most viral illnesses. The patient usually develops a primary immune response by days 10–14, which is followed by virus clearance. Therefore, theoretically, it should be more effective to administer the convalescent plasma at the early stage of disease. However, other treatments might have an effect on the relationship between convalescent plasma and antibody level, including antiviral drugs, steroids, and intravenous immunoglobulin. According to WHO, management of COVID-19 has mainly focused on infection prevention, case detection and monitoring, and supportive care. However, no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence. Most importantly, the current guidelines emphasise that systematic corticosteroids should not be given routinely for the treatment of COVID-19, which was also the recommendation in a Commnt in The Lancet. Evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients.[10]

CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. Pathogenicity of corona virus outbreak can be controlled by the use of naturopathy through growing immunity power by using natural remedy process and plasma therapy.

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