

MANAGEMENT OF CORONAVIRUS DISEASE 2019 (COVID-19) – IS THERE A ROLE FOR
COMPLEMENTARY AND HERBAL MEDICINAL PRODUCTS?

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Introduction

Coronaviruses (CoVs) constitute a large family of enveloped positive sense single-stranded RNA viruses, which, due to spiky projections on their surfaces, have crown-like appearance when viewed under the electron microscope. They are divided into four genera, namely, alpha-, beta-, gamma-, and delta-coronaviruses. These viruses, in general, can infect different types of animals as well as humans causing respiratory, gastrointestinal, and nervous system diseases (Huang *et al*, 2020). Prior to the recent CoV disease outbreak, six species of the viruses that infect humans were known, prominent among which are Severe Acute Respiratory Syndrome-CoV (SARS-CoV) and Middle East Respiratory Syndrome-CoV (MERS-CoV). The other four species (229E, HKU1, OC43, NL63) usually cause common cold symptoms (Rothana and Byrared, 2020). Thus, they are pathogens with the human respiratory system as their primary target. Coronaviruses have peculiarity in the sense that they have large genetic diversity and their genomes frequently undergo recombination or mutation. These characteristics result in the periodic emergence of new strains of the virus that have different virulence characteristics. In December 2019, the appearance of a novel coronavirus was reported in Wuhan, Hubei Province of China. This new CoV, just like the earlier known SARS-CoV and MERS-CoV, is zoonotic and belongs to the genus beta-coronavirus. It was identified and called severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2), and also named Coronavirus Disease 2019 (abbreviated COVID-19) by World Health Organization (WHO). The symptoms in patients with SARS-CoV-2 include fever, cough, fatigue, dyspnea, runny nose, other upper respiratory symptoms and pneumonia, and these symptoms manifest after an incubation period which ranges from 2 to 14 days. The disease is asymptomatic in many people, mild to moderate in most cases, while it may be severe in the elderly and those with comorbidities resulting in severe pneumonia, acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. The virus is more contagious and spreads faster than its predecessors (SARS-CoA and MERS-CoA) and its fatality rate has been estimated to range from 2 to 5% (Huang *et al*, 2020; Rothan and Byrared, 2020).

Therapeutic agents for Covid-19

The WHO has published detailed guidelines for the management of COVID-19 patients, but as of date, no drug has received approval from regulatory authorities for COVID-19 treatment. Since COVID-19 is a new pathogen, it will take some time to discover specific new drugs. However, an efficient therapeutic strategy is to explore existing drugs for the virus that could have efficacy against the pathogen, and this approach is called repurposing. Drug repurposing is an attractive approach in the discovery of new class of medicines. The strategy facilitates the detection of new classes of medicines, and the process is also associated with lower costs and requires less time for the drug to receive a final approval to be used for the new indication. Currently, several existing drugs are undergoing clinical studies to test their safety and efficacy in the treatment of COVID-19. Also, based on the experiences with SARS-CoA and MERS-CoA, numerous antiviral agents and immunotherapies are being investigated for efficacy against the virus. As of date, more than 900 clinical trials on COVID-19 potential treatments and interventions are underway world-wide (NIH ClinicalTrial.gov). These treatments and potential interventions can generally be classified as follows:

- (a) Anti-infective Agents with Antiviral Activity
- (b) Antiviral Agents
- (c) Adjunctive Therapy: Immunosuppressant and Immunomodulatory Agents
- (d) Complementary and Herbal Medicinal Products

Anti-infective Agents with Antiviral Activity

- i. **Chloroquine and Hydroxychloroquine:** Chloroquine phosphate, an old antimalarial drug which is also used for rheumatoid arthritis, has been demonstrated in multicenter clinical trials to be effective in COVID-19 patients. The literature indicates that this anti-malarial has broad-spectrum antiviral activity. The hydro-derivative of chloroquine (Hydroxychloroquine) has also been reported to be associated with significant reduction in viral load in COVID-19 patients. Hydroxychloroquine has the advantage of having a better safety profile compared to chloroquine. However, clinical studies are still inclusive on the safety and efficacy of these antimalarial drugs and there are concerns about their known side-effects. These drugs received immediate attention for testing on COVID-19 because earlier studies had shown that Chloroquine inhibits the ability of SARS-CoV to replicate in human cells, and similar findings were made with the new coronavirus (Liu *et al*, 2020).
- ii. **Azithromycin:** This is a macrolide antibiotic used for treatment of a broad range of bacterial infections. Also, macrolide antibiotics are reported to have antiviral properties through a mechanism that is yet to be fully ascertained. In a study with COVID-19 patients that received either hydroxychloroquine alone or hydroxychloroquine in combination azithromycin, those that received the drug combination had a more rapid decline in the viral load, indicative of a synergistic interaction (Gautret *et al*, 2020). However, a more recent study showed no evidence of more rapid antiviral clearance with the combination of both drugs in patients with severe COVID-19 (Molina *et al*, 2020). Thus, clinical trial results are inconclusive.
- iii. **Carrimycin:** Like azithromycin, this is a macrolide antibiotic with effects against some gram-positive bacteria. It is undergoing clinical trials for efficacy against COVID-19 (Rosa and Santos, 2020). There is no evidence yet to prove the efficacy of the drug in COVID-19 patients.

Antiviral Agents

Several antiviral drugs used for different indications are currently undergoing clinical studies of their efficacies and safety in the treatment of COVID-19. Table 1 shows a summary of findings with the antiviral drugs which include lopinavir-ritonavir, remdesivir, favipiravir, rivabirin, arbidol, darunavir and oseltamivir.

Table 1: Antiviral drugs undergoing clinical trials for COVID-19 treatment (Sanders *et al*, 2020; Liu *et al*, 2020; Rosa and Santos, 2020)

Drug	Approved Drug Use	Comments
Lopinavir–ritonavir	Antiretroviral (HIV infection)	Some studies have shown that in patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care.
Remdesivir	A broad spectrum drug developed for Ebola	Under clinical evaluation for the efficacy and safety in COVID-19. There are promising results.
Favipiravir	Viral Infections	Undergoing clinical studies with promising results observed
Ribavirin	Hepatitis C, some viral hemorrhagic fevers	Undergoing clinical evaluation. Data with other CoVs show inconclusive efficacy and coupled with its high toxicity, it is suggested that it may have limited value for treatment of COVID-19
Arbidol	Influenza antiviral drug	Some data indicate that arbidol may be superior to lopinavir/ritonavir in treating COVID-19
Darunavir	HIV infection	Under clinical evaluation for the efficacy and safety in COVID-19.
Oseltamivir	Influenza virus types A and B	Under clinical evaluation and its efficacy currently remains uncertain.

Adjunctive Therapy: Immunosuppressant and Immunomodulatory Agents

Similar to the observations in SARS-CoV and MERS-CoV, COVID-19 also induces cytokine storm which is related to the severity and prognosis of the disease. This provides a basis for the use of cytokine inhibitors and immunosuppressants as adjuncts in the treatment of COVID-19. Adjunctive therapies that are undergoing clinical trials for COVID-19 treatment include anti-cytokines, immunomodulatory agents and immunoglobulin therapy.

1. Anticytokines
Tocilizumab is a recombinant anti-human IL-6 receptor monoclonal antibody currently used mainly for rheumatoid arthritis. Studies have shown that the drug significantly improves clinical symptoms in severe COVID-19 patients (Xu *et al* 2020). Several clinical trials of tocilizumab, administered alone or in combination to COVID-19 patients with severe pneumonia are underway (Sanders *et al*, 2020).
Sarilumab is another IL-6 receptor antagonist approved for rheumatoid arthritis and currently undergoing clinical trials in hospitalized patients with severe COVID-19 (Sanders *et al*, 2020).
- ii. Other monoclonal antibodies/ immunomodulatory agents: There are monoclonal antibodies apart from anti-cytokines that inhibit pathways identified to contribute to COVID-19 symptoms. **Bevacizumab** is a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) and is approved for the treatment of patients with metastatic colorectal cancer. Its potential use in COVID-19 is based on the observation of increased blood levels of VEGF in COVID-19 patients. VEGF is a potent vascular permeability inducer that can cause pulmonary oedema. The drug is undergoing clinical trials for COVID-19 treatment for improvement of acute respiratory distress syndrome (ARDS). Another drug undergoing clinical studies is **Fingolimod**, an immunomodulator approved for multiple sclerosis. It is a sphingosine-1-phosphate receptor modulator which prevents development of ARDS. (Sanders *et al*, 2020; Rosa and Santos, 2020).
- ii. Interferons: Several studies are currently investigating the safety and efficacy of different interferons, especially α -interferon, Interferon β -1a and interferon- α 2 β in the treatment of COVID-19. This is based on the efficacy of interferon α 2 β in combination with other agents in the initial treatment of SARS-CoV and MERS-CoV. They are being used with the understanding that interferon can activate the immune system such as natural killer cells and macrophages, thereby increasing the host's defense mechanism (Rosa and Santos, 2020). Interferons are approved for use based on their effects against some viruses, including hepatitis B virus and hepatitis C virus.
- iii. Immunoglobulin Therapy: This is the use of plasma from recovered patients which contain high levels of the specific immunoglobulins (antibody). There have been reports on the efficacy of convalescent plasma in SARS-CoV and MERS-CoV patients. Convalescent plasma has been used with promising results for severe SARS-CoV-2 infection in China. It is currently undergoing full clinical trials.

Complementary and Herbal Medicinal Products

Herbal medicines contain numerous phytochemical compounds that usually mediate a broad range of pharmacological activities. These phytoconstituents can be acting synergistically such that an individual compound isolated from a herbal medicinal product (HMP) may not reproduce the effect of the whole herbal extract. Traditional medical practice has been in existence for thousands of years, and has been fully established and well documented in many countries, especially China and India. Traditional Chinese medicine (TCM) is practiced in parallel with orthodox medicine. For example, following the outbreak of COVID-19 in Hubei Province of China, it was reported that more than 3100 medical staff were dispatched to participate in the treatment of the disease. Also, guidelines on the treatment of COVID-19 currently includes the TCM scheme (Yang *et al*, 2020).

There are several news reports (not in scientific journals) on effective applications of complementary and herbal products in COVID-19 patients but, such claims that are not backed by clinical trials cannot be relied upon. Most of these herbal remedies claimed to have been used contain herbs known to be immune system boosters (e.g. garlic, ginger, turmeric, ginseng, lemon, and so on).

Studies from Africa

In Africa, there are efforts from different countries aimed at exploring herbal remedies for COVID-19. For example, in Madagascar, the Malagasy Institute of Applied Research developed a herbal remedy branded COVID-Organics which contains Artemisia, the herb from which the antimalarial drug artemisinin is isolated. There is abundant literature describing the broad-spectrum antiviral activity of artemisinin and its derivatives. It was reported that trials and tests conducted with COVID-organics demonstrated its effectiveness in reducing COVID-19 symptoms and efficacy in treating some patients. For this HMP to have a global application, it will go through the standard clinical trial processes to establish its safety and efficacy. A group of scientists from the University of Ibadan, Nigeria, have recommended that aqueous extract of a medicinal plant called *Euphorbia Hirta* can alleviate some of the symptoms associated with COVID-19. This is based on established effectiveness of the HMP in curing fever, dry cough, and respiratory diseases, among others, which are the major manifestations of COVID-19. This will require further clinical studies. In Ghana, it is reported that the Centre for Plant Medicine Research is collaborating with the Ministry of Health and other stakeholders in research to develop a herbal remedy for COVID. The outcome is still pending. There are several assertions by individuals and groups on having HMPs with potential efficacy in COVID-19 treatment. Some of

these claims contain *Azadirachta indica* (neem), a medicinal plant with a broad range of pharmacological activities including antimalarial, immunomodulatory and antiviral. These claims are awaiting substantiation.

The examples provided hereunder are on HMPs and complementary medicines that are undergoing clinical trials as well as those with experimental evidence indicating their potentials for effectiveness in COVID-19 treatment.

1. Traditional Chinese Medicine (TCM)

There are not less than 10 ongoing clinical trials for the treatment of COVID-19 with TCM. The application of TCMs in COVID-19 treatment is based on experiences acquired from the treatment of SARS-CoV. Several clinical studies have confirmed the efficacy and safety of these herbal remedies in SARS-CoV infection. Studies on the mode of action of the TCM indicated that they contain compounds that directly inhibit SARS-CoV by acting on multiple ribosomal proteins, while some of the compounds act on pathways that result in alleviation of the main symptoms of the disease.

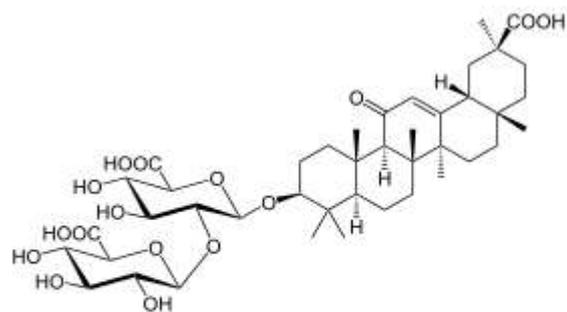
All the TCMs for COVID-19 treatment are prepared from multiple herbs and a typical example is *Qingfei Paidu* decoction (QPD). This is a decoction prepared from as many as 20 different herbs. Medicinal plants used in more than five formulations include *Scutellaria baicalensis*, *Pogostemon cablin*, *Glycyrrhiza* spp., *Magnolia officinalis*, *Ephedra* spp., *Armeniaca* spp., *Atractylodes macrocephala* and *Forsythia suspensa*.

These TCMs are shown to be effective in alleviating the symptoms of COVID-19 and also associated with more rapid decline in the viral load. (Yang *et al.* 2020). Other patented TCM formulations under clinical trials for COVID-19 treatment include Huoxiang Zhengqi capsules, Lianhua Qingwen capsules and Radix isatidis granula.

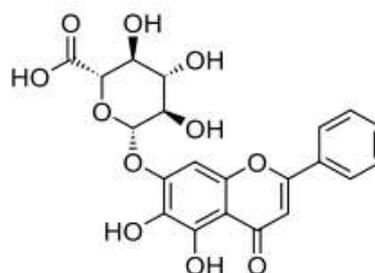
Based on studies with the related SARS-CoV and MERS-Co, some phytochemicals that possess anti-CoV efficacies have been identified from the TCMs. A review by Yang *et al.* (2020) shows that these natural compounds include Glycyrrhizin, Scutellarin, Herbacetin, Quercetin, Nicotianamine and Baicalin, Their chemical structures are presented in Figure 1. They could serve as lead compounds for further structure-activity relationship studies for enhancement of effectiveness since their modes of action have been deduced. For example, Glycyrrhizin is shown to inhibit viral adsorption and penetration, and has been demonstrated to be a potent antiviral agent with significant effect against hepatitis C virus. Scutellarin inhibits viral pathway affecting the ATPase activity and its antiviral action has also been shown in inhibition of HIV-1 replication. Herbacetin and quercetin are flavonols that act by inhibiting the cellular entry of SARS-CoV. Nicotianamine and baicalin inhibit angiotensin -converting enzyme (Yang *et al.*, 2020). The use of angiotensin receptor blockers has been reported to present a novel therapeutic approach for COVID-19 treatment since angiotensin-converting enzyme plays a key role during the viral infection process, and this is the basis for the randomized controlled trial of Losartan (an angiotensin receptor blocker) for patients with COVID-19 (Liu *et al.*, 2020; Vellingiri *et al.*, 2020).

ii. Other Complementary and HMPs undergoing Clinical Trials

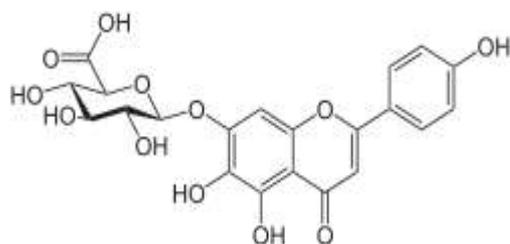
There is sparse information on registered clinical studies on COVID-19 treatment with HMPs that are not TCMs. Two of such studies are on Natural honey and *Nigella sativa*. There are numerous scientific investigations carried out over the years that have validated *Nigella sativa* as a strong booster of the immune system with potent antiviral action. Also, results of several investigations show that natural honey is a potent antimicrobial and can be used for the treatment of some viral infections. A clinical study is investigating the efficacy of natural honey in the treatment of COVID-19 patients, while another clinical trial is on the efficacy of *Nigella sativa* combined with natural honey against the virus (US National Library of Medicine, Clinical Trials.gov).



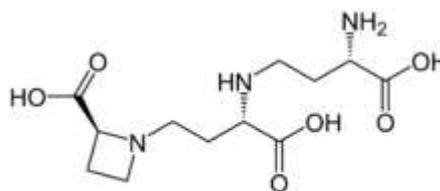
Glycyrrhizin (or glycyrrhizic acid)



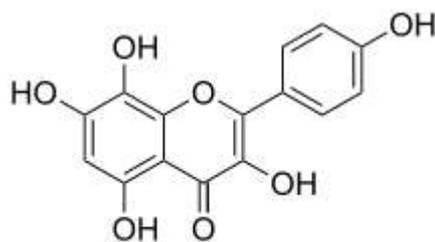
Baicalin



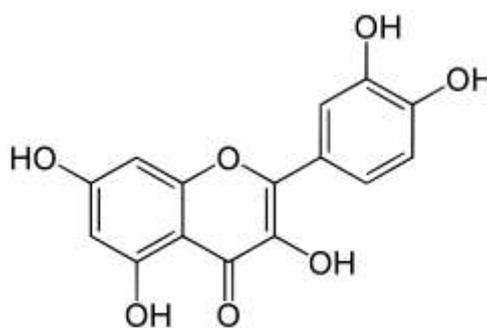
Scutellarin



Nicotianamine



Herbacetin



Quercetin

Figure 1: Chemical compound with anti-coronavirus activities isolated from Herbal Medicines used for COVID-19 treatment

iii. HMPs with Anti-viral Activities and Potentials for use in COVID-19

Several HMPs are known to have proven efficacies in treatment of viral infections and some of them have been found beneficial in SARS-CoV, which is structurally very similar to COVID-19. It is hoped that these products can be repurposed as treatment options for COVID-19. Just as is the practice in orthodox medicine, repurposing of HMPs can speed up the drug development process. Thus, there are numerous medicinal plants that are potential therapeutic agents against Covid-19. Some of these herbs include:

***Glycyrrhiza glabra*, *Strobilanthes Cusia* and *Allium sativum*:** These are promising candidates against COVID-19, since studies have shown that extracts from these medicinal plants inhibit the viral replication of SARS-CoV (Vellingiri *et al.* 2020).

***Boerhaavia diffusa*, *Coriandrum sativum*, *Coscinium fenestratum*, and *Cynara scolymus*:** These medicinal plants are known to exert inhibitory effects against angiotensin-converting enzyme and this mechanism has

been identified as a pathway for activity against COVID-19. Further studies are required to examine the specific effects of these herbs on coronavirus (Vellingiri *et al.* 2020).

Eugenia jambolana, Euphorbia granulate, Vitex negundo, Ocimum sanctum, and Acacia nilotica: Extracts of these medicinal plants have been demonstrated to have potent activities against HIV by exerting inhibitory actions on HIV proteases and reverse transcriptase activity. They can be studied for activity against COVID-19 just as some orthodox antiretroviral drugs are undergoing clinical studies for efficacy against the disease (Vellingiri *et al.* 2020).

Conclusion

Numerous existing orthodox drugs are undergoing clinical studies on their safety and efficacy in the treatment of COVID-19. Also, several HMPs known to have proven efficacies in treatment of viral infections and SARS-CoV are potential therapeutic options for the infection. Drug repurposing done with orthodox medicines can equally be applied to complementary and HMPs with demonstrable potentials. Therefore, there is an undisputable role for Complementary and HMPs in treatment of COVID-19.

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