Use of Traditional Chinese and Modern Medicines in the Treatment of COVID-19: A Minireview

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ABSTRACT COVID-19 pandemic has affected human life worldwide since the first discovery of human SARS-CoV-2 infection. Due to scarce understandings of this novel coronavirus, therapeutic interventions regardless of modern or traditional medicines are implemented according to previous knowledge on other virus outbreaks. Besides antiviral drugs, traditional Chinese medicine has concomitantly shown to alleviate clinical symptoms associated with this disease. Recently, emerging studies also indicate that integrating modern medicine and traditional Chinese medicine (TCM) could bring more significant benefits to COVID-19 patients. This minireview provides a summary on the earliest therapeutic approaches recommended by World Health Organization and approved by China FDA for COVID-19 treatment since the outbreak, which are based on the outcomes obtained from preclinical or clinical trials performed until December 2020. The underlying molecular actions of these medicines on COVID-19 that have progressively revealed are also deliberated here. However, the mechanistic actions of these medicines still required intensive research and clinical investigations as some mechanisms are *in silico* predicted. Due to the treatment urgency, the main limitation of these studies is small group of patients in the trials. Nevertheless, they serve as an important stepping stone for further therapeutic intervention.

KEYWORDS: Coronavirus; Modern medicine; Traditional Chinese medicine; COVID-19
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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) was first reported in Wuhan, Hubei Province, China. Due to high infectivity and transmissibility of this novel virus, the World Health Organization (WHO) announced a global COVID-19 pandemic. As of 8 April 2021, there are about 132.73 million worldwide confirmed cases, and more than 2.88 million deaths (WHO, 2021).

Once invading the host, the onset of SARS-CoV-2 symptoms is around 2-14 days (Cheng & Shan, 2019). The typical symptoms are fever, dry cough, and fatigue, while other serious symptoms such as difficulties in breathing, speech or movement, and chest pain. Some patients also experience other non-common symptoms like myalgia, diarrhea, anorexia, conjunctivitis, and nausea (Guan *et al*., 2020). In severe cases, patients can also develop acute respiratory distress syndrome (ARDS), severe sepsis, disseminated intravascular coagulation (DIC), acute heart failure and kidney injury, pneumonia and cardiorespiratory failure (Huang *et al*., 2020). It has also caused a phenomenon called "cytokine storm" implying excessive inflammatory responses (Henderson *et al*., 2020). In addition, patients may develop neurological symptoms, including headache, dizziness, changed mental state, anosmia, and hypogeusia (Bougakov *et al*., 2020).

SARS-CoV-2 has helically symmetrical nucleocapsids within the envelope which is uncommon compared to other RNA viruses. Four major structural proteins found in the coronaviral genome are spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. These structural proteins play roles in host infection, membrane fusion, viral particle assembly and release. This novel coronavirus also consists of 15 non-structural proteins, facilitating the replication and transcription

of the viral genome (Mittal *et al*., 2020). Comparative genomic analysis found high similarity (96%) and identity (80%) in SARS-CoV-2 and SARS-CoV genome (Wu *et al*., 2020a). SARS-CoV-2 contains a multibasic furin-like cleavage site in spike (S) glycoprotein, instead of an arginine residue (Coutard *et al*., 2020). It also binds angiotensin-converting enzyme 2 (ACE2) receptor but with greater affinity. Upon binding to ACE2 receptor, S protein undergoes conformation change exposing a cleavage site for furin and transmembrane serine protease 2 (TMPRSS2), which facilitating viral invasion (Hoffmann *et al*., 2020).

Although there is still no precise treatment for COVID-19 and vaccines are mostly in phase 3 clinical trials, several countries have begun COVID-19 vaccination. However, conventional treatment and TCM will remain relevant for the foreseeable future. Many antiviral drugs which are proven to be useful in treating other coronavirus diseases such as SARS or MERS are in use to treat COVID-19. Amid modern medicines under the evaluation of National Institutes of Health (NIH) are remdesivir, chloroquine or hydroxychloroquine, lopinavir/ritonavir and others (NIH, 2020). Besides that, traditional medicines have also played a crucial role in combating diseases for decades. Despite scepticism in term of efficacy and adverse effects, WHO has recognized the practice of traditional, complementary and alternative medicine and also embarked collaborative research with countries in Africa and Asia to search for the effective treatment for COVID-19 (WHO, 2020). In Asia, especially China has recommended the use of Traditional Chinese Medicine (TCM) in fighting this pandemic either as medication or prevention (Luo *et al*., 2020). This minireview is to summarize on the earliest therapeutic approaches recommended by World Health Organization and approved by China FDA for COVID-19 treatment since the outbreak. The information is based on the outcomes obtained from preclinical or clinical trials performed until December 2020. In addition, the modes of action of these medicines against SARS-CoV-2 are also deliberated although some of their mechanistic insights are established *in silico*.

MODERN MEDICINE

Remdesivir (GS-5734) is a nucleotide analog prodrug which binds to RNA-dependent RNA polymerase to stop viral replication. It was an effective therapeutic drug against SARS and MERS (Brown *et al*., 2019). Remdesivir is a promising candidate against SARS-CoV-2 with an inhibitory effect of EC50 = 0.77 μM (Wang *et al*., 2020a). It had also reduced viral copies and lung damage in the remdesivir-treated macaque (Williamson *et al*., 2020; Spinner *et al*., 2020). Beigel et al. recently showed that COVID-19 patients treated with remdesivir had shorter recovery time and reduced respiratory tract infection than placebo (Beigel *et al*., 2020). Currently, remdesivir is the only COVID-19 drug approved by the US Food and Drug Administration (FDA). It is also recommended for patients who require supplemental oxygen. However, for those with moderate or severe COVID-19, no significant clinical benefits were reported by Spinner et al. and Wang et al., respectively (Beigel et al., 2020; Wang *et al*., 2020c).

Chloroquine (CQ) and hydroxychloroquine (HCQ) are commonly used for treating malaria. Several studies found that they are effective against SARS-CoV-2 by preventing the fusion between virus and host cell membrane. Besides that, they also caused endosomal acidification, leading to increased pH (Wang *et al*., 2020a). Wang et al. demonstrated both CQ and HCQ act as ACE2 blockers that prevent the attachment of SARS-CoV-2 spike pseudotyped virus to host cells (Wang *et al*., 2020b). However, HCQ was found to be more toxic compared to chloroquine. They also inhibited virion delivery during vesicular transport from early endosomes to endolysosomes (Liu *et al*., 2020). In contrast to remdesivir, no evidence demonstrated that HCQ alone or in combination with azithromycin provided in vivo protection for macaques infected with SARS-CoV-2 (Maisonnasse *et*

al., 2020). Findings from the Solidarity Trial showed no decrease of mortality rate in hospitalized patients compared to the standard care group. Thus, WHO announced the termination of HCQ use in COVID-19 treatment.

Lopinavir (LPV) is an anti-retroviral drug with protease inhibitory activity which used together with a booster, ritonavir for human immunodeficiency virus (HIV) treatment. Comparing to HIV, COVID-19 patients required a much higher concentration of lopinavir/ritonavir (LPV/r) due to liver damage induced by SARS-CoV-2 and alteration of the expression of drug-metabolizing enzymes (Baldelli *et al*., 2020). This has led to concerns regarding the safety and toxicity of LPV treatment. LPV showed an inhibitory effect on infected Vero E6 cells with an EC50 of 26.63 μM. Nonetheless, the effective dosage required to inhibit the in vivo replication of SARS-CoV-2 is still unknown (Schoergenhofer *et al*., 2020). On the other hand, lopinavir showed no positive effect on mortality, viral loads, and clinical improvement (Cao *et al*., 2020). Despite contradictory findings on the effectiveness of LPV/r, its combination with interferon beta-1b and ribavirin for mild to moderate patients showed rapid viral clearance and better clinical impacts ((Hung *et al*., 2020).

Corticosteroids are not a typical drug for viral therapy. However, they are in use for COVID-19 patients with the severe and critical condition to lessen pro-inflammatory response. Dexamethasone (DEX) is anti-inflammatory and immunosuppressive drugs for various ailments. The DEX treatment showed a reduction in mortality incidence for COVID-19 patients on ventilators and that required oxygen only were 29.3% and 23.3%, respectively, compared to the control groups (41.4%, 26.2%). For those who did not need breathing aid, there were no differences (RECOVERY Collaborative Group, 2020). Several trials using hydrocortisone have also supported these observations (Angus *et al*., 2020; Dequin *et al*., 2020; Tomazini *et al*., 2020). It was postulated that DEX acts as a 3C-like protease inhibitor, allowing the transport of histone deacetylase into the nucleus, thus impairing cytokine storm effects triggered by SARS-CoV-2 (Ferner *et al*., 2020). Depending on the severity of COVID-19, remdesivir is also co-administrated with DEX. Besides DEX, alternative glucocorticoids like hydrocortisone and prednisolone are also under clinical investigation (Ferner *et al*., 2020).

Nevertheless, due to the small size of patients involved in these reported trials, differences in the point of care in handling varying stages of COVID-19, different treatment scenario in health centres and other considerations, variations and conflicting observations in clinical surveillance are inevitable. Despite the effectiveness of integrative approaches, the underlying mechanisms are still lacking, and comprehensive understanding of their interactions still needs more time and further research as adverse effects are also associated to the dosage and treatment periods. For example, a small and non-random study demonstrated that HCQ was effective in reducing viral load and enhancement was seen with azithromycin (Gautret *et al*., 2020). On the other hand, a multinational study showed HCQ is safe for short-term and its administration together with azithromycin might increase the risk of cardio-associated problems (Lane *et al*., 2020).

TRADITIONAL CHINESE MEDICINE

Lianhua Qingwen (LHQW) has been accepted as a treatment for SARS in 2003. It is composed of 11 Chinese herbs, gypsum and methanol (Wang *et al*., 2016). Previous studies showed that LHQW exhibited antiviral activities against influenza A virus H3N2 and influenza B virus by inhibiting the production of pro-inflammatory cytokines (Ding *et al*., 2017; Yang *et al*., 2020a). This herbal mixture is recommended for used in mild and moderate COVID-19 patients. Besides, LHQW inhibited SARS-COV-2 replication with an IC_{50} of 411.2 μg/ml and protected host cells by suppressing manner (Runfeng *et al*., 2020). LHQW prescription, in combination with the usual treatment of COVID-19,

has significantly improved the recovery rate and clinical symptoms like fever, fatigue, cough, expectoration, chest tightness, and anorexia (Hu *et al*., 2021; Cheng *et al*., 2020). Recently, LHQW capsule has granted international approval by the Pharmaceutical and Herbal Medicine Registration and Control Administration of Kuwait for mild and moderate COVID-19 treatment (PR Newswire, 2020).

Xuebijing (XBJ) injection is previously approved to treat H1N1, H7N9, dengue fever, MERS and ebola (Tong *et al*., 2020). It is a combination of extracts from *Carthamus tinctorius*, *Paeonia lactiflora*, *Ligusticum chuanxiong*, *Salvia miltiorrhiza* and *Angelica sinensis* (Li *et al*., 2021). XBJ injection is recommended for treating severe and critical COVID-19 patients. Clinical studies carried out on 31,913 patients suggested XBJ is safe, with only 0.3 % of patients experienced adverse effects such as itchy skin, rash, chest tightness and fever. It has reduced lung injury by attenuating viral proliferation and expression of pro-inflammatory cytokines (Ma *et al*., 2020). It has also reduced the mortality rate of severe COVID-19 patients and shortened patients' recovery time in the intensive care unit. Besides, the main chemical compounds of this remedy such as hydroxysafor yellow A, anhydrosafflor yellow B, chlorogenic acid, rutin and salvianolic acid B found to have high affinity to 3CL hydrolase of SARS-CoV-2 (He *et al*., 2020; Xing *et al*., 2020). Besides that, compounds such as quercetin, luteolin, apigenin could exhibit their effects by targeting TNF, MAPK1 and IL6 expression (Xing *et al*., 2020).

Jinhua Qinggan (JHQG) is a patented medicine comprised of *Lonicerae japonicae* Flos, *Artemisiae annuae* Herba, *Fritillariae thunbergii* Bulbus, Forsythiae Fructus, gypsum, Herba Ephedrae, Scutellariae Radix, Armeniacae Semen Amarum, Anemarrhenae Rhizoma, Fructus Arctii, Menthae Haplocalycis Herba, and Glycyrrhizae Radix et Rhizoma (Ren *et al*., 2020). It was proprietary developed for H1N1 influenza treatment and useful for relieving mild and moderate COVID-19 symptoms (Liu *et al*., 2020). COVD-19 patients given with JHQG showed a decrease in IL-6 plasma level, but elevated IFN-γ level was observed (Kageyama *et al*., 2020). Recent molecular docking studies found that the three representative components of JHQG (chlorogenic acid, forsythiaside A, ephedrine) show high affinity toward 3CL hydrolase and spike protein thereby preventing the virus replication and invasion of SARS-CoV-2 (Ren *et al*., 2020).

The formulation of Huoxiang Zhengqi (HXZQ) consists of ten kinds of Chinese herbs, including *Atractylodes chinensis*, *Citrus reticulata*, *Magnolia officinalis*, *Angelica dahurica*, *Poria cocos*, *Areca catechu*, *Pinellia ternata*, *Glycyrrhiza uralensis*, *Pogostemon cablin* and *Perilla frutescens* (Deng *et al*., 2020). Its traditional usage is for treating cold, fever, nausea and vomiting, abdominal distension, and diarrhea (Zhuang *et al*., 2020). Similar to SARS, COVID-19 patients, showed lung damage and increased creatine kinase (CK) and lactate dehydrogenase (LDH) (Poggiali *et al*., 2020). Because HXZQ found to suppress CK and LDH levels in SARS patients and to relieve inflammatory effect (Li *et al*., 2014), therefore, it could be useful for SARS-CoV-2 infection. Molecular docking also demonstrated that bioactive compounds (quercetin, isorhamnetin and irisolidone) of HXZQ regulates multiple signalling pathways by targeting to ACE2 (Deng *et al*., 2020). Recent clinical study had also suggested that HXZQ can use as complementary medicine for improving the pathological symptoms in COVID-19 patients (Xiao *et al*., 2020).

Qingfei Paidu (QFPD) decoction is a mixture of 21 Chinese herbs, including Ephedrae Herba, processed Glycyrrhizae Radix et Rhizoma, Armeniacae Semen, Gypsum Fibrosum, Cinnamomi Alismatis Rhizoma, Polyporus, Atractylodis Macrocephalae Rhizoma, Poria, Bupleuri Radix, Scutellariae Radix, Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine, Zingiberis Rhizoma Recens, Asteris Radix, Farfarae Flos, Belamcandae Rhizoma, Asari Radix et Rhizoma, Dioscoreae

Rhizoma, Aurantii Fructus Immaturus, Citri reticulatae Pericarpium and Pogostemonis Herba. QFPD is a personalized prescription with remarkable efficacy in COVID-19 treatment. It has been used together with modern medications (LPV/r, methylprednisolone sodium succinate, moxifloxacin hydrochloride, sodium chloride, and interferon α2b) for treating patients with severe COVID-19 symptoms (Luo *et al*., 2020). Besides that, patients treated using the combination therapy (QFPD plus lopinavir, interferon or arbidol) showed less inflammation in the lung and improved clinical symptoms (Xin *et al*., 2020). Network pharmacology-based studies indicated that the active compounds such as quercetin, luteolin and kaempferol modulate immune and inflammatory responses by targeting AKT1, JUN, MAPKs, IL-6, RELA, STAT1 (Wu *et al*., 2020b). Ma Xing Shi Gan (MXSG), one of the components in QFPD contributing to the effectiveness of QFPD. Transcriptomic analysis showed that MXSG-mediated anti-inflammation via the regulation of thrombin and Toll-like receptor (TLR) signaling in LPS-induced pneumonia mice (Yang *et al*., 2020b).

Shufeng Jiedu (SJFD) is used for treating acute upper respiratory tract infections caused by H1N1 influenza, Coxsackievirus B4 and B5, and herpes simplex virus (type 1 and 2) (Ji e tal. 2020). The herbs found in SJFD are *Polygonum cuspidatum*, *Forsythia suspensa*, *Isatis indigotica*, *Bupleurum chinense*, *Patrinia scabiosifolia*, *Verbena officinalis*, *Phragmites communis* and *Glycyrrhiza uralensis*. It is an early-stage treatment for COVID-19 patients. Using mouse infected with HCoV-229E, SJFD decreased the expression of interleukin-6/10, tumor necrosis factor-alpha, and interferon-gamma with a concomitant increase of CD4/CD8 positive T cells. These observations associated with multiple inflammatory and immunomodulatory pathways. Polydatin, quercetin, and wogonin compounds of SJFD exerted antiviral activity by binding to the non-structural protein, main protease (M^{pro}) (Xia *et al*., 2021). The combination of lopinavir/ritonavir (Kaletra®) and umifenovir (arbidol) with SFJD have also significantly shortened the recovery time by alleviating pain, fever and cough in infected patients (Xia *et al*., 2021; Chen *et al*., 2020a). In contrast, treatment with antiviral drugs alone have failed to improve clinical symptoms (Chen *et al*., 2020b).

TCM differs from modern medicines in both aspects of concepts and practices which not only focusing on treatment but also prevention. TCM has an ancient history in combating infectious diseases despite its lack of scientific evidence and unknown mechanisms (Ni *et al*., 2020). Nonetheless, it becomes handy especially in managing unanticipated outbreaks like SARS or COVID-19 when no cure has been identified. Chinese authority has also developed COVID-19 treatment protocols according to disease stages: mild, moderate, severe, critical, and convalescence using Western and traditional Chinese medications have also been well documented. With the advanced progress in integrative omics studies, it is foreseeable that the efficacies of traditional medicines will be supported with evidence-based findings in the near future.

CONCLUSION

Though large-scale vaccination for COVID-19 has been implemented for emergency use in several countries such as the United Kingdom and the United States, modern medicine and TCM or integrative medicine remain relevant as therapeutic options for this disease. The efficacy and safety of currently available vaccines, especially for the new variants still require further observations. Besides that, emerging studies have also demonstrated the combination of TCM and modern medicine could have more significant benefits in alleviating the disease symptoms. Without doubt, identifying bioactive compound(s) and understanding the complex mechanisms of a formulation of TCM are challenging. Given rigorous international collaborations formed among various countries and technology advancements, it is anticipated that these will contribute to better and safer therapeutic intervention against this pandemic.

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