Therapeutic traditional medicine on covid-19 and other influenza diseases

Tom hoody

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ABSTRACT

Anthocyanins Coronavirus disease 2019 (COVID-19), first reported in Wuhan, China, has rapidly spread worldwide. Traditional Chinese medicine (TCM) has been used to prevent and treat viral epidemics and plagues for over 2,500 years. In the guidelines on fighting against COVID-19, the National Health Commission of the People's Republic of China has recommended certain TCM formulas, namely Jinhua Qing An Granule (JHQGG), Lianhua Qingwen Granule (LHQWG), Qingfei Paidu Decoction (QFPDD), Xuanfei Baidu granule (XFBD), Xuebijing injection (XBJ), and Huashi Baidu granule (HSBD) for treating COVID-19 infected individuals. Among these six TCM formulas, JHQGG and LHQWG effectively treated mild/moderate and severe COVID-19 infections. XFBD therapy is recommended for mild COVID-19 infections, while XBJ and HSBD effectively treat severe COVID-19 infections. The internationalization of TCM faces many challenges due to the absence of a clinical efficacy evaluation system,

INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) was first reported in Wuhan in December 2019, caused by the coronavirus SARS-CoV-. This disease has spread rapidly worldwide because of its prolonged incubation and high pathogenicity. COVID-19 has a low fatality rate and a high transmission rate from human to human compared to the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 and the Middle East Respiratory Syndrome (MERS) outbreak in 2012. The existence of many asymptomatic SARS-CoV-2 human carriers exerts a Xworldwide. SARS-CoV-2 is a singlestranded, non-segmented RNA virus with a 30 kb genome size, insufficient research evidence, and a lack of customer trust across the globe. Therefore, evidence-based research is crucial in battling this infectious disease. This review summarizes SARS-CoV-2 pathogenesis and the history of TCM used to treat various viral epidemics, with a focus on six TCM formulas. Based on the evidence, we also discuss the composition of various TCM formulas, their underlying therapeutic mechanisms, and their role in curing COVID-19 infections. In addition, we evaluated the roles of six TCM formulas in the treatment and prevention of other influenza diseases, such as Influenza A (H1N1), Severe Acute Respiratory Syndrome (SARS), and Middle East Respiratory Syndrome (MERS). Furthermore, we highlighted the efficacy and side effects of single prescriptions used in TCM formulas.

Key Words: Anthocyanin; Influenza; Efficacies; Mechanisms; Traditional; Chinese medicine

isolated from COVID-19 infected patients who shared 79.5% genome sequence similarity with SARS-Co-V. The long latency, high infectivity, and complex curing features have made COVID-19 a major threat to global health and the economy [1].

SARS-CoV-2 is transmitted from infected to healthy people via aerosol particles such as sneezing and coughing. Based on the evidence of rising global infection rates, the possibility of virus transmission by asymptomatic human carriers has dramatically increased. The COVID-19 infected individuals showed respiratory disorders ranging from mild to severe, i.e., fever, cough, myalgia, diarrhea, fatigue, loss of smell or taste, muscle pain, body aches, and lung damage. In severe infections, complications may occur, i.e.,

Editorial office, Journals of Emerging Diseases and Preventive Medicines, United Kingdom

Correspondence Tom hoody, Editorial office, Journals of Emerging Diseases and Preventive Medicines United Kingdom, Email preventivemed@theresearchpub.com

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acute myocardial injury, blood clotting, acute respiratory distress syndrome, liver/kidney disorder, septic shock, or death. These disorders complicate global COVID-19 prevention and treatment. Oxygen therapy and fluid supply are recommended for treating severe infections. For mild COVID-19 infections, the WHO has recommended guidelines for COVID-19 treatment together with adequate nutritional support to cure pain and fever. Supportive measures and potential antiviral drugs such as remdesivir, hydroxychloroquine, and ribavirin (used to treat other viral infections) have been repurposed for treating mild SARS-CoV-2 infected people. However, due to a lack of large-scale randomized clinical trials or potential side effects, effective anti-COVID-19 therapy has not yet been reported. Due to the low success rate against the mutant SARS-CoV-2 strain, developing a vaccine for COVID-19 prevention is complex, challenging, and expensive. Therefore, despite the vaccine development, scientists are trying to develop new antiviral drugs or restructure existing drugs to neutralize this deadly SARS-CoV-2. Although efforts to combat COVID-19 infections have been made, a lack of safe and effective antiviral drugs remains a critical factor in preventing and treating the global COVID-19 pandemic. Angiotensin-Converting Enzyme 2 (ACE2) is a cell surface protein found in the gastrointestinal tract, heart, and kidneys that regulates blood pressure and vasoconstriction. In addition, ACE2 serves as a receptor for SARS-CoV-2 attachment and entry into the cell cytoplasm. The SARS-CoV-2 spike protein mediates the virus fusion with the host membrane protein (ACE2) to initiate the infection process. Coronavirus adopts two routes for fusion and entry into the host cells. First, SARS-CoV-2 fuses with the target cell membrane with the help of Transmembrane Protease Serine 2 (TMPRSS-2) to release the virus genome into the host cell cytoplasm [2]. Second, virus spike protein undergoes conformational changes before binding to the host ACE2 receptor and employs TMPRSS-2 to facilitate virus entry into the cytoplasm. In the absence of the membrane proteases, the coronavirus may use a non-clathrin or clathrin-mediated endocytosis pathway. In this pathway, cathepsin activation influences viral fusion with the host cell. These findings show that the availability of membrane proteases and the target cell membrane govern SARS-CoV-2, SARS-CoV, and MERS-CoV entry into the cell cytoplasm. SARS-CoV-2 releases genomic RNA and takes control of the host replication machinery, allowing it to replicate and spread. The viral mRNA undergoes ribosomal frameshift during translation, resulting in ORF1a and ORF1b, which encode polypeptides pp1a and pp1b. Viral 3-chymotrypsin like protease (3CLpro) further processes these polypeptides to form sixteen Non-Structural Proteins (NSPs). ORF1a encodes the first eleven NSPs, while the remaining four NSPs are encoded by ORF1b. NSP5 (3CLpro) and NSP3 (papain-like protease) are required for virus replication and other cellular processes and thus can be used to detect SARS-CoV-2 in biological samples [3]. The virus genomic RNA also translates into four structural proteins, i.e., nucleocapsid protein, envelope protein, membrane protein, and spike protein and eight accessory/auxiliary proteins, namely, 7b, 3a, 7a, 3b, 9b, p6, 8b, and ORF14. After post-translational modifications in the Endoplasmic reticulum (E. reticulum), these proteins are transferred to the E. Reticulum-Golgi apartment. Once the genome

has been translated for virions, it will interact with the nucleocapsid protein to form a nucleocapsid, which will then be transferred to the E. Reticulum-Golgi apartment In this complex apartment, the viral nucleocapsid will interact with other structural components to form vesicles that will eventually be released from the infected host cell via exocytosis. The eight accessory proteins are not required for coronavirus replication; however, they may affect viral pathogenesis, stability, and release.

TCM anti-SARS-CoV-2 mechanisms and virus pathogenesis. (a) replication of SARS-CoV-2 and antiviral mechanisms of TCM formulas. Coronavirus enters the host cell cytoplasm via an endosomal pathway or fuses spike protein to the human membrane ACE2. The viral RNA is unveiled and transcribed into viral 3CLpro in the infected cell cytoplasm. The 3CLpro cleaves the two polypeptides (pp1b and pp1a) into 16 non-structural proteins (NSPs), such papain-like as protease. serine-type chymotrypsin protease, helicase, and RNA-dependent RNA polymerase. The treatment of Xuanfei Baidu Granule (XFBD), Huashi Baidu Granule (HSBD), Qingfei Paidu Decoction (QFPDD), and Xuebijing Injection (XBJ) inhibits the proteolysis of the 3CLpro enzyme. The two most important TCM formulas, JHQGG and LHQWG, prevent the 16 NSPs from forming the replicationtranscription complex. RNA-dependent RNA polymerase and helicase enzymes are combined for synthesizing negative strand guide RNA (gRNA) and RNAs. These RNAs are important for viral replication and transcription. The newly synthesized viral genome is translated and produces spikes, envelopes, nucleocapsids, and membrane proteins. These structural proteins are then transported to the E. Reticulum-Golgi body apartment for assembly (encapsulated viral genomic RNA) to form new viruses. The newly synthesized viruses are released from the cytoplasm of human cells via exocytosis. (b) LHQWG, JHQGG, XFBD, and HSBD therapies have anti-inflammatory, antipyretic, and immunomodulatory effects on COVID-19 infections. (c) Anti-cytokine storm, anti-oxidation, and immune-regulating properties of LHQWG, HSBD, XBJ, and XFBD therapies. TCM treatment regulates the levels of cytokines, chemokines, and MAPKs in COVID-19-infected cells. (d) A cytokine storm can lead to myocardial injury, kidney/liver dysfunction, septic shock, blood clots, acute respiratory distress syndrome, and death in severe cases.

Traditional Chinese Medicine (TCM) has a long history of treating infectious viral diseases since the Chinese Qin-Han dynasty (221 BCE-220 CE). During the Ming-Qing dynasty (1368–1912 CE), a TCM theory describing infectious diseases caused by toxic qi was developed, i.e., a pathogen from an infected host spreads via aerosol inhalation and infects the lungs . According to TCM theory, an epidemic disease is an acute infection with a sudden onset, rapid transmission, and severe infection. TCM theories of treating predisease, such as yin and yang theory, holistic theory, and five elements theory, i.e., visceral meridian theory, etiology and pathogenesis theory, and qi doctrine, were initiated in the Shang and Yin dynasties and took shape in the Yellow Emperor's Inner Classic (Huangdi Neijing: ancient Chinese medical book). Several studies have shown that the therapeutic effects of TCM are safe, effective, and

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economical for H1N1, SARS, and MERS infections. During the H1N1 outbreak in 2009, the Beijing Municipal Government released ten million RMB for a clinical trial to screen and treat H1N1 infections through TCM. In the light of TCM theory, pathogen dampness-toxin and host healthy-qi deficiency characterize COVID-19 disease. China has contributed significantly to the prevention, detection, and treatment of COVID-19. According to China's clinical guidelines and experience in treating SARS and MERS patients, TCM formulas can effectively treat SARS-CoV-2 patients

During the outbreak, Chinese experts explored several TCM formulas to treat COVID-19 patients in clinical trials. Finally, they screened the six most effective TCM formulas, namely Jinhua Qinggan Granule (JHQGG), Lianhua Qingwen Granule (LHQWG), Qingfei Paidu Decoction (QFPDD), also known as lung cleansing and detoxifying decoction, Xuanfei Baidu Granule (XFBD), Xuebijing Injection (XBJ), and Huashi Baidu Granule (HSBD) for COVID-19 treatment. Previous researchers have shown that treating COVID-19 patients with TCM improves cure rates, shortens disease duration delays disease progression from mild to severe stages, and lowers mortality rates. The China National Health Commission declared that TCM combined with conventional medicine effectively treated 92% of COVID-19 patients in China, of which 90% of the patients either recovered or improved their health status. It is also worth noting that COVID-19 has affected over 77,200 people in China, all of whom have recovered after treatment with TCM formulas or TCM combined with conventional medicine. TCM treatment exerts an auxiliary effect, improves blood oxygen saturation, and cures dyspnea in severe/critical COVID-19 patients. Formulated TCM has effectively been used in managing SARS outbreaks in 2003, MERS in 2012, and other seasonal influenza outbreaks, which reduced the patient hospitalization period and side effects compared with conventional medicines. After the Human Swine Flu (H1N1) virus outbreak in Mexico in 2009, the Chinese authorities recommended guidelines for diagnosing and treating swine influenza. China's National Health Commission highly recommends JHQG, LHQWG, and XBJI treatments for preventing acute respiratory distress syndrome, lung injury, and kidney damage in COVID-19 infected individuals [4].

Leading six TCM influential roles in treating COVID-19

Six TCM formulas showed an influential role in curing COVID-19 patients, with JHQGG and LHQWG being recommended for mild/severe COVID-19 cases. XFBD is recommended for curing mild/moderate COVID-19 infections, whereas XBJ and HSBD effectively treat severe COVID-19 patients. During the outbreak, several TCM formulas were included in the Chinese National Health Commission's guidelines for the diagnosis and treatment of COVID-19.

JHQGG treatment on COVID

The jhqgg formula, developed for treating influenza h1n1 patients, has therapeutic benefits for covid-19 patients during medical observation. the host surface protein ace2 act as a primary receptor for sars-cov-2 attachment and entry into the cell cytoplasm to initial infection F.

according to previous findings, covid-19 infected patients in china who received jhqgg treatment had a lower fatality rate and relatively better clinical outcomes. the china food and drug administration has recommended a jhqgg prescription for preventing and treating covid-19 infections. this tcm formula can effectivelyrelieve covid-19 clinical symptoms, delay disease progression from mild to severe stage, and reduce mortality in patients. jhqgg formula's underlying therapeutic mechanisms primarily reduce sars-cov-2 pathogenesis, organ protection, immune regulation, and anti-inflammatory actions. furthermore, jhqgg treatment showed broad-spectrum antiviral activities, i.e., target and inhibit sars-cov-2 life cycle, immune regulation, and anti-inflammation, indicating the importance of the jhqgg formula. at least three jhqgg ingredients, baikal huangqin, zhimu, and niubangzi, can stop sars-cov-2 transcription and replication, suggesting underlying therapeutic mechanisms of this formula. the most common active components reported in the jhqgg formula were luteolin, myricetin, quercetin, rutin, ursoli acid, and wogonin, which could have a therapeutic effect by targeting and suppressing il6 production in covid-19 patients in another similar study, jhqgg treatment significantly decreased il6 and increased ifn- γ levels in the plasma of treated individuals, indicating that jhqgg has immunomodulatory activity against covid-19 infection. chinese and western medical experts jointly approved jhggg treatment for covid-19 patients due to the presence of hundreds of previous tcm prescriptions for various disease treatments, such as febrile diseases. clinical studies showed that jhqgg treatment significantly improved mild covid-19 symptoms, including fever, anxiety, fatigue, cough, and expectoration [5]. it was also reported that seven-day jhggg treatment increased the viral clearance rate and reduced pneumonia in covid-19 individual. usually, jhggg treatment is recommended for mild covid-19 patients with clinical manifestation, body pain, weakness, fever, cough, headache, and sore throat.

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