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Traditional Chinese herbal medicine at the forefront battle against COVID-19: Clinical experience and scientific basis

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Abstract

Background

Throughout the 5000-year history of China, more than 300 epidemics were recorded. Traditional Chinese herbal medicine (TCM) has been used effectively to combat each of these epidemics' infections, and saved many lives. To date, there are hundreds of herbal TCM formulae developed for the purpose of prevention and treatment during epidemic infections. When COVID-19 ravaged the Wuhan district in China in early January 2020, without a deep understanding about the nature of COVID-19, patients admitted to the TCM Hospital in Wuhan were immediately treated with TCM and reported later with >90% efficacy.

Approach

We conducted conduct a systematic survey of various TCM herbal preparations used in Wuhan and to review their efficacy, according to the published clinical data; and, secondly, to find the most popular herbs used in these preparations and look into the opportunity of future research in the isolation and identification of bioactive natural products for fighting COVID-19.

Results

Although bioactive natural products in these herbal preparations may have direct antiviral activities, TCM employed for fighting epidemic infections was primarily based on the TCM theory of restoring the balance of the human immune system, thereby defeating the viral infection indirectly. In addition, certain TCM teachings relevant to the meridian system deserve better attention. For instance, many TCM herbal preparations target the lung meridian, which connects the lung and large intestine. This interconnection between the lung, including the upper respiratory system, and the intestine, may explain why certain TCM formulae showed excellent relief of lung congestion and diarrhea, two characteristics of COVID-19 infection.

Conclusion

There is good reason for us to learn from ancient wisdom and accumulated clinical experience, in combination with cutting edge science and technologies, to fight with the devastating COVID-19 pandemic now and emerging new coronaviruses in the future.

Keywords: Medicinal herb, Phytotherapy, SARS-CoV-2, Viral infection

Abbreviations: ACE2, angiotensin-converting enzyme II; AIV, avian influenza virus; ALI, acute lung injuries; AVP, arginine vasopressin; c-AMP, cyclic adenosine phosphate; CASP3, caspase 3; CCL2, CC chemokine ligand 2; CDC, Center for Disease Control and Prevention; CoV, coronavirus; COVID-19, coronavirus disease 2019; COX-2, cyclooxygenase-2; CXCL, C-X-C- motif chemokine; ECMO, extracorporeal membrane oxygenation; FM1, FM1 coronavirus; GCGJ, *Gancao ganjiang* decoction; HIV, human immunodeficiency virus; HSV-1, herpes simplex virus 1; ICU, intensive care unit; IEC-6, rat intestinal epithelial cell line 6; IL, Interleukin; iNOS, nitric oxide synthase; JEV, Japanese encephalitis virus; LH, *Lianhuaqingwen* capsule; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MDCK, Madin-Darby Canine Kidney cells; MXSG, *Ma xing shi gan* decoction; NF-κB, nuclear factor kappa B cells; NO, nitric oxide; PA, patchouli alcohol; PGE2, prostaglandin E2; PTGS2, Prostaglandin-endoperoxide synthase 2; QFPD, *Qingfeipaidu* decoction; RSV, respiratory syncytial virus; SARS, Severe Acute Respiratory Syndrome; SMD, *Sheganmahuang* decoction; SOD, superoxide dismutase; TCM, traditional Chinese medicine; TLR-4, Toll-like receptor-4; TNF, tumor necrosis factor; WHO, World Health Organization

1. Introduction

When COVID-19 ravaged the Wuhan district in China in early January 2020, no one knew about the nature of COVID-19. In retrospective analysis, it revealed that COVID-19 infection actually started a few weeks earlier and rapidly spread around the area of Wuhan's animal market. In fact, people in Wuhan, including temporary workers who were busy with New Year shopping, were planning to go home to celebrate the Chinese New Year. Unfortunately, these holiday activities greatly facilitated the spread of COVID-19. Suddenly, thousands of people contracted the novel coronavirus, and patients were rushed to the local hospitals. Unfortunately, with inadequate knowledge of the coronavirus, limited intensive care units (ICU) and inadequate equipment, many medical staff were also infected and succumbed to this devastating coronavirus epidemic. On January 10, the Chinese Center for Disease Control and Prevention shared the complete gene sequence of the virus with the World Health Organization and other countries ([China-CDC, 2020]). On January 29, Chinese scientists reported the complete genome sequences of COVID-19 ([Lu et al., 2020]). This timely report allowed the scientific community worldwide to gain a better understanding of the virus and provided clues for medication and vaccine development. This early phase of the epidemic infection in China was later viewed as the most contagious period, because patients were placed everywhere in the emergency room and no adequate protection equipment was afforded even for medical staff. One week later, the government locked down Wuhan City and entire country of China faced its darkest moments, which lasted 75 days. Surprisingly, two month later, this sad phenomenon repeated in other parts of the world, including Italy, Spain, and recently in the United States and Brazil. Obviously, the Wuhan experience was not taken seriously in countries outside of China. On January 30, 2020, WHO declared COVID-19 a pandemic. As predicted, it quickly turned into a world pandemic, with almost 50 million confirmed cases and more than 1.2 million deaths (as of Nov 6, 2020), with unknown dark figures and the number is still increasing (https://www.worldometers.info/coronavirus/). Several western drugs, such as remdesivir and hydroxychloroquine with high expectations were tested in the early stage in China. However, hydroxychloroquine is highly controversial. Recent clinical trials showed that hydroxychloroquine was ineffective ([Geleris et al., 2020]). On the other hand, remdesevir significantly reduced the mortality of COVID-19 patients in a randomized, placebo-controlled trial with 1063 patients ([Beigel et al., 2020]). The later clinical Phase 3 SIMPLE trial reported a 62% reduction in mortality in COVIS-19 patients. One early limitation of remdesivir involved its use in severely ill hospitalized patients to broaden its availability, an inhalable remdesivir medication is currently being developed for earlier stage patients. Nevertheless, vaccine developments remain to be the only hope to save people's lives during this pandemic infection. At present, a total of 18 vaccine projects are running. In the past, the fastest vaccination programs took at least four years. The current hopes and promises estimate that it might take 6 months to one year to complete the clinical evaluation of new vaccines, before they could become available to the public. This promise still has to be fulfilled quickly to meet the demands.

Therefore, it is necessary to pay attention to TCM medications, which are immediately available. In fact, TCM formulae were successfully used to fight COVID-19 in Wuhan and to provide the scientific communities with a reliable summary report for following up research and refining TCM preparations with scientific methods. Evidence-based TCM treatments have the potential not only to treat COVID-19, but also to prevent an outbreak of another new coronavirus in the future.

Patients admitted to the local hospitals in Wuhan were primarily treated with western medicine as frontline treatment, except in a few TCM hospitals, where patients were treated directly with TCM. According to several recent reports that patients received TCM treatment directly showed >90% efficacy and only a few of them were admitted to the ICU (http://www.gov.cn/xinwen/2020-03/23/content_5494694.htm). In comparison, western methods of treatments, including the use of antibiotics and painkillers, resulted in 10 times more patients ending up in the ICU. Because of the effectiveness of TCM treatment, even in the western hospitals, such an integrative treatment has become a standard practice in fighting COVID-19 in Wuhan and many other hospitals in China. Although the effectiveness of TCM treatment of coronavirus were witnessed in Wuhan and other TCM hospitals in China, supportive scientific data are still sparse. There is an urgent need to establish solid scientific knowledge to validate the effectiveness of treatment with TCM.

It is estimated that there are more than 100 herbal TCM formulae developed throughout China's history for the purpose of saving people's lives during epidemic infections. These historic experiences of using TCM in fighting epidemics were capitalized during the Wuhan epidemic and widely employed in all hospitals in China. TCM is now credited for the successful battle against COVID-19 in China ([Lu and Lu, 2020]).

Before going into each individual TCM formula, we need to review the TCM theory, which always guides the practice of TCM, including acupuncture and herbal medicine. Since the lungs are the primary respiratory target of COVID-19, we focus on TCM theory regarding lung diseases. According to *Huang Di Nei Jing*, 12 meridian lines run through the human body and play a pivotal role in maintaining a balanced immune system and good health. Based on the TCM theory of exterior-interior correlation, the lung meridian line, which functionally interconnects with the large intestine, is the most important meridian teaching for controlling body fluid (water). The lung meridian communicates with the large intestine meridian, creating an exterior and interior relationship between these two organs. The two organ systems influence each other closely. The large intestine is called the "Minister of Transportation" (传导之官: *Chuan Dao Zhi Guan,* Yellow Emperor's Internal Classic, 2600 BC). It controls the transformation of digestive wastes from liquid to solid state and transports it for excretion outwards through the rectum. It plays a major role in the balance of bodily fluids and assists the respiratory function of lung by controlling the skin's pores and perspiration. This ancient TCM theory may be interpreted by human physiology, in which water molecules serve as lubricants during oxygen and carbon dioxide exchange by pulmonary cells and the large intestine serves as water reservoir of the human body. Expelling phlegm and relaxing the bowels with laxative are common methods for treating lung diseases. Therefore, maintaining a smooth and open channel is an important function served by the lung meridian line. This explains why the lung meridian is connected to the large intestine. For instance, previous studies demonstrated that *Rheum palmatum* could not only effectively improves the intestinal obstruction in chronic obstructive pulmonary disease (COPD) patients and rats with COPD, but also effectively improves dyspnea and gas exchange function ([Zhang et al., 2014]). Thus, the primary guiding theory of treating COVID-19 is to expel the toxic moisture from the upper respiratory system and to improve intestinal obstruction. In essence, TCM is to maintain the balance of the lung meridian system, and to restore the balance between lung and intestine. It makes sense that TCM theory always guides the practice of TCM, including acupuncture and prescription of herbal medicine.

2. Clinical treatment of COVID-19 patients with TCM

COVID-19 is spread by droplets of containing the coronavirus from an infected person's cough, sneeze, or breath. These virus particles float in the air or adhere to a surface that your hands contact before touching your eyes, nose, or mouth. This is the common mode of infection of coronavirus to the mucous membranes of the respiratory systems. Within 2 to 14 days, the body's immune system responds with symptoms including: cough, difficulty breathing, fever, chills, muscle pain, sore throat, and loss of taste or smell. There is currently no treatment specifically approved for COVID-19, and vaccines are currently under active investigation. As shown in Table 1 , current treatments focus on managing symptoms along the course of infection. In general, current treatments for COVID-19 include: remdesivir and hydroxychloroquine, which showed varying efficacy in early, preliminary studies. However, with recent clinical studies, remdesivir was only used in late stage patients, and FDA cautions against the use of hydroxychloroquine or chloroquine for COVID-19 due to risk of heart rhythm problems. In contrast, TCM used in Wuhan showed 89% to 92% efficacies in 692 studies registered on Clinical Trial.gov.

Table 1

Clinical treatments of COVID-19 patients

Type of treatment	Therapeutic agent or device
Oxygen therapy	Nasal cannula Non-invasive mechanical ventilation Invasive mechanical ventilation ECMO*
Antibiotics combination	Amoxicillin Azithromycin Fluoroquinolones
Antivirals	Lopinavir/ ritonavir Ribavirin Favipiravir (T-705) Remdesivir Oseltamivir Chloroquine Interferon
Corticosteroids	Methylprednisolone
Antibody therapy	Convalescent plasma
NO therapy	Nitric oxide
Traditional Chinese medicine	*Ma xing shi gan* decoction *Qingfeipaidu* decoction *Sheganmahuang* decoction *Lianhuaqingwen* capsule

Since the outbreak of COVID-19, TCM has been used as first-line treatment with encouraging results. *Qingfei Paidu* decoction treated 214 confirmed cases. Three days is a course of treatment. The total effective rate is more than 90%, in which, more than 60% of patients have improved symptoms, and 30% have stable symptoms without aggravation. The rate of TCM treatment of COVID-19 in China was 87 %, and the total effective rate of TCM treatment was 92 %, of which only 5% of patients have worsened clinical manifestations (Yang et al., 2020a).

Looking upon the value of TCM recipes in viral disease management other than COVID-19, we drew our attention to the SARS epidemic of 2002/2003. Most of the herbal drugs used to treat SARS (**Supplementary file**) are also used to treat COVID-19. A meta-analysis of Liu et al. (2012) evaluated 12 randomized clinical trials. Concerning the primary outcome parameter (mortality), the addition of these Chinese herbs to Western medicine, did not improve the patients' survival compared to Western medicine alone. Some improvements were seen regarding the secondary outcome parameters such as the pulmonary infiltrate absorption, the decrease of corticoid dosage. Improvement of life quality, and shortening of the days of hospitalization. It has to be seen, which clinical benefit these herbal remedies will show for the treatment of COVID-19.

The Chinese government announced that TCM is one of the recommended therapeutic options for the treatment of COVID-19 in the third version COVID-19 treatment guidelines, which was published on January 23, 2020. In general, more than 30 TCM formulae were used in Wuhan to fight the COVID-19 pandemic and there were 121 registered protocols of TCM for COVID-19 identified from Chinese Clinical Trial Registry (www.chictr.org.cn) and ClinicalTrials.gov (Table 2). Basically, these TCM formulae were used according to the different stages of the infection: early stage, treatment stage and recovery stage.

Table 2

Clinical trials for treatment of COVID-19

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2.1. TCM used in the early phase of the coronavirus infection

In the early phase, patients showed clinical symptoms of fever, myalgia, cough, and sore throat and other systemic symptoms. Therefore, following the teachings of TCM, the focus is to strengthen the body's immune system and to restore the balance of *Qi*, which is the important bio-energy circulating in the body through the inter-connected 12 median lines. The two most popular TCM formulae used in the early phase of the infection are:

2.1.1. *Ma xing shi gan* decoction (MXSG) MXSG decoction consists of 4 herbs including *Ephedra sinensis*, Semen armeniacae amarum*, Glycyrrhiza, Gypsum fibrosum.* According to the TCM theory, the main function is to regulate pungent and cool in nature and dispersing the lung, clearing away heat and relieving asthma. It is mainly used for the treatment of lung heat, cough and asthma.

2.1.2. *Gancao ganjiang* decoction (GCGJ) GCGJ decoction consists of 2 herbs including Radix glycyrrhizae and Rhizoma zingiberis. The main function is to regulate pungency and coolness from nature and disperse from the lung. It mainly used for treatment of *yang* deficiency of spleen and stomach, cold hands and feet, weak and frequent urination, dizziness, short and weak pulse. It is used for epigastric pain, acid vomiting, intestinal pain, abdominal drainage, chest and back pain, dizziness, asthma, menstrual abdominal pain, etc.

2.2. TCM used in the treatment-phase of the infection

The most common symptoms of COVID-19 infection are: fever, muscle soreness, cough, vomiting, chest pain, and diarrhea was the most common GI manifestation of COVID-19 The following TCM formulae were often used as first-line treatment in the TCM hospitals of Wuhan.

2.2.1. *Qingfeipaidu* decoction (QFPD) *Qingfeipaidu* decoction is an optimized combination of several prescriptions for the treatment of exogenous diseases caused by cold pathogenic factors in "Treatise on Febrile and Miscellaneous Diseases nowadays" (伤寒杂病论: *Shang Han Za Bing Lun*). It includes *maxingshigan* decoction, *wuling* powder, *xiaochaihu* decoction and *sheganmahuang* decoction. Among the above drugs, *Ginseng, Ziziphus jujuba* and *Schisandra chinensis seeds* were removed and yam, *immature bitter orange, t*angerine peel and *Agastache rugose* were added. Q*ingfeipaidu* decoction consist of 21 herbs including *Ephedra sinensis,* Radix Glycyrrhizae, Semen Armeniacae Amarum, *Gypsum fibrosum*, Ramulus Cinnamomi, Rhizoma Alismatis, *Polyporus umbellatus, Atractylodes macrocephala, Poria cocos, Bupleurum chinense, Scutellaria baicalensis,* Pinelliae Rhizoma Praeparatum Cum Zingibere, Rhizoma Zingiberis Recens, Radix Asteris, Flos Farfarae, Rhizoma Belamcandae, Herba Asari, Yam, Immature bitter orange, Tangerine peel, and *Agastache rugosa (* [Chen J, 2020a] *;* [Yang et al., 2020b] *).* It is suitable for early, lightly, and heavily infected patients. It was also recommended for the treatment of critical patients. Although the pathogenesis of COVID-19 is still not clear, the lung infection and the inflammatory process are clear. Therefore, anti-inflammatory and antiviral therapy are important. It is conceivable that TCM has anti-influenza viral, anti-inflammation, cough-relieving and immune regulation activities. *Qingfeipaidu* decoction, a formula consisting of 21 components including both herbs and mineral drugs, has been included in the 6th edition of the guidelines as the primarily recommended formulae. According to the 6th and 7th edition of COVID-19 treatment guidelines ([Zhao et al., 2020]), *qingfeipaidu* decoction (QFPD) is effective for patients at all stages, and the total effective rate was 92%.

The outcomes of the 102 confirmed cases, treated integrative medicine on the basis of *qingfeipaidu* decoction, were assessed by two chief physicians, majored in TCM and western medicine, respectively. The symptoms were stable in 5 cases, partially relieved in 31 cases, completely relieved in 64 cases, aggravated in 2 cases, and the total symptom relief rate accounted for 93% ([Liu et al., 2020a]). The results of network pharmacology ([Zhao et al., 2020]) showed that *qingfeipaidu* decoction includes 948 different kinds of chemical composition, which has effects on 790 potential target proteins. Interactions between these targets can form a molecular network, which may affect virus invasion, viral replication and secondary inflammation factors that cause multiple organ damage. The *qingfeipaidu* decoction is likely to target immune related pathways and suppress the activation of cytokines, and eliminate inflammation.

These reports support the effects of TCM on lung-clearing and detoxification decoction.

2.2.2. *Sheganmahuang* decoction (SMD) *SMD* decoction consist of 9 herbs including Rhizoma Belamcandae*, Ephedra sinensis* Rhizoma Zingiberis Recens, Asarum sieboldii, Radix Asteris, Flos Farfarae, *Ziziphus jujube*, Pinelliae Rhizoma Praeparatum Cum Zingibere, *Schisandra chinensis* seeds, which relieves asthma and reduces airway restriction. It not only helpful to dispel heat and reduce poison, but its active ingredients have significant anti-inflammatory and antiviral effects (Eng et al., 2019). SMD is also used to treat bronchial asthma by regulating immune inflammatory pathways (Lin et al., 2020). Recent studies showed that SMD regulated the cellular immune function of the body by regulating the $CD4^{+}/CD8^{+}$ ratio of T cells and the expression of interleukin-5 (IL-5) and interleukin-10 (IL-10) immune factors in patients with asthma (Yang et al., 2015). SMD reduced the inflammatory response by down-regulating IL-17A, TNF-α and IL-6, and increasing IL-10 to inhibit the accumulation of inflammatory cells in the airway of asthmatic mice (Sui et al., 2017a; Sui et al., 2017b). SMD also down-regulated the expression of thymic stromal lymphogenin (TSLP), toll-like receptor 4 (TLR-4), and nuclear factor κB (NF-κB) in lung tissue, thereby reducing lung pathological damage and inflammatory response in asthmatic rats and enhancing the immune effects (Chen et al., 2020b; Yang et al., 2015; Sui et al., 2017a).

2.2.3. *Maxingshigan* decoction (MXSG) MXSG decoction improved the immune function of the body, regulated the expression and secretion of cytokines, thereby reducing lung inflammation and improving the general condition of influenza virus pneumonia in animal studies (Li et al., 2018). The MXSG decoction down-regulated the secretion and protein expression levels of IFN-α and IFN-β macrophages infected with influenza virus and played an antiviral role (Zhang et al., 2019). The MXSG decoction protected against acute lung injury caused by influenza virus infection by inhibiting the activation of Toll-like receptor 4 / myeloid differentiation factor 88 / tumor necrosis factor receptor-associated factor 6 signaling pathway (Li et al., 2017). The MXSG decoction also improved the immune system of the body, up-regulated the protein expression and secretion levels of IL-2 and IL-4, and down-regulated the protein expression and secretion levels of TNF to treat viral pneumonia (Li et al., 2018). In addition, MXSG decoction significantly reduced the pulmonary inflammation *in vivo* as evidenced by pathological examination. MXSG decoction attenuated the LPS-induced inflammation in lung tissues. It is conceivable that MXSG decoction acts on COVID-19 by targeting IL-6, TNF-α, MAPK-8, MAPK-3, CASP-3, TP53, IL-10, CXCL-8, MAPK-1, CCL-2, IL-1β, IL-4, PTGS-2, etc. Among them, IL-6 is currently a clinical early-warning indicator for severe COVID-19 diagnosis and one of the major therapeutic targets.

2.2.4. *Lianhuaqingwen* capsule (LH) LH capsule consists of 11 herbs including Fructus Forsythiae, *Lonicera japonica, Ephedra sinensis,* Semen Armeniacae Amarum, *Isatis tinctoria,* Rhizoma Dryopteridis Crassi Rhizomatis, Herba Houttuyniae, *Agastache rugosa, Rheum palmatum,* Radix et Rhizoma Rhodiolae Crenulatae, *and Glycyrrhiza,* along with menthol and a traditional Chinese mineral medicine, *Gypsum fibrosum* (Jia et al., 2015). It is used in the treatment of influenza, and the main symptoms are fever, aversion to cold, muscle pain, nasal congestion runny nose, cough, headache, pharynx dry pharynx pain. LH capsule not only has good anti-influenza virus activity, but also has antibacterial, antipyretic, analgesic, anti-inflammatory, cough relieving, phlegm and immune function regulating effects. LH capsule can also block the vicious circle of multiple pathological links, mobilize the body's ability of disease resistance and rehabilitation (Zheng, 2010). LH capsule have the function of clearing heat and detoxification, antibacterial and anti-inflammatory, and analgesia. They improved the clinical symptoms of patients, reduce the treatment time of patients, and improve the quality of life of patients (Peng et al., 2016). LH capsule inhibited the decrease of $CD4^{+}$ and $CD4^{+}/CD8^{+}$ levels and protect the cellular immune function (Guo et al., 2007). The Fructus Forsythiae extract inhibited the adsorption and fusion of IAV and MDCK cells, thus exerting antiviral effects. The polysaccharide in *Lonicera japonica* showed immune promotion and inhibition of inflammatory response, and was often used for prevention and treatment of influenza virus infection (Jia et al., 2018). There was a close correlation between *Lonicera japonica* and the expression of functional proteins in serum of mouse influenza model caused by influenza virus (Song et al., 2011). Ingredients such as Semen Armeniacae Amarum, *Ephedra sinensis,* Rhizoma Dryopteridis Crassi Rhizomatis and *Glycyrrhiza* effectively act as expectorant and antitussive and exert anti-inflammatory and anti-allergic pharmacological activities. *Agastache rugose* and *Isatis tinctoria* effectively improved and optimized the basic immune function of patients and modulate the physiological process of viral genetic material replication and synthesis (Qimuge, 2019). The active components of Radix et Rhizoma Rhodiolae Crenulatae improved microcirculation, reduce the oxygen consumption of the body, and had an obvious protective effect on rats suffering from acute pulmonary edema (Wang et al., 1996; Li et al., 2001). Interestingly, LH capsule significantly inhibited SARS-COV-2 replication, affected virus morphology and exerted anti-inflammatory activity in vitro (Li et al., 2020). These findings suggest that LH capsule may protect against the coronavirus attack and may serve as novel strategy fighting the COVID-19 disease. In a prospective multicenter open-label randomized controlled trial with LH capsule in confirmed cases with COVID-19, patients were randomized to receive standard treatment alone or in combination with LH (4 capsules, thrice daily) for 14 days. The primary endpoint was the rate of symptoms (fever, fatigue, coughing) recovery. Indeed, LH capsule considerably ameliorated clinical symptoms of COVID-19 (Li et al., 2020).

2.2.5. *Jinhuaqinggan* granules (JHQG) JHQG granules consists of *Maxingshigan* decoction and *Yinqiao San*, which is composed of Honeysuckle, *Ephedra sinensis, Gypsum fibrosum*, Semen Armeniacae Amarum, *Scutellaria baicalensis*, Fructus Forsythiae, Bulbus Fritillariae Thunbergii, Rhizoma Anemarrhenae, Fructus Arctii, Herba Artemisiae Annuae, Herba Menthae Haplocalycis, *Glycyrrhiza*.(Liu et al., 2020). JHQG granules is used for relieving symptoms such as fever, sore throat, stuffy nose, thirst, coughing or coughing with phlegm. The extract of Fructus Forsythiae reduced the mortality of mice infected with influenza virus, prolonged the survival time and significantly improved the symptoms of pneumonia in mice. The activity of influenza A virus was significantly reduced *in vitro* (Pu et al., 2010). Du et al. (2017) found that Honeysuckle down-regulated the expression of Toll-like receptor 3 and tank-bound kinase 1 caused by respiratory syncytic virus infection and down-regulated the expression of phosphorylated interferon regulatory factor 3. Therefore, Honeysuckle inhibited the overexpression of parasitoid interferon achieving anti-viral effects and avoiding inflammation and tissue damage.

2.3. TCM used in the recovery phase of the infection

According to the recommendations of Wuhan TCM Hospital, *Ginseng* and *shengmai san* were frequently prescribed to patients in the recovery phase of the COVID-19 infection. *Ginseng* is widely used in patients for a speedy recovery. *Shengmai san* is known to improve blood circulation and heart function. It is conceivable that a good blood circulation enhances the recovery of lung damages by improving the microcirculation of the lung cells.

3. Analysis of the frequency of medicinal herbs appeared in the TCM formulae fighting COVID-19 infections

TCM has been prescribed to COVID-19 patients according to the status of their disease. As shown in Table 2, there are 4 stages: mild, moderate, severe, and critical. According to the statistical results of the 31 convalescent prescriptions recommended by the Chinese diagnosis and treatment program during the period of COVID-19 infection showed that 72 TCM herbs were used. Among the top 5 were *Glycyrrhiza* (19 times), *Poria cocos* (18 times), *Tangerine peel* (18 times), *Ophiopogon japonicus* (17 times) and *Astragalus membranaceus* (16 times) (Zhang and Li, 2020). Another report with 73 patients showed that 24 medicinal herbs were used more than 30 times, among which the top three were *Glycyrrhiza* (4.28%), *Scutellaria baicalensis* (4.11%) and *Tangerine peel* (3.37%) (Yan et al., 2020). Another study showed that the frequency of 93 medicinal herbs used in various TCM prescriptions, the top 10 medicinal herbs were: *Astragalus membranaceus, Saposhniovia divaricata root, Glycyrrhiza, Atractylodes macrocephala,* Honeysuckle, Tangerine peel, *Atractylodes lancea, Agastache rugosa, Platycodon grandiflorus,* Fructus Forsythiae (Shi et al., 2020).

The results of analysis on the treatment prescription of 875 confirmed patients showed that a total of 233 TCM herbs were employed and 20 high-frequency drugs were identified as: *Scutellaria baicalensis,* Fructus Forsythiae, Rhizoma Belamcandae, *Agastache rugosa, Glycyrrhiza,* Szechuan fritillary bulb, Semen Armeniacae Amarum, Yam, Radix Glycyrrhizae, *Platycodon grandiflorus, Poria cocos,* Herba Menthae Haplocalycis*, etc.* The most frequently used of the medicinal herb was *Scutellaria baicalensis* (Chen et al., 2020). Throughout the statistical analysis of the medicinal herbs used in 149 prescriptions, 14 drugs were used more than 30 times, including: *Glycyrrhiza,* Semen Armeniacae Amarum, *Ephedra sinensis*, Tangerine peel, *Gypsum fibrosum, Atractylodes lancea, Agastache rugosa,* ginseng*, Poria cocos, Astragalus membranaceus, Lonicera japonica*, Pinelliae Rhizoma Praeparatum Cum Zingibere*, Atractylodes macrocephala* and *Scutellaria baicalensis* (Cheng et al., 2020). Another analysis of 56 prescriptions of TCM for prevention and treatment in 17 regional hospitals in China showed that a total of 79 herbs were employed, and the top five medicines were: *Astragalus membranaceus, Lonicera japonica, Glycyrrhiza, Atractylodes macrocephala* and *Saposhniovia divaricata* root (Wang et al., 2020). Table 3 summarizes the use of TCMs in the treatment of COVID-19 following basic theories of Chinese medicine. The combination of clinical symptoms can be used as a “different kind of biomarkers” for Chinese medicine practitioner to diagnoses TCM symptoms and choose appropriate TCMs.

Table 3

The TCM symptoms of COVID-19

TCM	Symptoms	Clinical manifestations
Ma xing shi gan decoction	Wind-heat attacks the lungs, wind-cold transformed into heat, *wen bing* - *qi* stage lung heat	Cough with thick sticky, yellow sputum,sore, red, swollen throat, thirst, with desire to drink cold liquids, runny or blocked nose with thick yellow discharge, vertigo, dry throat, dizziness, fever with or without perspiration, slight chills, aversion to wind, headache, dyspnea with flared nostrils and pain
Gancao ganjiang decoction	Deficiency cold lung atrophy, abdominal pain due to spleen and stomach deficiency, bleeding due to spleen *yang* deficiency, externally generated fevers with internal cold	Cold extremities,no thirst,dry throat,excessive salivation with spitting up of clear fluids,no coughing,spontaneous sweating,a bland taste in the mouth,cold breath, frequent, clear urination, irritability
Qingfei paidu decoction	Lung heat	High fever, no chills, aversion to heat, cough, asthma, restlessness, thirst, dark yellow urine
Shegan mahuang decoction	Wind-cold with cold thin mucus*tan yin*, cough and asthma due to cold,retention of cold-phlegm in the lungs	Pronounced coughing,pronounced wheezing, aversion to cold, headache, rales, dyspnea, profuse, clear, watery sputum orscanty, clear sputum, a feeling of fullness and a stifling sensation in the chest and diaphragm,rattling sounds in the throat
Lianhua qingwen capsule	Detoxification, ventilating lungs and heat.	Fever or high fever,aversion to cold,muscle aches, nasal congestion and runny nose, cough, headache, dry throat, sore throat, red tongue, yellow or greasy coating
Jinhua qinggan granules	Disperse wind and lungs, clear heat and detoxification	Fever, head and body pain, sore throat, dry cough, stuffy nose, red tongue,zhin yellow tongue coating
Shengmai san	Lung and kidney *qi* deficiency, heart and lung *qi* deficiency, lung *qi* and *yin* deficiency, atrophy disorder (*wei* syndrome) due to lung heat with fluid deficiency	Chronic cough with sparse sputum, sputum difficult to expectorate, shortness of breath,spontaneous perspiration, dry mouth and tongue, dry skin, palpitations with a stifling sensation in chest, fatigue,i rritability

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4. Pharmacological basis of Chinese herbs used frequently in fighting COVID-19 in Wuhan

A total of 76 medicinal herbs were used in more than 30 TCM formulae for treating COVID-19 in China. The frequency of each herbs used were arranged in descending order with the highest on the top: *Glycyrrhiza* (17 times), *Scutellaria baicalensis* (11 times), Rhizoma Zingiberis Recens (11 times), *Paeonia lactiflora* root (9 times), *Ziziphus jujube* (9 times), Pinelliae Rhizoma Praeparatum Cum Zingibere (8 times), *Ephedra sinensis* (7 times), Ramulus Cinnamomi (7 times), Semen Armeniacae Amarum (5 times), *Ginseng* (5 times), *Bupleurum chinense* (5 times), *Gypsum fibrosum (Sheng Shi Gao)* (5 times), *Platycodon grandiflorus* (5 times), *Magnolia officinalis* (5 times). The remaining TCM herbs occurred less than 5 times.

Based on the statistical analysis, the top 15 frequently used TCM herbs fighting COVID-19 were identified and reviewed for their specific pharmacological targets and profiles, in order to encourage the follow-up investigation for the bioactive compounds which may play a clear and better role fighting COVID-19.

4.1. Ephedra sinensis

Ephedra methyl ephedrine contains L-ephedrine and pseudoephedrine D, which have anti-influenza virus activity by inhibiting pathways of viral replication, modulating inflammatory reaction and adjusting the host Toll-like receptors (TLRs; Zhang et al., 2019), and retinoic acid inducing gene protein (RIG-I) (Wei et al., 2019). Ephedrine inhibited the infection of canine renal cells by H1N1 influenza virus in a concentration-dependent manner (Hyuga et al., 2016). Tannic acid of *Ephedra sinensis* extract inhibited the acidification of endosomes and lysosomes in a concentration-dependent manner, thereby inhibiting the growth of influenza A virus in canine renal cells (Mantani et al., 1999). Meanwhile, the research team found that (+) -catechin in *Ephedra sinensis,* inhibited the acidification of adenylate and the growth of PR8 influenza virus, proving that (+) -catechin was one of the antiviral active components in the *Ephedra sinensis* extract (Mantani et al., 2001).

4.2. Astragalus membranaceus

Astragalus membranaceus has a variety of pharmacological effects, such as antiviral activity, regulating the body's immune function etc. It is widely used in clinical practice and has significant curative effects. *Astragalus membranaceus* regulates the secretion of mucous of respiratory tract and enhances the immune function of respiratory system (Qin et al., 2017). *Astragalus membranaceus* not only increases the number of multinucleated white blood cells and blood white blood cells, promotes cellular immunity and humoral immunity, but also serves as immune-enhancing agent and plays a bidirectional regulating role. *Astragalus membranaceus* reduced the level of inflammatory transmitters, induced interferon resistance to viruses, and played a role of broad-spectrum antiviral (Wang et al., 2017). *Astragalus polysaccharides* (APS), as one of the main components of *Astragalus membranaceus* has been proven to be an immunomodulator (Deng et al., 2016), and it regulates the secretion of mucous membrane of respiratory system and digestive system. It also has an important influence on the first-line of immune defense of the human body. *Astragalus flavones* promoted the activation of lymphocytes, macrophages and neutrophils, improved the phagocytosis of macrophages, responded quickly to invading pathogens, and had non-specific anti-infection effects (Qin et al., 2007). A recent study suggested that viral infections such as COVID-19 are not only associated with lung infection, but also with immune dysfunction (Xu et al., 2020). Recent studies have shown that multiple organ injuries caused by COVID-*19* may be related to inflammatory storms and accumulation of oxidative stress-free radicals in the body. *Astragalus membranaceus* inhibited the activation of the MAPK/NF- B signaling pathway, down-regulated the levels of IL-6, IL-8, TNF-α and other inflammatory factors and chemokines, and reduced the inflammatory response. *Astragaloside IV* activated the PI3K/Akt/mTOR signaling pathway, up-regulated the level of superoxide dismutase (SOD), strengthened the scavenging of free radicals, and protected the body (Zhang et al., 2020).

4.3. Agastache rugosa

Agastache rugosa strongly inhibited the replication of H1N1 influenza virus *in vitro* (Wu et al., 2013). In the mouse model with lethal levels of FM1, patchouli alcohol (PA) significantly improved the survival rate and prolonged the survival time of mice infected with influenza virus, and significantly reduced lung inflammation. This effect was achieved by regulating the level of inflammatory cytokines in the lung (Li et al., 2012). The antiviral effect of patchouli oil *in vitro* was shown to be anti-adenovirus, possibly by destroying the virus capsid protein Hexon gene and preventing the virus from adsorbing cells (Wei et al., 2013). PA is a methanol extract from *Agastache rugosa*, which contains the main bioactive component of *Agastache rugosa* (Kiyohara et al., 2012).

4.4. Glycyrrhiza

SARS-CoV-2 enters cells through the angiotensin-converting enzyme II (ACE2) cell receptor. Glycyrrhizin, the major bioactive component of *Glycyrrhiza*, was confirmed to interact directly with ACE2, therefore, suggesting that glycyrrhizin may be a potential therapeutic agent against COVID-19 (Zhou et al., 2020). In search for antiviral drugs to treat SARS, the antiviral potential of ribavirin, 6-cytidine, pyrazolfurin, mycophenolic acid and glycyrrhizin towards two coronavirus strains (FFM-1 and FFM-2) was evaluated (Cinatl et al., 2003). Glycyrrhizin was the most active compound to inhibit the replication of FFM-1and FFM-2 viruses among these compounds. Glycyrrhizin did not only inhibit the replication of FFM-1 and FFM-2 viruses, but also interfered with the cycle of adsorption and osmotic replication of the two viruses. Furthermore, the water extract had anti-herpes simplex virus 1 (HSV-1) activity, and the mechanism of action may through its strong anti-adhesion, which directly inhibited the attachment process of HSV-1 virus (Sabouri Ghannad et al., 2014).

4.5. Honeysuckle (Flos Lonicerae Japonicae)

Honeysuckle (Flos Lonicerae Japonicae) has a broad spectrum of antiviral effects on influenza virus, respiratory syncytial virus (RSV), avian influenza virus H9 subtype (H9-AIV), enterovirus EV71, herpes virus and so on (Liu et al., 2020b). The alcohol extract significantly reduced ear swelling caused by xylene and the foot swelling caused by carrageenin in mice in a dose-dependent manner (Zhang and Chen, 2019). These authors reported a modified lime sulfur method of extracting *Lonicera japonica* active ingredients and a bacteriostatic circle method to evaluate the antibacterial effects against *Bacillus subtilis, E. coli, Pseudomonas aeruginosa* and *Staphylococcus aureus.* The *Lonicera japonica* extract exerted good antibacterial effects for the treatment of bacterial infectious diseases (Zhang et al., 2019) . The *Lonicera japonica* water extract inhibited a variety of bacteria (cocci, bacilli and *Klebsiella pneumonia*), in addition to its good inhibitory effect on influenza A virus (Hu et al., 2015).

4.6. Polygonum cuspidate

The ethyl acetate extract of *Polygonum cuspidate* had anti-inflammatory effects, which may be caused by inhibiting the synthesis of the proinflammatory prostaglandin E2 (PGE2), inhibiting cellular immunity and being related to the pituitary-adrenal cortex system. Emodin and other anthraquinone compounds in *Polygonum cuspidate* have confirmed for their antiviral effects. The positive results against hepatitis B favor its use for the treatment of acute icteric hepatitis and chronic hepatitis (Zhang et al., 2003). *Polygonum cuspidate* directly inhibited the proliferation and blocked the infection of the hs-1 strain of herpes simplex virus (HSV-1), which was more potent than the control drug acyclovir (Wang et al., 1999). Anthraquinone compounds had anti-HIV effects, among which emodin in *Polygonum cuspidate* had an anti-hiv-1 activity of IC50 of 36.3 μmol/L (Schinazi et al., 1990). Furthermore, emodin had inhibitory activity against HSV-1 and HSV-2, pseudorabies influenza, parainfluenza viruses, vaccinia virus, etc. (Sydisk et al., 1991). *Staphylococcus aureus* and *Hepatitis dicoccus* were inhibited by emodin, emodin -8-glucoside, etc. Emodin also has antibacterial activity (Zhu et al., 1985).

4.7. Scutellaria baicalensis

Baicalin and baicalin in *Scutellaria baicalensis* inhibit the growth of many Gram-positive and -negative bacteria. *Scutellaria baicalensis* had strong antibacterial and antiviral effects and significantly inhibited the pathogenic skin fungus (Li, 2018). *Scutellaria baicalensis* had strong antibacterial and antiviral effects and significantly inhibited the pathogenic skin fungus reduced the growth of the *Acinetobacter* calcium acetate ndm-1 strain, and effectively eliminated drug-resistant plasmids. Among the various extraction methods, alcohol extraction was more effective to inhibit the transmission of clinical infections of hyper-resistant *Acinetobacter* (Liu et al., 2017). The antibacterial activity of *Scutellaria baicalensis* was good, especially against *Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Vibrio parahaemolyticus, Vibrio alginosa*, etc (Bai et al., 2018).

4.8. Rheum palmatum

Rheum palmatum showed considerable antiviral effect and is regularly used to treat respiratory diseases. Anthraquinone compounds extracted from *Rheum palmatum* inhibited the infectivity of some viruses, effectively inhibited virus synthesis and replication, and even directly inactivated the virus (Xie et al., 2013).

4.9. Isatis tinctoria

Alkaloids are the key components of anti-virus action of *Isatis tinctoria.* The total alkaloids of *Isatis tinctoria* had a protective effect on mice infected with influenza A virus (He et al., 2014). The methanol extract, indigo and indiindium not only inhibited the activity of Japanese encephalitis virus (JEV), but was also less cytotoxic than other components. In particular, indiindium had a strong protective effect on mice infected with JEV (Chang et al., 2012). In fact, indiindium did not directly inhibit the virus, but inhibited the expression of activated chemokines (normal T cells and the secretory factor RANTES) in human bronchial epithelial cells infected with influenza virus (Mak et al., 2004).

4.10. Atractylodes lancea

The ethanol extract of *Atractylodes lancea* given to mice by gavage continuously for 7 days significantly improved the carbon clearance rate in the murine reticuloendothelial system, significantly enhanced the degree of mouse ear swelling caused by dinitrochlorobenzene sensitization, and resisted the decrease of mouse serum hemolysin level caused by chicken red blood cell immunity (Xu et al., 2005). The volatile oil of *Atractylodes lancea,* the water extract of *Atractylodes lancea* to remove volatile oil, the dry paste of solution after water extraction, and the alcohol precipitation of *Atractylodes lancea* all stimulated the proliferation of spleen lymphocytes *in vitro.* The active components of *Atractylodes lancea* improved the non-specific immunity, specific cellular immunity and humoral immunity (Zhu et al., 2007). Chen et al. established a murine immune deficiency model through cyclophosphamide and observed the effect of the extract of Chinese medicine on the immune function of immune deficiency mice. *Atractylodes lancea* significantly improved the activity and phagocytosis of mononuclear macrophages, thus achieving the effect of promoting innate immunity (Chen et al., 2015).

4.11. Tangerine peel

Tangerine peel mainly contains flavonoids and other edible and medicinal ingredients. *Tangerine peel* extract strongly inhibited the oxidation of lard and scavenging hydroxyl free radicals (•OH). *In vivo* experiments showed that the water extract of tangerine peel strongly inhibited lipid peroxidation in brain, heart and liver tissues of mice, and significantly enhanced the relative activity of SOD (Jing et al., 2003). Hydroxyl radicals caused lipid peroxidation of erythrocyte membranes and significantly increased malondialdehyde (MDA) content, while hesperidin, the major bioactive compound in tangerine peel significantly reduced membrane MDA content, significantly improved membrane lipid fluidity and membrane re-sealing ability, and protected from membrane oxidative damage. Hesperidin had a significant scavenging effect on •OH in a concentration-dependent manner. *Tangerine peel* extract cleared superoxide anion free radicals produced by hypoxanthine oxidase system and the OH produced by Fenton reaction, and inhibited the peroxide of rat myocardial homogenate tissue induced by oxygen free radical generation system, indicating that tangerine peel has a potent antioxidant effect (Wang et al., 2000).

4.12. Poria cocos

Poria cocos enhanced the specific cellular immune function of mice. In addition, *Poria cocos* had free radical scavenging effects, suggesting that it may have effect on delaying the aging process. *Poria cocos* extract inhibited the acute rejection of heterotopic heart transplantation in rats. Tuckahoe polysaccharide enhanced the body's immunity, and its immune-enhancing effects were mainly manifested in the anti-thymic atrophy, anti-splenic enlargement and anti-tumor growth, and enhanced cellular and humoral immunity (Duan et al., 2016). *Poria cocos* significantly promoted the growth of the rat intestinal epithelial cell line IEC-6, and regulated the immunity of the whole body through the regulation of intestinal epithelial cells (Tu et al., 2016). The esterified derivatives of triterpenoid 1 and triterpenoid 12 promoted the proliferation of T cells in mice. The esterified derivatives of triterpenoid 12 and triterpenoid 1 inhibited the proliferation, while triterpenoid 15 regulated immune functions (Li et al., 2016).

4.13. Atractylodes macrocephala

Atractylodes polysaccharides stimulate the immune system. *Atractylodes* polysaccharides enhanced the phagocytotic function of macrophages, increased the expression of TLR4, and promoted the secretion of TNF-α, IFN-γ and NO (Ji et al., 2014). By adding largehead *Atractylodes* polysaccharide to ovalbumin vaccine, significantly increased levels of anti-ovalbumin specific antibodies and subclasses of antibodies were found in the serum of mice (Chai et al., 2013). *Atractylodes* polysaccharide improved the phagocytosis and intracellular acid phosphatase activity of mouse Kupffer cells on neutral red A540 (Jiao et al., 2013). *Atractylodes* polysaccharide promoted the proliferation of mouse lymphocytes. The higher the degree of purification of *Atractylodes* polysaccharide was, the stronger was its promoting effect (Guo et al., 2012). *Atractylodes* polysaccharide antigen not only stimulated the body to produce IgG antibodies, but also stimulated the production of cross-antibodies, so as to produce immune function (Sun et al., 2011).

4.14. Bupleurum chinense

Bupleurum chinense significantly reduced the body temperature of dry yeast-induced rats, and *Bupleurum chinense* increased arginine vasopressin (AVP) in rat plasma, but no effect on cyclic adenosine phosphate (c AMP) was observed (Li et al., 2015). The antipyretic mechanism of *Bupleurum* saponin and *Bupleurum* decoction was related to the decrease of cyclic adenosine phosphate (cAMP) and PKA (cAMP dependent protein kinase) in the hypothalamus, the decrease of AVP level in the brain and abdominal septum and the increase of AVP level in plasma, and the inhibition of increased IL-1 in peripheral blood (Lu et al., 2013;Sun et al., 2016). The treatment with *xiaochaihu* decoction combined with commonly used antibiotics significantly reduced the patient's long-term fever and body temperature, reduced the recurrence of high fever, improved the efficacy of drugs, and reduced the frequency of adverse reactions (Yu, 2016). *Bupleurum* saponin-A and *Bupleurum* saponin-D inhibited the activity of lipopolysaccharides (LPS) and reduced the expression of cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) in cells, eventually leading to a cellular decrease of prostaglandin E2 (PGE2) and nitric oxide (NO) (Tu et al., 2016). In addition, both *Bupleurum* saponin-A and *Bupleurum* saponin-D showed significant anti-inflammatory activities in experiments of carrageenin-induced foot swelling in rats and increased the vascular permeability in mice induced by acetic acid (Lu et al., 2012).

4.15. Radix Rehmanniae

Radix Rehmanniae is a common ingredient used in many TCM formulae for treating viral infection. Catalpol, an iridoid glycoside extracted from the raw roots of *Rehmannia*, has been reported to protect against LPS-induced acute lung injury through a Toll-like receptor-4 (TLR-4)-mediated NF-kB signaling pathway (Ma et al., 2014). Zhang et al. (Zhang et al., 2016) demonstrated that post-treatment with catalpol (10 mg/kg) alleviated the LPS-induced microvascular hyperpermeability and hemorrhage; reduced mortality; ameliorated the alteration in the distribution of claudin-5 and the junctional adhesion molecule-1, as well as the degradation of collagen IV and laminin; and attenuated the increase of TLR-4 level, phosphorylation of Src tyrosine kinase, phosphatidyl inositol 3-kinase, focal adhesion kinase, and cathepsin B activation. In addition, surface plasmon resonance showed that catalpol could directly bind to TLR-4 and Src. These results clearly demonstrated that catalpol restored LPS-elicited microcirculation disorder by regulation of a network of signaling involving inhibition of TLR-4 and SRC. Sepsis, characterized by microcirculation disorder with disseminated intravascular coagulation (DIC) is a life-threatening complication and a clinical condition of COVID-19 infection. It will lead to organ failure and death without proper intervention. However, there is no safe and effective therapy. Catalpol provided an excellent case to support the clinical efficacy of *Radix Rehmanniae* in treating COVID-19 patients in ICU with a clear picture of mechanism of actions.

5. TCM enhances the Immune System

The immune system is an important system to protect the human being. It requires a constant check and balance to protect our body from infectious and harmful substances. If the immune system is activated, it will respond to antigens associated with infectious diseases. TCM has employed holistic approaches and sees the body as an organic whole. The correlations between the organs and tissues, as well as the human and the living environments, are organized in a specific order, which give rise to mutual balance between each physiological function. This integral stability and harmony are the root of disease defense and health maintenance. Under normal circumstances, the body relies on the immune system to fight against various infections and to clean up harmful materials in order to keep a clean environment. TCMs perform dual roles on immunological regulation: immunological activation and immunological suppression (Ma, 2013). Cell infected by pathogenic agents may trigger host humoral and cellular immunities which are essential to eliminate the viral infection (Florindo, 2020). Therefore, the induction of a balanced host immune response is crucial to control and eliminate infection, employing adaptive and innate immune responses, as well as events mediated by the complement system. Two important approaches to achieve balanced immunity to fight infection. Accumulating evidence indicates that TCMs and their components can activate immune responses at the earliest stage by targeting key functions of dendritic cells, including their differentiation, maturation, cytokine production, survival, antigen uptake and presentation, and trafficking (Ma, 2013). TCM actions on T lymphocytes has been validated. These results suggest that TCMs can promote T lymphocyte proliferation and transformation, stimulate cytotoxic T lymphocyte generation, adjust the imbalance of TH1 and TH2 responses, affect T cell subsets, and regulate T cell-mediated immunity (Jiang et al., 2010). For instance, ginsenosides, the bioactive ingredients of Panax ginseng, have been reported to increase the immune activity of CD4+ T cells. Many TCM preparations such as ginseng spleen-invigorating pills and *colla corii asini* are used to induce hematopoiesis, enhance cellular immunity, and confer radioprotection (Attele et al., 1999; Lee et al., 2004; Lee and Han, 2006). Recent studies have suggested that a number of TCMs have effects on cytokines such as IL-4, IL-6, IL-10, TNF, and IFN-γ (Calixto et al., 2004; Spelman et al., 2006). In the past several years, studies were undertaken to investigate the possible role of TCM on immune system. The research in TCM has recently sparked renewed interests in the development of novel therapeutic strategies to suppress the abnormal inflammation to treat allergy.

6. Conclusion and perspectives

TCM has always played a pivotal role in treating diseases and maintaining health for thousands of years and stands as testimony to a holistic approach. Unfortunately, the mechanisms of action of TCM are still largely unknown and under investigation. In the general view of the West, TCM appears to be anecdotal and non-scientific. The Western approach emphasizes the fast relief of symptoms at the disease site, particularly under critical conditions. However, single chemical entities targeting single receptor sites may not be sufficient to restore the functional balance of the body. The holistic approach has gained increasing popularity, because herbal medicine with its multi-component, multi-targeted approach focuses on the functional balance of the entire body. Therefore, in a broader perspective, herbal medicine should have certain advantages in dealing with complex human diseases with distorted immune-balance especially under epidemic infection. Recent advances in physiology and systems biology provide evidence that human diseases are highly complex, and that there is an important balance of immunity to protect population health and well-being. We believe that disease development and progression are linked closely to dysfunctional inflammation and immunity regardless of their physical, environmental, or psychological nature. More importantly, TCM has a long history of viewing an individual or patient as a whole. This holistic philosophy of TCM is now recognized by emerging network pharmacology and network biology and by sharing the common requirements of overcoming complex human diseases, such as cancer, in a systematic manner. Therefore, we advocate for a lifestyle with balanced immunity at the patient level as well as at the local and national levels to enhance population health - especially in dealing with epidemic infections.

Based on the frequency of appearance of each medicinal herb and their corresponding pharmacological activities, the following TCM formula was reconstructed with the potential of treating COVID-19 infection. This TCM formula contains four top listed herbs and herbs with evidenced anti-virus activity along with reducing fever, removing dampness, expelling phlegm, and arresting coughing. It includes *Bupleurum chinense* (10 g), Ramulus Cinnamomi (10 g), *Scutellaria baicalensis* (10 g), *Glycyrrhiza* (15 g), *Atractylodes macrocephala* (10 g), Rhizoma Zingiberis (10 g), *Agastache rugosa* (10 g), *Stephania tetrandra* root (10 g), *Polygonum cuspidate* (10 g), *Rheum palmatum* (10 g), tangerine peel (10 g), Semen Armeniacae Amarum (10 g) and *Ophiopogon japonicus* root (10g). The formula was combined with *chaihu guizhi* decoction and *Glycyrrhiza* dried ginger decoction in "Treatise on Febrile and Miscellaneous Diseases nowadays" (伤寒杂病论: *Shanghan Zabing Lun,* 220 AD). Both of the two formulas were used for the treatment of exogenous diseases caused by cold pathogenic factors. They are currently used in this outbreak, which also conforms to the characteristics of covid-19 as an exogenous disease. In this Chinese herbal compound, *Bupleurum chinense*, Ramulus Cinnamomi, *Scutellaria baicalensis* and *Glycyrrhiza* can reconciliation *shaoyang*, harmony *ying-wei, Atractylodes macrocephala* invigorates the spleen and strengthening the body resistance, Rhizoma Zingiberis, *Agastache rugosa* warm and promote diuresis, at the same time, the Four Stamen *Stephania* root and *Polygonum cuspidate* also has the effect of eliminating dampness, the tangerine peel and Semen Armeniacae Amarum are used for relieving cough and lung symptoms. In addition, in modern pharmacology, *Rheum palmatum* and *Polygonum cuspidate* have significant antiviral effects due to their rich emodin content. Full prescription of 12 drugs, for the clinical treatment of COVID-19, will achieve satisfactory results.

In retrospective analysis of the efficacy of TCM fighting COVID-19 in Wuhan and other parts of China, reached an important consensus that TCM is effective in the early phase and treatment phase of virus infection. In comparison with western treatment, TCM showed superiority in preventing infected patients escalated to severe cases and reduced the number of patients admitted to the ICU. In the Jin-Chang Hospital, the efficacy rate of TCM treatment was almost 100% (99.2%). TCM is also used regularly in assist patients in the ICU receiving western treatments. If patients released from ICU, TCM also showed efficacy in recovery phase of the infection. Although, TCM has been used widely in China, however, its safety and efficacy were first clearly evidenced in almost all hospitals in Wuhan and entire China and recognized by general public and government officials. TCM should play a more important role in treating human diseases especially in infectious disease in the future. However, in order to convince the world outside of China, the scientific basis of TCM in treating COVID-19 must be validated. Especially, TCM theory such as the meridian system which guides all TCM treatments of human diseases has not been accepted in the western world. In this review, we provide strong scientific data supporting the treatment of COVID-19 infection with TCM formulae, particularly for the treatment of acute lung injuries (ALI) which is a common symptom in COVID-19 patients, and there is no other effective medication. For instance, MXSGT is a TCM formula used for treatment of respiratory system diseases, which has been investigated in the LPS-induced rat ALI, particularly with a focus on its effect on lung microvascular hyperpermeability and inflammatory reaction. Post-treatment with MXSGT ameliorated lung microvascular hyperpermeability and inflammation reaction, resulting in an elevation of survival rate of the rats after LPS exposure (Ma et al., 2014). As we know, TCM may not be the best strategy in directly killing coronavirus or preventing infection at the entry level. Ma's study indicated the involvement of TLR-4, SRC, and NF-kB in the signaling pathway as responsible factor for the treatment effect of MXSGT on ALI. Therefore, it is conceivable that TCM formula such as MXSGT could be used as a safe and effective therapy aiming at ameliorating lung fluid accumulation and inflammatory infiltration. In view of the urgent need to heal the COVID-19 patients with acute lung injuries, TCM ought to play an important and active role in fighting the worldwide COVID-19 pandemic.

This review article attempts to provide information for western health practitioner for a better understanding of TCM in treating epidemic infections including COVID-19, and the pharmacological effects of bioactive compounds used frequently in TCM formulae. Hopefully, we can benefit from the wisdom of ancient TCM by using cutting edge science and technologies in the 21st century.

Credit Author Statemen

DYWL is responsible for the conceptual design of the paper and writing the draft QYL and JL are involved in clinical work and they contributed with writing the clinical parts.TE participated with writing, correcting and editing of the manuscript.All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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