The American Journal of Chinese Medicine, Vol. 48, No. 4, 763–777

Institute for Advanced Research in Asian Science and Medicine
DOI: 10.1142/S0192415X2050038X

Becoming a Faithful Defender: Traditional Chinese Medicine against Coronavirus Disease 2019 (COVID-19)

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Published 29 April 2020

Abstract: The outbreak caused by COVID-19 is causing a major challenge to clinical management and a worldwide threat to public health. So far, there is no specific anti-coronavirus therapy approved for the treatment of COVID-19. Recently, as the efficacy and safety of traditional Chinese medicine (TCM) is widely acknowledged, it has been brought to a crucial status by the public, governments, and World Health Organization (WHO). For a better popularization of TCM, governments have made several advances in regulations and policies for treatment and measures of novel coronavirus pneumonia (NCP). Therefore, on the basis of epidemiology and virology information, we reviewed relevant meta-analysis and clinical studies of anti-coronavirus therapeutics by TCM, in the aspect of mortality, symptom improvement, duration and dosage of corticosteroid, incidence of complications and the like. In addition, we also summarized preclinical rationale for anti-coronavirus activity by TCM in terms of virion assembly and release, as well as viral entry and replication, which could be a useful contribution for figuring out effective Chinese herbal medicine (CHM) for coronavirus, including ingredients from single monomeric compounds, Chinese herbs, Chinese herb extracts and Chinese herb formulas, or potential targets for medicine. We would like to see

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these relevant studies, ranging from basic researches to clinical application, could provide some idea on effects of CHM to combat COVID-19 or other coronaviruses, and also offer new thinking for the exploration of therapeutic strategies under the guidance of TCM.

Keywords: Coronaviruses; Traditional Chinese Medicine; Intervention Effect; Review.

Introduction

Human coronaviruses (HCoVs) received relatively little attention due to their less frequent explosions in humans until 2002, when cases of severe atypical pneumonia were first described in Guangdong Province, China, emerging from animal reservoirs to cause a travel-related global epidemics with alarming morbidity and mortality, and later became well known as severe acute respiratory syndrome (SARS) (WHO, 2004). In additional, Middle East Respiratory Syndrome (MERS), a lethal zoonotic disease of humans endemic that was initially identified in Kingdom of Saudi Arabia in 2012, which appeared continuously through intermittent sporadic cases, community clusters, and nosocomial outbreaks. By December 2019, a total of 2494 confirmed cases of MERS patients and 858 deaths with a case fatality rate near 34.4% (WHO, 2019). The recent outbreak of clusters of novel coronavirus pneumonia (NCP) caused by COVID-19, previously named nCOV-2019, seems be initially hosted by bats, then as a result of uncertain causes that might epidemiologically link to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China in late December 2019.

With the progression of COVID-19 epidemic, increasing statements and treatment plans released by State Administration of Traditional Chinese Medicine of the People's Republic of China (SATCM) and National Health Commission of People's Republic of China (NHC) officially stressed the advantages of traditional Chinese medicine (TCM), encouraged the in-depth development of integrated traditional Chinese and Western medicine to cover the whole period of patients with COVID-19, and made TCM the leading role (Jin *et al.*, 2020).

Therefore, we summarize epidemiology and virology information, advances made in regulations and policies for treatment and measures of NCP, as well as researches performed for discovery and development of potential targets, in order to provide some idea on effects of Chinese herbal medicines (CHMs) to combat COVID-19 or other coronaviruses, and this also offers new thinking for the exploration of therapeutic strategies under the guidance of TCM.

Measures and Affects of TCM against NCP

The Initial Effect of TCM in the Treatment of NCP

On January 23, 2020, NHC and SATCM have officially included the TCM treatment plan into the NCP diagnosis and treatment plan (trial version 3) (NHC, 2020c) for the first time. Four days later, in the version 4, it was proposed to strengthen the combination of TCM

and Western medicine, establish a consultation system of integrated Chinese and Western medicine, determine the prescription drug composition and dose of the TCM treatment plan, and to put forward the application of Chinese patent medicine in the clinical observation period (NHC, 2020a). This marked the early intervention of TCM recognized by the state.

From January 24–25, academicians of TCM led teams to Wuhan to fight against the epidemic successively. At the same time, Chinese Academy of Sciences Institute of Materia Medica had identified 30 drugs, active natural products, and CHM (such as polygonumcuspidatum and sophoratonkinensis), which may have a therapeutic effect on COVID-19. Therefore, these were recommended to be considered for the clinical treatment of NCP patients. On January 26, the first Chinese medical team arrived at the Jinyintan hospital and carried out medical treatment work officially.

From January 27 to February 5, four pilot provinces used "Qingfei Paidu Decoction" to treat 214 confirmed patients with 3 days as a treatment course. The total effective rate was over 90%, among which over 60% of the patients showed substantial improvement in symptoms and imaging manifestations, and 30% had stable symptoms. On February 5, the designated medical institutions in Wuhan made sure all patients are taking CHM. At the same time, some provinces such as Shanghai, Guangxi and Henan had implemented CHM for all confirmed cases. The combined treatment of Chinese and Western medicine had brought good curative effect. On February 6, the first group of 23 patients (three severe cases) were cured and discharged from hospital by adopting TCM as the main treatment of integrated traditional Chinese and Western medicine. In conclusion, for common patients, TCM can improve symptoms and shorten the course of treatment; for severe and critical patients, it can reduce the exudation of the lungs, control the over-reaction of inflammation and prevent the deterioration of the disease; for convalescent patients, it can promote the recovery process. With the development of the epidemic, the committee of the communist party, health commission and the administration of traditional Chinese medicine in all provinces (districts and cities) had introduced TCM prevention and treatment programs for NCP in succession.

To find an effective medicine, over 165 running or pending clinical trials on potential therapies for COVID-19 have been registered since the first on January 23, among which about 46 clinical trials are expected to include more than 6000 patients on a variety of TCM-related treatments. In particular, one of the largest randomized open, parallel controlled and multi-center clinical trials was registed in Chinese Clinical Trial Register (ChiCTR) on February 7. This clinical trial aims to evaluate the clinical efficacy and safety of Shuang-Huang-Lian for the treatment of NCP patients, which is a kind of Chinese herbal medicine extracted from Forsythiae fructus.

By February 15, the National TCM system had sent 2,220 medical staff to support the frontline of prevention and control in Hubei, and the four batches of national TCM medical teams had admitted 248 confirmed and suspected patients with 159 having improved symptoms. During diagnosis and treatment, it was found that the time of nucleic acid detection turns negative in the integrated traditional Chinese and Western medicine group was significantly shorter than that in the Western medicine group, and the 10 symptoms

such as fever, cough, weakness and loss of appetite were significantly improved compared to the Western medicine group. Moreover, the mean hospitalization time of integrated traditional Chinese and Western medicine group was shorter than that of Western medicine group with statistical significance.

Comprehensive Application of TCM in the Treatment of NCP

On February 17, the State Council said at a press conference that 701 confirmed cases using "Qingfei Paidu Decoction" in 57 designated medical institutions in 10 provinces had been under observation. Among them, 130 cases were cured and discharged from hospital, 51 cases' symptoms disappeared, 268 cases' symptoms improved, and 212 cases had stable symptoms without aggravation. The results showed that the clinical effective rate of "Qingfei Paidu Decoction" was more than 90%. On February 19, NHC published the sixth edition of the NCP diagnosis and treatment plan with separately recommending to use "Qingfei Paidu Decoction" (NHC, 2020b). It was also suggested that doctors can flexibly change dosage according to the condition, especially in critical cases. Based on previous treatments and according to the treatment plan of many provinces and cities, the new plan added Redonin injection, Tanreqing injection, and Shenmai injection for the first time, and attached the specific usage of TCM injections for severe and critical patients. It is convenient for Western medicine and provides more options for doctors to treat severe and critical cases. On February 22, in order to accelerate the recovery of NCP patients during the convalescence, the State Council organized relevant experts to formulate the "Guidance and Suggestions on TCM rehabilitation during the convalescence of new coronavirus pneumonia (trial)", TCM treatment will be carried through the beginning and end of NCP.

By February 24, five groups of national TCM medical teams, more than 4,900 TCM medical personnel from all over the country had been sent to the frontline of prevention and control in Wuhan. Patients in the C5 and C7 wards of Raytheon Mountain Hospital received the routine diagnosis and treatment of Western medicine according to diagnosis and treatment plan (trial version 6) combined with external treatment of TCM, such as Chinese herb decoction, acupuncture, plaster therapy, and traditional Chinese medicine exercise. By February 27, there are 471 NCP patients were cured in Vulcan Mountain Hospital with more than 97% treated with Chinese medicine decoction by means of using cipher prescription to mild and normal patients and personalized medicines to severe and critical patients. By February 28, a total of 7,246 confirmed cases had been admitted to 43 designated TCM hospital with 97.71% of TCM usage rate, and fever, fatigue, cough and any other symptoms and imaging features of patients were significantly improved.

Jiangxia mobile cabin hospital is the only one which was organized and taken over by the TCM team. On the basis of "Xuanfei Baidu Decoction" and "Qingfei Paidu Decoction," doctors treated specific cases according to different conditions. In addition to the main use of traditional Chinese medicine, medical workers carefully cared for patients supplemented by Tai Chi, Ba Duan Jin, auricular point therapy, traditional Chinese medical massage, meridian flapping, and any other unique ways of TCM. Since opening on February 14 to closing on March 10, Jiangxia mobile cabin hospital treated 564 patients,

71% for mild patients, 29% for normal patients, and 482 patients were cured and discharged from the hospital. Patients all were adopted with the combination of traditional Chinese and western medicine the whole time and all process, with 100% for treatment rate of TCM and 100% for daily inspection rate of Chinese medical specialist. When closing, none of the patients became severe, and none of nucleic acid detection turns positive of patients after leaving module hospital. However, 32 (9.7%) patients of 330 mild patients who received almost no TCM treatment became severe in another hospital.

Data of SATCM shows: by early march, 92.58% for the confirmed cases in our country were treated with TCM. A total of 11,740 patients were admitted to 16 mobile cabin hospitals in Wuhan, while distributing prescription and four kinds of Chinese patent medicine, such as "Jinhua Qinggan Capsules" at the same time with 99.93% for TCM usage rate. The Wuhan government gave out nearly 321,000 doses of prescription and 248,000 doses of Chinese patent medicine to the persons under isolation.

As of March 13, 1261 NCP patients in 10 provinces were treated with "Qingfei Paidu decoction", 1102 cases were cured, 29 cases' symptoms disappeared, and 71 cases' symptoms improved. Among them, after 40 severe patients treated with it, 28 cases have been discharged from hospital, 12 cases were treated in hospital, 10 cases' symptoms improved, from severe to mild as well. The results showed that the total effective rate of "Qingfei Paidu Decoction" was 93.12%. The cumulative utilization rate of traditional Chinese medicine reached 91.91% in Hubei province, the utilization rate in mobile cabin hospital exceeded 99% and reached 94% in central isolation points. A total of 18,750 people been under rehabilitation observation in 284 central isolation points in Wuhan, and a total number of inspection of traditional Chinese medicine has reached 79,114 man-time. Additionally, there were 508 Chinese medicine patent applications related to antiviral with 62.9% for composition. It indicates that the invention of composition is the focus of research and development and protection in the field of TCM.

TCM Treats NCP from Chinese Battlefield to World Battlefield

With the rapid development of outbreak overseas, a team of five Chinese medical experts arrived in Iran on February 29 to help fight the outbreak of NCP which is spreading around the world. At the same time, quantity demanded for Chinese medicine increase quickly in New York, and people began to boil Chinese decoction in Hungary. On March 9, the transoceanic "anti-epidemic" online diagnosis platform was officially launched, providing online medical consulting services of traditional Chinese and Western medicine for free. Thirty thousand Chinese medicine granules for prevention, 20,000 anti-epidemic sachets, and 480 boxes of Ganoderma spore powder will be sent to Italy to help overseas Chinese and local patients to fight the epidemic.

With the premises regarding TCM, primary physicians pay more attention to treat the patient on the basis of syndrome differentiation individually and also use early treatments to avoid the turn of mild to severe disease in accordance to the TCM theory. Meanwhile, the public accept the significance that prevention before illness is better than treatment after getting diseased. Even more encouraging, there have being many patients cured and

discharged from the hospital through the integrated treatment of TCM and Western medicine. Currently, it estimates that approximately 60,000 patients have been treated with TCM accounting for 85%. TCM showed the unique advantages of a full course of treatment and a full range of treatments. It not only focuses on diseases but also mobilizes the body's capacity to resist diseases. Furthermore, it has unique efficacies in many aspects, such as improving clinical symptoms, reducing complications, and improving quality of life.

Interventions and Approaches to Anti-CoVs by TCM

So far no specific anti-coronavirus therapy has been approved for the treatment of COVID-19. As the efficacy and safety of TCM widely acknowledged in recent years, it has been brought to an important status by the public, governments, and even to World Health Organization (WHO). Therefore, numerous CHM studies have been done or are moving forward ranging from microcosmic to macroscopic, and from basic research to clinical application.

Generally speaking, electron micrographs of negative-stained COVID-19 particles were spherical with pleomorphism, the same morphology is observed as Coronaviridae family, and the diameter was measured at approximately 60–140 nm. Virus particles possesed pretty different spikes, mean while providing the appearance of solar corona for virions. Besides, extra cellular free virus particles and inclusion bodies were suffused with virus particles in membrane bound vesicles in cytoplasm, which had been found in the human airway epithelial ultrathin sections (Zhu *et al.*, 2020). Furthermore, to characterize the virus, the novel coronavirus (CoV) was identified to have about 89% nucleotide sequence similarity to two previously published bat-derived SARS-like CoV (bat-SL-CoVZC45, MG772933.1 and bat-SL-CoVZXC21, MG772934.1) genome (Lu *et al.*, 2020; Ren *et al.*, 2020). Given those similarities in gene sequence and possible host, the therapeutic strategies of SARS are expected to provide some experience for COVID-19, especially in Traditional Chinese Medicine (TCM).

The primary clinical manifestations of SARS are characterized by influenza-like symptoms. Except for fever, cough and breathing difficulties, SARS may be associated with other symptoms such as headache, muscular stiffness and pain, night sweats, loss of appetite, malaise, dizziness, rash, chills, confusion, nausea, and diarrhea. Although COVID-19 is similar to SARS-CoVin nucleotide sequence, the COVID-19 infection appears clinically milder than SARS overall in terms of severity, case fatality rate, and transmissibility, which increases the risk of cases remaining undetected. As of February 13, 2020, about 74280 cases have been confirmed in China and 924 in other countries, and a total of 2009 deaths from COVID-19 accounts for less than 3%. Common symptoms mainly include fever (>90%), dry cough (80%), shortness of respiratory distress (15%) and breath (20%). However, a small number of patients are likely to initially present with gastrointestinal symptoms (such as nausea or diarrhea) a few days previous to fever, which indicates fever is dominant but not the premier symptom of COVID-19. Although the symptoms of infection are less severe and advanced than SARS, COVID-19 is highly

contagious with R0 value of 3.77, which is slightly and obviously stronger than that of 2–5 for SARS and less than 1 for MERS, respectively (Bauch and Oraby, 2013; Kim *et al.*, 2020). Additionally, on the basis of current data, it seems that COVID-19 spread through human-to-human transmission, most common by contact, droplet, and aerosols routes (Zu *et al.*, 2020). Beyond that, according to the latest research, live virus is known to be existing in human feces, which indicates there has probably been fecal–oral transmission. What makes it terrible is that it might still be contagious, even if nucleic acid examination turned negative.

At present, there is no certain evidence from clinical trials to support specific drug treatment against the new CoV in suspected or confirmed cases. For SARS or COVID-19, the therapies involve various disciplines, and optimal recommendations are mainly based on the methods of Western medicine, including drug treatments (such as antiviral, antibiotic, corticosteroid therapy), oxygen therapy, symptomatic treatment, ECMO, nutrition support treatment, and so on (Chen *et al.*, 2020). However, the effectiveness for SARS and COVID-19 was limited especially in the first and recovery stages, and the adverse effects of Western medicines was inevitable during and after the treatment period. Many Chinese physicians thought that TCM could play a crucial role in all phases of the disease, even in prevention (Luo *et al.*, 2020), which takes effects in controlling disease progression, reducing hormone dosage, reducing fever symptoms, and reducing complications. Encouragingly, the WHO thought TCM has significant contribution to the whole value research field of global medical system and witnessed TCM plays a significant role during the period of SARS on 2003. This reflected a remarkable recognization, in which the organization acknowledged TCM in its clinical efficacy and safety of SARS in many ways, including symptom improvement, dosage reduction of glucocorticoid, and antiviral agents with less side effects, risk reduction of low oxygen saturation for its stabilization, recovery of periphery T lymphocyte and immunoglobulin, degradation of ALT, AST and BUN and preservation of normal liver function, absorption of pulmonary inflammation and alleviation of leukocyte-independent inflammatory reaction (Fig. 1).

Clinical Discovery of Anti-CoV Therapeutics by TCM

Clinical discovery of CHM with potential anti-CoVs activity is important for treatment. The CHM therapies, including ingredients from Chinese herbs, single monomeric compounds, Chinese herb extracts, and Chinese herbs formula have been proven to have anti-CoVs effect *in vivo* and *in vitro*.

Although the evidence from a meta-analysis published in Cochrane Database (Liu *et al.*, 2012) demonstrated that CHM in combination with Western medicine has no obvious benefit on mortality when compared with simple Western medicine, significant effects in symptom improvement, duration of symptoms and days to loss of fever, were observed. But contrary to the conclusion from meta-analysis, some reports confirmed that TCM is an effective therapeutic method to reduce the mortality and increase the survival time. What is contributing to the similar mortality is complex: firstly, most of the studies only had a short duration of less than one month, in such cases, TCM played an important role, but the effect was still limited by a short period of time; secondly, the results of mortality maybe

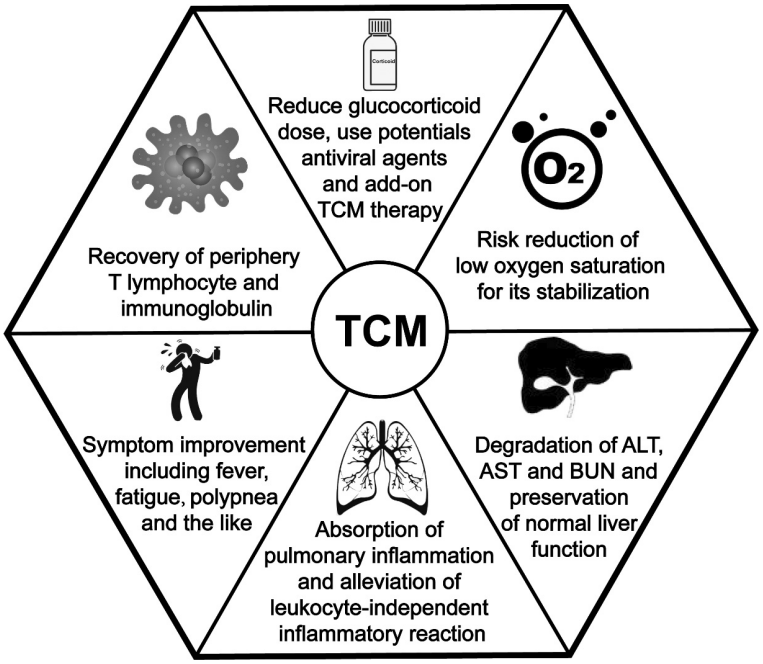

Figure 1. The potential benefits of TCM to human corona viruses infection.

interfered due to the limited sample size and different baseline characteristic of enrolled patients with SARS; thirdly, it is entirely possible to make a difference directly to TCM curative effect with a later or unstandardized intervention. In addition, when compared to Western medicines alone, CHM combined with Western medicines were more effective in shorting the ventilator used time from (14.21 ± 4.04) d to (5.17 ± 2.90) d (Ren *et al.*, 2004), and improving the absorption of pulmonary infiltration, including duration from (23.88 ± 14.79) d to (18.88 ± 9.20) d (Li *et al.*, 2004), and increasing oxygen saturation from 10.6 d to 8.5 d (Li *et al.*, 2003), although this comparison was not powered by statistical analysis. With regard to corticosteroid treatment, under the help of CHM, combination therapy not only could shorten the duration of corticosteroid treatment from (35.79 ± 14.48) d to (27.50 ± 10.28) d (Li *et al.*, 2004), but also reduce the total dosage of corticosteroid at the end of treatment from (1257.14 ± 247.90) mg to (699.29 ± 111.66) mg (Li *et al.*, 2003). What is more, original data from clinical trials suggested that integrated Chinese and Western medicines improved the quality of life in respect of the score of total from (28.32 ± 11.79) to (19.93 ± 3.69) in synergetic group, when compared to that from (28.00 ± 11.47) to (22.10 ± 4.90) in the control group, and psychological emotional factors from (11.97 ± 5.39) to (7.95 ± 2.10) in the synergetic group, when compared to that from (11.74 ± 4.96) to (9.35 ± 2.52) in the control group for the patients with SARS (Bian *et al.*, 2003), and shortened the number of days spent in hospital from (45.58 ± 14.09) d to (36.92 ± 9.17) d (Li *et al.*, 2004), but weak evidence suggested that CHM is more beneficial in cutting down the course of illness. Furthermore, it has

been shown that the improvement in the synergistic group (CHM plus Western medicine) was superior to that in the Western medicines group in respect of the incidence of complications.

Preclinical Rationale for Anti-CoVs Activity by TCM

Based on the clinical evidence, CHM for patients with SARS has proven to be potentially effective to improve the anti-CoVs effect and give clinical support to explore more therapeutic strategies to enhance the efficacy of SARS. Herein, we take the following several agents as an example to explain their impact on CoVs (Table 1).

Table 1. Intervention Effect of Chinese Herbal Medicine Therapies for CoV Infections

No.	Chinese Herbal Medicine (or Its Extract)	Type of CoV	IC_{50}	Target
1	Kang-Li potion	IBV	—	Unclear
2	Herba Houttuyniae	MHV-3	22.06 μg/mL	Unclear
3	Shuang-Huang-Lian	MHV-3	304.9 μg/mL	Unclear
4	Allitridin	MHV-3	2.7 μg/mL	Unclear
5	Saikosaponins	HCoV-229E	1.7 μmol/L	Unclear
6	Caffeic acid	HCoV-NL63	3.54 μM	ACE2
7	Fangchinoline	HCoV-OC43	1.01 μM	N and S protein
8	Tetrandrine	HCoV-OC43	0.33 μM	N and S protein
9	Cepharanthine	HCoV-OC43	0.83 μM	N and S protein
10	Resveratrol	MERS-CoV	—	N protein
11	Rheum palmatum	SARS-CoV	13.76 μg/mL	3CLpro
12	Tanshinones	SARS-CoV	14.4–226.7 μM	3CLpro
13	Tanshinones	SARS-CoV	0.8–30 μM	PLpro
14	Tanshinones	SARS-CoV	—	S protein
15	Isatisindigotica root	SARS-CoV	217–1210 μM	3CLpro
16	Houttuynia cordata	SARS-CoV	—	3CLpro and RdRp
17	[1]Rhizoma Cibotii	SARS-CoV	8.42μg/mL	3CLpro
18	[2]Rhizoma Cibotii	SARS-CoV	>10μg/mL	3CLpro
19	Torreya nucifera	SARS-CoV	8.3–280.8 μM	3CLpro
20	Emodin	SARS-CoV	—	Accessory 3a protein
21	Emodin	SARS-CoV	200 μM	S protein and ACE2
22	Lycoris radiata	SARS-CoV	2.4 μg/mL	Unclear
23	Artemisia annua	SARS-CoV	34.5 μg/mL	Unclear
24	Pyrrosia lingua	SARS-CoV	43.2 μg/mL	Unclear
25	Lindera aggregata	SARS-CoV	88.2 μg/mL	Unclear
26	TSL-1	SARS-CoV	30–70 μg/mL	Unclear
27	Aescin	SARS-CoV	6.0 μM	Unclear
28	Reserpine	SARS-CoV	3.4 μM	Unclear
29	Di-Kang	SARS-CoV	0.056 mg/mL	Unclear
30	Lian-Hua-Qing-Wen	SARS-CoV	0.11 mg/mL	Unclear
31	Fu-Fang-Lian-Pu	SARS-CoV	0.49 mg/mL	Unclear
32	Glycyrrhizin	SARS-CoV	0.3–2.4 mg/mL	Unclear

Note: IC_{50}, concentration producing a 50% reducing in activity.

Anti-CoV Treatment Options in Virion Assembly and Release

Viral envelope (E), membrane (M), nucleocapsid (N), and some accessory proteins play a crucial role in virion assembly. Therefore, agents that target its specific binding sites or functions have broad-spectrum activity against CoVsor other viruses.

Encouragingly, an increasing number of CHMs that target specific binding sites or functions of these proteins are being discovered. Take for instance, the accessory open-reading-frame 3a protein of SARS-CoV had been verified previously to form a cation-selective channel that might express in the infected cell and be involved in virus release. Hence, agents against the channel formed by the accessory protein 3a were expected to suppress virus release. Such as Emodin, a anthraquinone compound derived from rheum palmatum, is an inhibitor of the SNE-encoded accessory 3a protein as an ion channel (Schwarz *et al.*, 2011). Moreover, previous studies also have demonstrated that Emodin not only disrupted the viral envelope during the period of virus release, but also resulted in RNA reduction, which indicated Emodin-dependent inhibition of virus release (Ho *et al.*, 2007).

However, these agents are likely to be narrow-spectrum as the binding sites and functions of these proteins are unique to individual CoVs. Therefore, agents that aim to exhibit broad-spectrum activities against numerous enveloped viruses might be active against CoVs.

Anti-CoV Treatment Options in Viral Entry and Replication

CoVs are one of the most diverse and rapidly mutating types of viruses and always emerge repeatedly at unpredictable times. Therefore, anti-CoV agents that specifically target the replication apparatus should be investigated. It has been shown that natural plants contain antiviral activities to CoVs and the mechanism of action of these herbal products is mainly via inhibition of viral replication. A previous study selected over 200 extracts of CHM that have been historically used for the treatment of virus-induced infectious diseases. Four of those extracts, Lycorisradiata, Artemisia annua, Pyrrosia lingua, and Linderaaggregata exhibited significant inhibition effects on SARS-CoV, and subsequent study had determined that lycorine, the main extract of *L. radiata* was chosen for the identification of the active component in it (Li *et al.*, 2005). Another research demonstrated that Kang-Li potion, with the main functions of removing heat and damp, strengthening the stomach and removing the phlegm, could inhibit the viral replication, improve the general clinical symptoms and respiratory symptoms, lower the high body temperature, and also decrease the mortality rate in the infectious bronchitis virus (IBV) infected model. Further study verified that Kang-Li potion repaired the pathological damage in the bronchus and lung tissue of the IBV model and increased the serum titer of the antibody against IBV which would eventually speed up the chick's recovery from IBV infection (Yi, 2006). In addition, TSL-1, Aescin, and Reserpine, the main active compounds from some natural products, have also confirmed their anti-SARS or anti-MERS activities *in vitro* by slowing down the viral replication process (Wu *et al.*, 2004; Chen *et al.*, 2008). CHMs targeting the

replication of virus have been comfirmed for the treatment of CoVs infections and further optimization of the delivery of the specific mechanism may strengthen their clinical use.

The viral replication cycle can be blocked by the administration of specific agents against the host receptor, which could inhibit the replication of CoVs *in vitro* and in animal models. The functional host receptors, determining the pathogenicity, tissue tropism, and host range of the virus, mainly utilized by human pathogenic CoVs include ACE2, DPP4 and so on. Thus, qualifying as potential anti-CoV drug candidates are some of the ACE2 or DPP4 binding inhibitors. For example, Sambucus FormosanaNakai, a species of elderberry, is a Chinese herb with anti-inflammatory and anti viral activity. Specifically, its stem ethanol extract displayed the strong antiviral potential against HCoV-NL63, which was associated with sub-G1 fraction, cytopathicity, plaque formation, virus yield, and attachment (Weng *et al.*, 2019). What is more, cell experiment also found caffeic acid could be the vital component with anti-HCoV-NL63 activity by inhibiting the virus replication and blocking virus attachment, as suggested to influence the catalytic activity of HCoVNL63 to the co-receptors (heparan sulfate proteoglycans) and its receptor (ACE2). In addition to caffeic acid, Emodin also could abolish SARS-CoV infection by competing the binding site of spike (S) protein with ACE2 (Ho *et al.*, 2007), indicating that the ACE2 binding site could be a target for drug development. However, none of receptor-directed agents have been found for the treatment of CoVs infections, their anti-CoVs ability areal most narrow-spectrum for different CoV interact with different host cell receptors.

Another type of anti-CoV agents involved in the viral replication is facilitated by the inhibition of viral entry. For example, in mouse models with fulminant hepatitis caused by a kind of murine coronavirus (Murine hepatitis virus strain 3, MHV-3), Herba Houttuyniae and Shuang-Huang-Lian, Allitridin injections showed inhibitory activities against MHV-3 through decreasing the viral load within liver tissues, among which Shuang-Huang-Lian was the strongest, and recently it even has been reported to possess anti-COVID-19 activity. In cell models, all three injections also succeed to inhibit the replication of MHV-3, which might be involved in the process of viral absorption to and penetration cells (Yi, 2006). Similarly, Saikosaponins, isolated from medicinal plants suc Bupleurum spp, have been reported to possess anti-CoVs activity and also showed an inhibitory effect on attachment and penetration of viral replication (Cheng *et al.*, 2006). Additionally, Di-Kang injection, Lian-Hua-Qing-Wen capsule, and Fu-Fang-Lian-Pu pellet were all proven to have inhibitory effects on the SARS-CoV cultured in Vero-E6 cells, among which have multiple single herbs with antivirus activity, including radix isatidis, fructus forsythia, liquorice, honeysuckle, and so on, with most studies focusing on liquorice (Zhu *et al.*, 2003). Of all the compounds extracted from liquorice, the most active in inhibiting replication of SARS-associated virus was glycyrrhizin, which also plays an important role in inhibiting adsorption and penetration of the virus in the early steps of the replicative cycle. (Cinatl *et al.*, 2003). What is more, recent research have yet found that Tanshinones derived from *S. miltiorrhiza*, as well as Fangchinoline (FAN), Tetrandrine (TET), Cepharanthine (CEP) from *Stephania tetrandra* or other related species of Menispermaceae showed specific ability against S protein of HCoVs, which is involved in blockingviral entryat the early stage of viral infection (Kim *et al.*, 2018, 2019).

Beyond that, viral E, M, N and accessory proteins are not only essential for virion assembly, but also have functions to inhibit the host immune response to facilitate viral replication. Example of resveratrol, with the function of inhibiting existing MERS-CoV infection and prolonging cellular survival, was identified to decrease the expression of N protein. Subsequently, the study showed that resveratrol alleviated the monolayer destruction infected by MERS-CoV with less cytotoxicity through reducing the RNA expression and viral yield, simultaneously suppressing the apoptosis induced by MERS-CoV by inhibiting Caspase 3 cleavage (Lin *et al.*, 2017). Moreover, except for S protein, FAN, TET, and CEP also suppressed the replication of HCoV-OC43 against N protein (Kim *et al.*, 2019).

Furthermore, all of the major enzymes and proteins of CoVs that are involved in viral replication are potential drug targets. 3C-like protease (3CLpro) and papain-like protease (PLpro) are major CoV proteases that cleave the large replicase polyproteins 1a (pp1a) and pp1ab to produce non-structural proteins (NSPs) such as RNA-dependent RNA polymerase (RdRp) and helicase during the transcription and replication of the virus, and its inhibitors show broad-spectrum activities against CoVs for substrate recognition. The plant-derived phenolic compounds from rheum palmatum have a high level of antivirus activity against SARS-CoV3CLpro, which is a key enzyme in the process of viral replication (Luo *et al.*, 2009). Except for rheum palmatum, Tanshinones (Park *et al.*, 2012), Isatis indigotica root (Lin *et al.*, 2005), Houttuyniacordata (Lau *et al.*, 2008), RhizomaCibotii (Wen *et al.*, 2011), and Torreya nucifera (Ryu *et al.*, 2010) showed the most potent 3CLpro inhibitory effect against SARS in blocking the cleavage processing. Besides, Houttuynia cordata also exhibited significant inhibitory effects on RdRp, and Tanshinones on PLpro.

Numerous CHMs have been found to inhibit the replication and entry of CoVs in cell culture or animal models, but their activity *in vitro* and even in animal experiments does not necessarily translate into efficacy in humans. Therefore, some of these anti-CoVs drugs should be evaluated in clinical trials in the first place to make it available in clinical practice as soon as possible.

Discussion and Prospective

Nowadays, similar to SARS and MERS, COVID-19 is causing a major challenge to clinical management and a worldwide threat to public health. This brief review has demonstrated that substantial efforts on TCM have been completed or are in progress to explore effective CHM for COVID-19 infections. At present, at the direction of the Central Government, many hospitals, companies, organizations, and all parts of society have participated in the development of intervention and approach to anti-CoVs. Over the past weeks, related departments and administrations constantly emphasized the importance of TCM in the management of COVID-19 infection, as well as brought forward some TCM-related regulations and policies for NCP in response. Meanwhile, a great many hospitals in all localities have widely applied the TCM therapies and Western medicine in combination to improve clinical symptoms and reduce morality of COVID-19 patients. Furthermore, researchers in China have begun testing multiple CHMs for prevention and treatment of

COVID-19 infection in clinical trials, and there is already some evidence to suggest they have the potential to fight CoVs.

Although primary efforts have been made to cover the whole period of COVID-19 patients with TCM therapies, due to the restrictions in a scientific approach to testing CHM, there are still several deficiencies existing in clinical trials, and there is an urgent need for further improvement and perfection. Consequently, to evaluate the clinical efficacy and safety of TCM therapies with high accuracy and rationality, more randomized open, parallel controlled and multi-center clinical trials with rigorous design and large sample conducting with protocol registration, ethical approval, and implementation should be executed as soon as possible to produce reliable evidence for TCM intervention of COVID-19 or similar merging CoVs infectious diseases in the future.

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