Application of Traditional Chinese Medicine in Prevention and Treatment of COVID-19

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Abstract

Corona Virus Disease 2019 (COVID-19) caused by SARS-CoV-2 has become a global pandemic. COVID-19 can result in acute respiratory distress syndrome and multiple organ failure due to its strong infectivity and extensive spread, so it is urgent to prevent and control the epidemic. Traditional Chinese medicine (TCM) has played a pivotal role in the early prophylaxis, clinical treatment and recovery of COVID-19. At present, the epidemic situation of COVID-19 in China has been controlled in stages, and most of the confirmed cases have obtained favourable results due to the interventional diagnosis and therapy of TCM. Given different individual conditions, different TCM treatment strategies have been provided, such as moistening dryness and removing fluid, dispelling heat and detoxification, aroma penetrating filth and releasing lung and reducing turbidity. To provide some references to the treatment of COVID-19 and related diseases and to lay a certain foundation for subsequent new drug research, this paper summarizes the application and the potential mechanism of TCM in the prevention and treatment of COVID-19.

Keywords: Active mechanism; COVID-19; Traditional Chinese Medicine (TCM); SRAS-CoV-2; Syndrome differentiation and treatment

Introduction

Corona virus disease 2019 (COVID-19) is a highly contagious acute respiratory disease. It has been considered as an international public health emergency by the World Health Organization due to its strong infectivity and extensive spread. As of May 27, 2021, a total of 168.04 million patients were diagnosed and 349.475 80 thousand patients died all around the world [1], which caused a major threat to the life safety of the people and seriously impacted the development of society.

Currently, no specific drugs for the treatment of COVID-19 have been recorded except that isolation treatment and symptomatic supportive treatment are the main ones. Being a great treasure in China and a significant part in world medicine, TCM has great advantages and value in the sanitation and remedy of COVID-19, playing a pivotal role in preventing and blocking the spread of the virus in the early stage, enhancing patient symptoms during clinical treatment, reducing sequelae and accelerating patient recovery. With intent to provide a reference to the control of COVID-19 and subsequent researches, this paper clarifies the etiology and pathogenesis of COVID-19, and summarizes the application and the potential mechanism of TCM in the prophylaxis and treatment of COVID-19, laying a certain foundation for subsequent research.

Syndrome Differentiation and Treatment for COVID-19

COVID-19 is an emerging infectious disease with the characteristics of infectivity, epidemics, common clinical manifestations and phased pathological changes. COVID-19 belongs to the category of epidemic diseases in TCM, and its etiology and pathogenesis is to feel the Xie-qi (pathogenic factors) dominated by “dampness”, mainly including cold epidemic, cold and wet epidemic, damp poison epidemic and damp heat epidemic [2]. Clinical manifestations of COVID-19 involve fever, dry cough, fatigue, dyspnea, accompanied by nasal congestion, runny nose, sore throat, myalgia and diarrhea [3,4].

The “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 8)” was issued by the National Health Commission of the People’s Republic of China [5], which divided COVID-19 into a medical observation period and a clinical treatment period (mild, moderate, severe and critical cases). According to the etiology and pathogenesis of each stage of COVID-19, the “Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 8)” recommends different treatment methods, and chooses the appropriate TCM prescriptions (Figure 1).

Application of TCM in Prevention and Treatment of COVID-19

Early prevention of COVID-19

TCM focuses on both internal and exterior factors in preventing diseases. On the one hand, TCM can enhance the body’s resistance to diseases. On the other hand, it can prevent external evils from...
invading the body. Therefore, the early prevention of COVID-19 can be carried out in *vivo* and *in vitro*

**Clinical treatment of COVID-19**

TCM has the characteristics of multi-target, multi-function and multi-pathway in the process of prevention and treatment of COVID-19 [14]. Regarding the different types and stages of COVID-19, personal physical condition of the patient, the doctor use Chinese medicine compounds as appropriate. TCM is more effective than Western medicine alone for the management of COVID-19 due to its enabling patients to receive maximum treatment efficacy with minimum side effects. For example, Wei et al., used Qingfei Paidu Decoction combined with Auricular-Point-Pressing Therapy and acupoint application treatment COVID-19 mild patient, showed that Qingfei Paidu Decoction reduced both the duration of diarrhea and the hospital stay duration [15]. In addition, Sun et al. reported that Qingfei Paidu Decoction can alleviate clinical symptoms, decrease the duration of fever and shorten the length of hospital stay, the effect is better than western medicine treatment [16]. Wang et al. discussed the clinical efficacy of Gegen Qinlian Pills in the treatment of COVID-19 and found that Gegen Qinlian Pills can improve patients’ symptoms such as fever, cough, fatigue, cough, chest tightness, and nausea [17]. The survey on Qingfeiyan’s treatment of COVID-19 combined with hypertension showed that Qingfeiyan is effective in lowering blood pressure while healing COVID-19, implicating TCM produce their efficacy through the synergistic effects of multi-ingredients, multi-targets, and multi-pathways [18].

Integrated traditional Chinese and Western medicine therapy have been the most effective method in the treatment of COVID-19 in China. Chinese doctors and scientists have conducted many clinical studies on the treatment of COVID-19 with the integration of TCM and western medicine. They studied that quantity TCM prescriptions have excellent efficacy in the treatment of COVID-19 patients, alleviate oxidative stress, but also can regulate the number of immune cell and lower the levels of inflammatory cytokines (Table 1).

<table>
<thead>
<tr>
<th>TCM prescriptions</th>
<th>Clinical stages</th>
<th>Test indicators</th>
<th>Cure rate(%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fu Zheng Xuan Fei Huashi Recipe</td>
<td>Mild and moderate cases</td>
<td>WBC, LYM, LYMPH, GRAN, PLT, Chest CT</td>
<td>96.40</td>
<td>[19]</td>
</tr>
<tr>
<td>Burzhong Yi Qi Decoction</td>
<td>Mild and moderate cases</td>
<td>hs-CRP, ESR, IL-6, PCT</td>
<td>88.89</td>
<td>[20]</td>
</tr>
<tr>
<td>Qing Fei Paidu Decoction</td>
<td>Critical cases</td>
<td>WBC, LYM, CRP, IL-2R, IL-6, IL-8, IL-10, TNF-α</td>
<td>91.67</td>
<td>[21]</td>
</tr>
<tr>
<td>Lianghua Qingwen Capsules</td>
<td>Mild and moderate cases</td>
<td>IL-10, PCT, hs-CRP</td>
<td>96.43</td>
<td>[22]</td>
</tr>
</tbody>
</table>

Table 1: Clinical application of TCM prescriptions intervention on COVID-19.

<table>
<thead>
<tr>
<th>TCM Recipe</th>
<th>Mild and Moderate Cases</th>
<th>WBC, LYM, Hb, NEU, PCT, hs-CRP, CRP, ALT, AST, BUN, CR, LDH</th>
<th>Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huashi Jedu Recipe</td>
<td>Mild and Moderate cases</td>
<td>WBC, LYM, NEU, PCT, hs-CRP, CRP, ALT, AST, BUN, CR, LDH</td>
<td>86.37 [23]</td>
</tr>
<tr>
<td>Qingfei Paidu Decoction</td>
<td>Mild and Moderate cases</td>
<td>WBC, LYM, hs-CRP, CRP, ALT, AST, BUN, CR</td>
<td>95.70 [24]</td>
</tr>
<tr>
<td>Shengmai San</td>
<td>Mild and Moderate cases</td>
<td>CRP, ESR, SpO2, Chest CT, nucleic acid</td>
<td>70.58 [25]</td>
</tr>
<tr>
<td>Yepingfeng San</td>
<td>Mild and Moderate cases</td>
<td>LYM, hs-CRP, ESR</td>
<td>93.33 [26]</td>
</tr>
<tr>
<td>Qingfei Paidu Decoction</td>
<td>Mild and Moderate cases</td>
<td>WBC, LYM, CRP, ALT, BUN, CR</td>
<td>97.22 [27]</td>
</tr>
<tr>
<td>Huashi Baidu Recipe</td>
<td>Severe cases</td>
<td>WBC, LYM, CRP, ESR</td>
<td>76.00 [28]</td>
</tr>
<tr>
<td>Finjinhua Oral Liquid</td>
<td>Mild and Moderate cases</td>
<td>ALT, AST, CR, BUN, FBG, UA</td>
<td>78.90 [29]</td>
</tr>
<tr>
<td>Xuanfei Huzaahuo Recipe</td>
<td>Mild, moderate and severe cases</td>
<td>WBC, LYM, hs-CRP, ESR, TBIL, ALT, AST, BUN, CR, LDH</td>
<td>100 [30]</td>
</tr>
</tbody>
</table>

Abbreviations: WBC = White Blood Cell Count; LYM = Lymphocyte count; LYMHPH = percentage of Lymphocytes; GRAN = neutrophil count; PLT = Platelet Count; hs-CRP = High-sensitivity C-reactive protein; ESR =erythrocyte sedimentation rate; IL-6 = Interleukin-6; SpO2 = peripheral oxygen saturation; PTC = Procalcitonin; AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; BUN = Urea nitrogen; CR = Creatinine; FBG = Fasting Blood Glucose; UA = Uric Acid; TBIL = Total Bilirubin; LDH = Lactate Dehydrogenase.

The analysis and evaluation of therapeutic efficacy on TCM for COVID-19 have been conducted by Chinese scholars, expressing that TCM has excellent advantages in curing COVID-19. For instance, Zhang et al. analyzed and inquired about the influence of early intervention of TCM on the disease outcome of severe patients with COVID-19. He found that TCM can significantly improve clinical symptoms and signs of COVID-19 patients, and have a better effect on the recovery of patients after illness [38]. He et al., stated that Shengmai San can ameliorate clinical symptoms such as dry throat, thirst and night sweats in convalescent patients, reduce inflammatory indicators, improve oxygenation, promote absorption of lung lesions and turn negative nucleic acid [25]. Besides, the investigation of the clinical efficacy of Yiqi Yangyuin Granules combined with recovery-promoting exercises shows that this method can significantly improve adverse symptoms, and better strengthen the lung function and immune function [39].

Potential mechanisms of TCM to combat COVID-19

The potential mechanisms of COVID-19 pathogenesis include direct virus invasion of lung tissue, systemic inflammation and cytokine storm, apoptotic response, immune crosstalk disorders and abnormal blood coagulation, the decline of immune function and abnormal cellular metabolism [40-46]. Focusing on the potential mechanisms of COVID-19, TCM treatment can help to cure the COVID-19 by reducing the expression level of inflammatory factors and apoptosis, inhibiting the cytokine storm, minimizing the damage of free radicals, and enhancing the immune function of the body [47].

Antiviral

COVID-19 is a new emerging pulmonary infection caused by SARS-CoV-2, so anti-viral infection is crucial for combating the COVID-19 pandemic. Lianhua Qingwen Capsules significantly protects against virus attacks by inhibiting SARS-CoV-2 replication, affects virus morphology and exerts anti-inflammatory activity in vitro [48]. Meanwhile, Tan et al., stated that Lianhua Qingwen Capsules exhibited an inhibitory effect on cytopathic changes caused by virus infection, appreciably reduced the number of vesicle virus particles, and had a strong inhibitory effect on SARS-CoV-2 [49]. Wang et al., confirmed that Qingfei Paidu Decoction can up-regulate intracellular γ-interferon (INF-γ) mRNA expression, and simultaneously induce the expression of Interferon-stimulated genes (ISGs), Oligoadenylate Synthase-1 (OAS1), PKR and IFITM3, which affects the combination of the S protein on the surface of the coronavirus and the cell surface receptor to restrain the invasion of SARS-CoV-2 [50].

Anti-inflammatory and suppressive cytokine storm

Secretion of pro-inflammatory cytokines in the lungs following SARS-CoV-2 infection represents a crucial step in promoting the inflammatory response in various lung diseases [51]. Therefore, inhibiting inflammatory cytokine storm is the key to curing COVID-19. Studies suggest that Xuebijing Injection can decrease pro-inflammatory factors such as TNF-α, IL-1, IL-6, IL-8, IL-17, and inhibit the expression of High Mobility Group Protein B1 (HMGB1). And it

neurological, genitourinary and other extra pulmonary systems [36]. In clinical cure cases, there is a considerable number of patients with varying degrees of sequelae and significantly decreased quality of life. The primary convalescence pathogenesis of COVID-19 is remained toxicity and lingering pathogen due to deficient vital qi, and it would lead to Qi and Yin deficiency and spleen and lung qi deficiency [37]. Therefore, it is essential to pay attention to dispel the evil qi caused by exogenous incubating pathogens, at the same time to strengthen spleen and tonify lung, nourish Qi and Yin, and restoring the balance of Yin and Yang. TCM has exclusive advantages in reducing the convalescent sequelae of COVID-19 and promoting patient rehabilitation. For example, Wang et al found that Qingfei Paidu Decoction combined with Western medicine treatment can significantly improve the clinical symptoms and signs of COVID-19 patients, and have a better effect on the recovery of patients after illness [38]. He et al., stated that Shengmai San can ameliorate clinical symptoms such as dry throat, thirst and night sweats in convalescent patients, reduce inflammatory indicators, improve oxygenation, promote absorption of lung lesions and turn negative nucleic acid [25]. Besides, the investigation of the clinical efficacy of Yiqi Yangyuin Granules combined with recovery-promoting exercises shows that this method can significantly improve adverse symptoms, and better strengthen the lung function and immune function [39].
showed excellent anti-inflammatory effect via inhibiting the Toll-like receptor 4 (TLR4) and nuclear factor-kB (NF-κB) signalling pathways [52]. At the same time, it can regulate the Th17/Treg balance in rat model of sepsis, trim down serum levels of TNF-α and IL-6, alleviate cytokine storm, and improve survival rate [53]. Besides, Jinhuo Qinggan Granules can significantly reduce IFN-γ and C- reactive protein (CRP) levels in the serum of influenza patients, and enhance the immune function of the body [54]. Lianhua Qinqing Capsule can decrease the levels of IL-10, IL-17, TNF-α and other inflammatory factors of patients with pneumonia, and slow down the impairment of lung function [55]. Preparations containing Glycyrrhiza glabra have great anti-inflammatory activity because it can reduce intracellular oxidative stress, decrease HMGB1 expression and inhibit NF-κB expression, and it is a potential drug for the treatment of COVID-19 [56].

Reduce oxidative stress and free radical damage

Multiple organ damage and failure caused by COVID-19 are associated with oxidative stress free radicals. When human body is infected with the virus, the immune system is activated, and the excessive immune response causes T lymphocytes to attack various organs, and also produces a large number of free radicals, which can affect the body’s organs. Many TCM exhibit an effect of reducing oxidative stress and have been applied to the different stages of COVID-19 treatment. For instance, the total flavonoids of licorice can down-regulate the phosphorylation of Extracellular regulated protein kinases (ERK) in the MAPK signaling pathway, decrease the accretion of free radicals via regulating the ERK/MAPK pathway, and reduce the damage to the organs [57]. Astragalisolate IV can activate the PI3K/Akt/mTOR signaling pathway, increase the activity of SOD, and reduce the accretion of free radicals [58]. Shengmai injection has an anti-oxidant effect by inhibiting the accretion of high levels of free radicals that are accompanied by excessive activation of the Ras/MAPK pathway [59].

Inhibit apoptosis

Some COVID-19 patients rapidly develop severe pneumonia symptoms and complications including Acute Respiratory Distress Syndrome (ARDS) or multiple organ failure due to damage to the pulmonary capillary endothelial cells and alveolar epithelial cells [60,61]. The study revealed that Xuebijing Injection can increase the proportion of Th1 cells in septic rats, promote the apoptosis of CD4+ CD25+ T cells, promote the apoptosis of CD4+ CD25+ T cells, inhibit the expression of Fas, Bax, PD-1 and other apoptosis-related proteins, and reduce the apoptosis of T cells and neutrophils [53]. Tongfu Qingying Decoction can down regulate the expression of Fas protein in lung tissue of model rats, inhibit the level of TNF-α inflammatory mediators, and have the effect of reducing inflammation and anti-apoptosis in rats with sepsis acute lung injury [62]. Jianpi Huatan Quyu Recipe can reduce the expression of Bax, Cyto C and Caspase3 in cardiomyocytes, increase the expression of Bel-2, and then reduce the apoptosis of cardiomyocytes in atherosclerotic Bama mini-pigs [63].

Discussion

As is known to all, TCM possesses a long history of preventing and treating diseases, and it emphasizes the overall concept, syndrome differentiation and treatment, which can treat even, prevent diseases, especially in the treatment of plague, which has unique advantages [64]. TCM can intervene in the prevention and treatment of COVID-19 in the whole process. In the early stage, some active measures such as TCM sachets, TCM fumigation, and preventive TCM compounds have produced positive effects in terms of blocking the transmission of the virus. During the clinical treatment, the doctors obtained excellent results by using the corresponding TCM compound and Chinese patent medicine according to the stage and type. When the patient is in the recovery stage, the use of appropriate TCM compound/adjuvant treatment can speed up the patient’s recovery and reduce the occurrence of sequelae. Moreover, the whole regulation, multi-target multi-ingredients and multi-links makes TCM have a better therapeutic advantage in treatment of COVID-19. TCM achieves the treatment of COVID-19 by anti-virus, reducing the expression level of inflammatory factors and apoptosis, inhibiting the cytokine storm, minimizing the damage of free radicals, and enhancing the immune function of the body.

In China, the epidemic situation of COVID-19 has been currently controlled in stages, and most of the confirmed cases have obtained favourable results due to the interventional diagnosis and therapy of TCM. As the COVID-19 has been developed into pandemics, there exist great challenges for global prevention and control of the pandemics. Therefore, we should give full play to the advantages of traditional Chinese medicine in the prevention and treatment of COVID-19, which can greatly alleviate the pressure of the epidemic on world development and contribute to the health and hygiene of mankind.

TCM has achieved great success in the prevention and treatment of COVID-19. Clinical practice has proved that many traditional Chinese medicines and compounds can significantly alleviate and improve the clinical symptoms of COVID-19 patients, but there are still some shortcomings. On the one hand, TCM combat COVID-19 are short of experimental studies on pharmacological actions and pharmacodynamic material basis, which makes it difficult for TCM preparations to form a unified standard. On the other hand, the primary cellular target(s) for TCM preparations and its mechanisms for treating COVID-19 remain to be elucidated, and therefore TCM may not be globally generalizable. Perhaps, we can predict the material basis and molecular mechanism of TCM against COVID-19 through network pharmacology and molecular docking, and then verify it by a complex set of proteomic, transcriptomic and metabolomic profiling of the chemostat phase. Meanwhile, we can further combine the clinical efficacy to conduct systematic research on the prevention and treatment of COVID-19 with Traditional Chinese medicine.

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