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## Review Article

## Multimode participation of traditional Chinese medicine in the treatment of COVID-19

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## ABSTRACT

**Background:** The outbreak of COVID-19 has swiftly spread across China and all over the world, resulting in severe contagious pneumonia. However, no specific anti-COVID-19 drugs or methods are available for the treatment of this acute and fatal disease. In recent years, as the efficacy and safety of traditional Chinese medicine (TCM) have been universally acknowledged, it has been brought to a crucial status domestically and overseas for the treatment of COVID-19.

**Methods:** We searched relevant literature, electronic databases, and official statements, diagnoses and protocols to retrieve studies and applications related to traditional Chinese medicine for COVID-19 in terms of regulations and policies, clinical evidence, preclinical rationale and big data analysis and then summarized the discovery and development of potential drugs and their targets.

**Results:** Clinicians, researchers, governments, the public, colleges, institutes and companies collected and classified associated policies, regulations and actual contributions, searched clinical trials and preclinical experimental outcomes from databases, studied potential TCM drugs with possible mechanisms, retrieved numerous big data analysis method and gathered pooled results of compounds along with their effective targets to make traditional Chinese medicine vital to cover all stages of patients in the treatment and control of COVID-19.

**Conclusion:** Traditional Chinese medicine provides new evidence to support the clinical value of TCM for COVID-19.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19), an epidemic disease, has spread across the planet since December 2019. The rapid spread of the 2019 novel coronavirus (SARS-COV-2) has resulted in an outbreak of COVID-19 in over 200 countries. Globally, as of the end of July 2021, there have been over 188 million confirmed cases of COVID-19, including over 4 million deaths, reported to the WHO.<sup>1</sup> Although the situation in China has almost reached a steady state, the number of confirmed cases outside China has boosted.

Currently, antiviral drugs, human immunoglobulins, corticosteroids and intestinal microecological regulators are characterized as principal Western medical therapies for COVID-19 in China. The

advantages of traditional Chinese medicine (TCM) over Western medicine are in the following three aspects. In terms of etiology, in the early days of the Wuhan epidemic, modern medicine could not determine what kind of virus caused it.<sup>2</sup> From the perspective of TCM, the etiology is clear, but the degree of pathogenicity is different.<sup>3</sup> Therefore, the original syndrome differentiation and treatment system can be used for treatment, and no new theory is required. In terms of treatment, modern medicine mainly aims to find direct antiviral drugs to kill and inhibit the virus. This idea requires us to find specific drugs with antiviral effects.<sup>4</sup> From the perspective of TCM, TCM treats the patient and the virus as a whole and differentiates treatment from the initial, middle, severe and recovery phases according to the progress and symptoms of the whole. In terms of medication, from the perspective of modern medicine, it takes a long time to find specific antiviral drugs, which requires *in vitro* experiments and confirmation of clinical experiments. *In vitro* experimental results alone without clinical trial confirmation cannot prove the ultimate effectiveness. Therefore, in the section on antiviral drugs in the national version of the diagnosis and treatment plan, the word 'trial' is clearly stated.<sup>5</sup> In contrast, there have been many times in the history of the development of Chinese medicine where TCM has fought and competed with epidemics.<sup>6</sup> For example, during the SARS period, Western medicine did not have a specific medicine for the SARS virus. TCM has corresponding effective prescriptions for prevention, treatment, and prognosis. It has accumulated valuable experience and resulted in many books and prescriptions. All TCMs are effective and are not trial medicines.<sup>7</sup>

With the progression of the COVID-19 epidemic, there have been a wide range of efforts made by clinicians, researchers, governments, the public, colleges, institutes and companies to make TCM vital to cover all stages of patients with COVID-19.<sup>8</sup> Therefore, we attempt to provide a timely and comprehensive review of the rapidly increasing number of publications on COVID-19, including TCM-related regulations and policies, clinical evidence, preclinical outcomes and big data analysis, which thus hold the promise to bring new strategies for the treatment and control of COVID-19.

## 2. Methods

### 2.1. National policies and regulations

Electronic databases, including PubMed, China National Knowledge Infrastructure (CNKI), CBM, Embase, WanFang, and WeiPu, and official institutions' websites, such as the National Administration of Traditional Chinese Medicine and National Health Commission of the People's Republic of China, were searched up to July 2021 by using keywords containing 'COVID-19', 'corona virus disease 2019', 'SARS-CoV-2', 'traditional Chinese medicine' and 'Chinese herbal medicine'. We screened the papers and reports we needed according to the titles or abstracts and then organized them in chronological order. We extracted three parts of information from them: policy support, diagnosis and treatment protocol and TCM practitioners' actions.

### 2.2. Clinical trials

Domestic and foreign clinical trial registration databases, such as the Chinese Clinical Trial Registry (ChiCTR) and *ClinicalTrials.gov*, were searched with the keywords mentioned above. We extracted, on the one hand, data from the clinical trials themselves, including drugs and means of intervention, sample size, institution and region. On the other hand, we fetched the outcome of a clinical trial covering the degree of completion and the rate of positive results obtained.

### 2.3. Preclinical and big data analysis

Electronic databases mentioned above were searched with the keywords consisting of 'basic research' and 'experiment' as well as the words mentioned above to look for the results of preclinical and big data analysis. In basic research, we summarized the potential mechanism of TCM against coronavirus. In big data analysis, we collated the drug targets and active components in the bioinformatics analysis.

## 3. Policies and regulations at the national level guide TCM to intervene in the prevention and treatment of COVID-19

After the outbreak of the epidemic, the central government of China attached great importance to the outbreak and quickly carried out relevant work.

### 3.1. Policy support to promote TCM

At the beginning of the epidemic, the central government issued many policies and instructions. As early as January 22, 2020, the State Administration of Traditional Chinese Medicine (SATCM) established a leading COVID-19 prevention and control group and an expert group to analyze and evaluate the progress of the epidemic, formulate TCM treatment plans, collect and treat cases, and propose scientific research needs and priority areas for TCM.<sup>9</sup> The SATCM not only held a meeting to emphasize the complementarity of traditional Chinese and Western medicine but also jointly issued several notices with the National Health Commission (NHC) repeatedly requiring TCM hospitals to continuously further improve prevention and control. Several provinces responded positively, such as Beijing, which not only integrated TCM clinical and scientific research but also implemented an emergency filing of TCM preparations to promote the transformation of clinical achievements.<sup>10</sup> Subsequently, various self-prescribed TCM preparations were approved, provincial medical insurance bureaus such as Shanxi issued plans to fully reimburse these TCM preparations, and other TCMs commonly used to treat COVID-19 were reasonably formulated to determine the self-payment proportion.<sup>11</sup>

With the aggravation of COVID-19 abroad, China provided TCM-related support and donated proprietary Chinese patent medicine and prescriptions, such as Lianhua Qingwen capsules, Jinhua Qinggan granules, Huashi Baidu formula and acupuncture needles, to more than 10 countries, such as Iraq and Italy.<sup>12</sup> In addition, China translated TCM diagnosis and treatment protocols, shared TCM experience and correlational studies through videos and international forums to over 60 countries worldwide,<sup>13</sup> and sent 37 anti-epidemic medical teams with the participation of TCM practitioners to 34 countries.<sup>14,15</sup>

As we enter the post epidemic era, an increasing number of sequelae have gradually appeared in patients who were completely cured, with more than 200 symptoms involved in various system organs, but Western medicine has been unsuccessful in controlling these symptoms effectively.<sup>16</sup> At this moment, suggestions such as integrated traditional Chinese and Western medicine methods should be actively adopted for the prevention and treatment of sequelae, and TCM mind-body treatments such as Baduanjin, Tai Chi or rehabilitation exercises of TCM should also be popularized energetically, have been brought up.<sup>17</sup> Furthermore, the NHC required all provinces to explore ways to use TCM for sequela prevention and treatment and to summarize relevant experiences.

### 3.2. TCM-related protocols guide COVID-19 diagnosis and treatment

Moreover, the central government has issued several versions of COVID-19 diagnosis and treatment plans to guide TCM practition-

ers. On January 23, 2020, the NHC and SATCM first formally incorporated TCM-related treatment into the 'Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 3).<sup>18</sup> Subsequently, from Versions 4 to 8, expert consultation, recommended prescriptions and their dosages, Chinese patent medicine and injection based on different severities, stages and syndromes were brought into effect in succession.<sup>5, 19-22</sup>

According to the protocol, there are two periods in total, covering the medical observation period and clinical treatment period, among which the clinical treatment period is divided into mild, moderate, severe, critical case and convalescence, each period having different patterns of 'cold-damp constraint in the lung pattern' or 'damp-heat accumulation in the lung pattern', 'damp-toxin constraint in the lung pattern' or 'cold-damp obstructing the lung pattern', 'epidemic toxin blocking the lung pattern' or 'blazing of both qi and yin patterns', 'internal blockage and the external desertion pattern', 'lung-spleen qi deficiency pattern' or 'deficiency of both qi and yin patterns'. More importantly, Qingfei Paidu decoction is suitable for mild, moderate and severe cases and can be used reasonably considering the actual conditions of critically ill patients. Meanwhile, Huoxiang Zhengqi capsules (pill, liquid, oral liquid), Jinhua Qinggan granules, Lianhua Qingwen capsules (granule), and Shufeng Jiedu capsules (granule) are highly recommended in line with different clinical symptoms in the medical observation period.

### 3.3. TCM practitioners involved in combating COVID-19

A TCM team and tens of thousands of TCM practitioners also actively participated in clinical treatment. After the outbreak, the SATCM immediately sent an expert group to Wuhan for early intervention with TCM. Then, more than 630 TCM hospitals in 28 provinces sent more than 4900 TCM practitioners by March 2020, accounting for approximately 13% of the total number of medical personnel assisting Hubei.<sup>23</sup> The SATCM sent five TCM medical teams successively, with a total of 773 people, including 2-3 experts assigned to 16 shelter hospitals, taking over 8 wards and Jiangxia Shelter Hospital.<sup>24</sup> The first of these national TCM medical teams consisted of 35 TCM practitioners who took charge of an independent critical care ward,<sup>25</sup> summarized systematic TCM diagnosis and treatment plans, realized randomized controlled clinical studies, and formulated and developed effective prescriptions. From the perspective of confirmed cases, until now, the number of people using TCM has reached 74000, of which over 61000 people in Hubei Province account for approximately 90%.<sup>26</sup> Moreover, 97 TCM-designated hospitals participated in the treatment to explore the integration of traditional Chinese and Western medicine and COVID-19 clinical research.<sup>27</sup>

## 4. TCM participates in the clinical trials of COVID-19 patients

From current treatment results, TCM has been suggested to be effective for COVID-19 in clinical practice.<sup>28,29</sup> According to clinical investigation, TCM treatments are accepted by approximately 80% and 90% of severe and mild patients, respectively. Even for those who are in quarantine, there were also many expectations to fight COVID-19 by TCM intervention, and its satisfaction accounts for approximately 70% of the visit results. To find more specific and effective compounds and some external treatments and to promote and publicize the efficacy of TCM, clinicians have carried out many clinical trials related to TCM.

To date, over 880 running or pending clinical trials in relation to COVID-19 have been registered to screen the effective agents for potent treatments and preventions of COVID-19 since the first clinical trial was registered by Wuhan Jinyintan Hospital on Jan 25, 2020, according to the Chinese Clinical Trial Registry (ChiCTR). In

these clinical trials on TCM and integrated Chinese and Western medicine, the two main contents are TCM treatments based on syndrome differentiation and Chinese patent medicine such as capsules, granular Chinese herbal formulas and injections, as well as some nondrug therapies, including acupuncture and massage therapy. The number of COVID-19 registered clinical trial participants ranges from 20 to 20000, among which the clinical trials with the largest proportion are those with a sample size of 100-199 people. Only approximately 3% of clinical trials involve more than 1,000 people. Clinical trials lasting 3-6 months accounted for approximately half of all trials, which is the largest proportion. Moreover, the main institution of these clinical trials is hospitals, where TCM hospitals and integrated Chinese and Western medicine hospitals account for the highest proportion, and other hospitals account for 27.4%, which indicates that TCM-related studies have also attracted attention in general hospitals. From the view of regional distribution, TCM-related clinical trials were performed on COVID-19 in Hubei, Shanghai, Guangdong, Beijing, Zhejiang, Sichuan, and others, which is likely to be correlated with the number of confirmed cases, but more remarkably, the top five are economically developed province-level regions. Since clinical trials need sufficient funds as support, the development of TCM in these regions is better.

To date, approximately 53% of the clinical trials on TCM in the treatment of COVID-19 have not yet started, 34% are in progress, and only 2% of the trials have been completed. There are many reasons that make it difficult to carry out TCM clinical trials, among which the most important reason is the syndrome differentiation and treatment of TCM. This characteristic requires TCM practitioners to treat each patient according to his or her personal situation; thus, it is difficult to unify the experimental interventions and methods. Moreover, due to the good control measures in China, the number of new infections in the late stage has decreased significantly,<sup>30</sup> which makes the sample size required for the clinical trials registered in the early stage insufficient.<sup>31</sup> In addition, there are other reasons, such as poor compliance of patients with TCM, poor implementation of clinical trials by units applying them, and low emphasis on TCM.

Now more than one thousand four hundred references on experimental studies of have been published, but only seven present positive results. Little effective data have been obtained from clinical trials for the following reasons. First, many of the registered trials are retrospective rather than prospective clinical trials,<sup>32</sup> so the conclusions lack representativeness. Then, some are single-arm experiments, and it is difficult to judge the treatment effect without contrast.<sup>33</sup> Third, the sample size of clinical trials is too small or inappropriate,<sup>34</sup> which makes the difference in outcome indicators lose statistical significance. Furthermore, some clinical trials lack random, blinding or allocation concealment designs, inconsistent baseline characteristics, unstandardized or later evaluation and intervention, and long-term follow-up. Moreover, the selection of outcome indicators is unreasonable, and ethical issues are not fully considered. Additionally, in the exploratory study, the risk of patients receiving ineffective treatment was increased, and because patients were unable to participate in other studies, the chance of receiving potentially effective treatment was reduced. Finally, the effect of TCM is not particularly significant, which enlarges the influence of the above reasons on the experimental effective data.

However, reliable conclusions could be drawn from the following studies, which can provide support for the diagnosis and treatment guidelines of COVID-19. Qingfei Paidu decoction, as a special prescription for the general treatment of cold dampness epidemic disease, has achieved significant clinical effects in COVID-19 clinical trials. In a clinical trial of 295 mild/common type COVID-19 patients in Wuhan treated with Qingfei Paidu decoction, Qingfei Paidu decoction helped relieve the mild and common symptoms

of COVID-19 patients, improving the outcome of chest CT imaging. Qingfei Paidu decoction alone has certain advantages over drug combined treatment in terms of average hospital stay, negative nucleic acid conversion time, advancements in sputum symptoms, and improvement in chest CT outcome.<sup>35</sup> Lianhua Qingwen, a CHM compound preparation based on the prevention and treatment theory of TCM on 'plagues', shows prominent efficacy in clinical trials. A paper on the clinical trial of Lianhua Qingwen for COVID-19 has been published.<sup>36</sup> Conducted in February 2020 in 23 hospitals in China, 284 patients in this trial were enrolled in an objective randomized parallel controlled trial design. Patients were randomly assigned to receive either conventional treatment alone or a combination of conventional treatment and Lianhua Qingwen capsules and a control group. This clinical trial is the first prospective, multicenter, open-label randomized controlled trial (RCT) using TCM to treat novel coronavirus, as reported by an international journal. The results showed that the duration of fever, fatigue, and cough in patients with COVID-19 was shortened by 1, 3 and 3 days, respectively. The recovery rate increased to 91.5%, which was significantly higher than that in the control group. Furthermore, two experiments on the treatment of COVID-19 with a Gengzi No. 3 prescription and Jinbei oral liquid showed that they could improve the symptoms of the disease, promote the recovery of the disease, and significantly shorten the course of the disease, according to the nucleic acid negative time, CT improvement rate, total course of disease and other indicators.<sup>37,38</sup> In addition, the trial results showed that the Jinqiang Xuanfei Jiedu mixture was effective in treating mild and moderate cases of COVID-19.<sup>39</sup>

Despite its clinical efficacy and safety for COVID-19 and its tendency to delay disease progression, TCM has not been recognized internationally. This is mainly because research on CHM ingredients is insufficient to provide scientific experimental evidence, such as the content of the main ingredients and the target of action; in addition, TCM syndrome differentiation emphasizes the individualization of treatment, so it is difficult to achieve standardization, which also limits the application of TCM in a wider range. To gain international recognition and application, more prospective cohort studies are needed, and there are many suggestions. First, we should concentrate on the implementation of promising multicenter major trials and organize large-scale clinical trials with effective data by using the support of the government and society. Next, clinical trials that are not promising,<sup>40</sup> such as those that were allowed to proceed based on data from *in vitro* cell studies during the COVID-19 pandemic, should be rejected. Furthermore, large-scale clinical trials should be led by professionals, and more frontline doctors should be encouraged to participate in clinical research. In addition, RCTs with rigorous designs and large samples are urgently needed to provide reliable evidence of the therapeutic effect of TCM for the treatment and prevention of COVID-19. Ultimately, with the implementation of these measures, the quality of TCM clinical trials will be improved, which will provide scientific and credible research evidence for the clinical efficacy of TCM and better promote the development of TCM.

## 5. Preclinical outcomes and big data analysis

Drug targets are the source of drug action and the most important biological basis for drug treatment of diseases. For a long time, due to the complex characteristics of its own components, revealing the target and the molecular pharmacological mechanism of TCM has not achieved breakthrough progress, which has seriously restricted the modernization and internationalization of TCM. Since then, with the development of frontier disciplines, people have constantly explored and established a series of identification methods for drug targets. The following is a summary of basic research and big data target research.<sup>41</sup>

### 5.1. Anti-COVID-19 approaches and strategies in basic TCM research

In terms of clinical therapeutic effects, applying TCM to patients with coronaviruses (CoVs) has been confirmed to have potential anti-CoV effects and provides support to identify more drugs and targets to fight COVID-19.<sup>42</sup> Furthermore, the clinical benefit of TCM should also be supported by basic research.

#### 5.1.1. TCM interferes with the entry of viruses

Among the potential anti-CoV targets, most of them are co-expressed with ACE-2, the host receptor of CoVs, which indicates that CHMs targeting ACE-2 that block CoV S-mediated cell fusion are expected to prevent CoV infection for viral entry.<sup>43</sup> For example, isorhamnetin,<sup>44</sup> corilagin,<sup>45</sup> ephedrine (EP), pseudoephedrine (PEP) and methylephedrine (MEP) from *Ephedra sinica*,<sup>46</sup> platycodin D from *Platycodon grandiflorum*,<sup>47</sup> proanthocyanidin C1 from *Uncaria tomentosa* (cat's claw),<sup>48</sup> and caffeic acid from *Sambucus Formosana Nakai*<sup>49</sup> all effectively compete for the binding site of the S protein with ACE-2 to inhibit SARS-CoV infection.

In addition to ACE-2, the surface structural spike protein (S) of CoVs is of great importance for antiviral activity due to its essential role in the binding of viruses entering host cells during the infection process, which is responsible for virus-cell receptor interaction and membrane fusion.<sup>50,51</sup> Tanshinones from *S. miltiorrhiza*<sup>52</sup> and fangchinoline, tetrandrine, and cepharanthine from *Stephania tetrandra*<sup>53</sup> have potential anti-CoV effects by inhibiting the S protein, which blocks viral entry at the early stage of viral infection.

#### 5.1.2. TCM involvement in viral replication

CoV enzymes control viral replication and serve as potential anti-CoV targets for TCM development to combat COVID-19. For example, 3C-like protease (3CLpro) and papain-like protease (PLpro) play a vital role in the transcription and replication of viruses<sup>54</sup>; thus, enzyme inhibitors targeting these proteases are likely to show inhibitory effects on CoVs. Epigallocatechin-3-gallate,<sup>55</sup> bioflavones and gas from *Ginkgo biloba* leaf extract (GBLE),<sup>56</sup> baicalin from *Shuanghuanglian* preparations,<sup>57</sup> extracts from *S. miltiorrhiza*,<sup>58</sup> *Rhizoma cibotii*<sup>59</sup> and *Torreya nucifera*,<sup>60</sup> herb-derived products that exhibited antiviral activity against SARS-CoV 3CLpro, and tanshinones were also proven to be PLpro inhibitors *in vitro*.<sup>58</sup>

Additionally, viral envelope (E), membrane (M), nucleocapsid (N) and accessory proteins also have the function of promoting viral replication and might be potential anti-CoV targets for further Chinese herbal medicine (CHM) development to suppress COVID-19. Examples of resveratrol, which restrain MERS-CoV infection and prolong cellular survival, were proven to induce MERS-CoV apoptosis by decreasing the expression of the N protein.<sup>61</sup> In addition, fangchinoline, tetrandrine, and cepharanthine also target the N protein to inhibit CoV replication.<sup>53</sup> Emodin, a compound extracted from *Rheum palmatum*, has an inhibitory effect on virion release during the viral replication cycle by suppressing cation-selective channel formation, which plays a role by targeting the SNE-encoded accessory 3a protein.<sup>62</sup>

#### 5.1.3. TCM enhances host immune responses

Researchers have emphasized the importance of immune responses to fight COVID-19<sup>63</sup>, showing the host cell's ability to combat the virus and recover from the infection. Recently, an increasing number of studies have focused on the immunomodulation of TCM for the prevention and treatment of virus infection and revealed that TCM could regulate the immune function of host cells and prevent overreaction due to viruses.<sup>64</sup> Both single herbs and Chinese herbal formulas exhibit immunomodulatory effects on viral pneumonia. This research mainly evaluates their immunomod-

ulatory effect by detecting the percentage of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells and B cells. For instance, Xu and his colleague<sup>65</sup> proved that caffeic acid and its esters are components of propolis, which can inactivate RAC and inhibit PAK1. The direct or upstream inactivation of PAK1 may weaken the pathogenesis of coronaviruses. PAK1 helps suppress B cells and T cells. PAK1 inhibitors can both help fight the virus and restore the normal immune response.

In addition to single herbs, the Biosafety Laboratory conducted animal experiments. They found that Chaiyin granules, Keqing capsules, Kesuting syrup and matrine sodium chloride injections significantly increased the proportion of CD4<sup>+</sup> T lymphocytes, CD8<sup>+</sup> T lymphocytes and B lymphocytes in peripheral blood.<sup>66-68</sup> For Chinese patent medicine, Nan and his colleague<sup>63</sup> reported that Sheng Jiang San could also improve the percentage of CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells and B cells.

#### 5.1.4. TCM reduces the serious complications caused by the virus

Cytokine storm syndrome (CSS), as a late complication of critically ill COVID-19, is connected with disease severity and even contributes to many deaths.<sup>69-71</sup> The major reason for CSS is that the immune system continues to be stimulated, and this prolonged stimulation causes an uncontrolled immune response among T lymphocytes, resulting in overwhelming release of proinflammatory cytokines in host cells,<sup>72</sup> which indicates that alleviating excessive immune responses and eliminating inflammation by specifically targeting relevant cytokines and their host receptors might be an effective way to combat COVID-19.<sup>73</sup> The expression of proinflammatory cytokines such as IL-6, IL-10, CCL-2/MCP-1, CXCL-10/IP-10, TNF- $\alpha$  and IFN- $\gamma$  was detected to evaluate their anti-inflammatory effect.

Phillyrin (KD-1) and Lianhuaqingwen capsules markedly reduced proinflammatory cytokine production at the mRNA level.<sup>36,74</sup> Compounds from the Qingfei Paidu decoction, Shufeng Jiedu capsules and Liu Shen capsules may directly interfere with regulating downstream signaling pathways, leading to the inhibition of the release of proinflammatory factors.<sup>75,76</sup> Researchers also showed that one major compound in the Ma Xing Shi Gan decoction, Glycyrrhizic acid, inhibited TLR agonist-induced IL-6 production in macrophages.<sup>77</sup>

#### 5.2. Target prediction and drug screening of TCM against COVID-19 based on big data

Recently, with the development of network targets and their applications in TCM, network pharmacology has been one of the new strategies for novel drug discovery based on single-target drug studies. By performing network pharmacology analysis, in line with the ADME screening index, such as oral bioavailability and drug likeness index, the potent targets of active compounds against COVID-19 and their related signaling pathways were preliminarily determined to establish an 'herb-compound-target-pathway' network, which aims to explore the possibility of CHMs acting on COVID-19 by analyzing the pathways based on bioinformatics annotation and interactions among targets.<sup>78</sup>

In this way, abundant prescriptions have proven to be effective due to their targets and pathways offering antiviral benefits. In addition to data mining alone, analysis of specific targets and relevant pathways could be performed when combined with network pharmacology. For instance, Wang and her colleague collected published Chinese herbal formulas for COVID-19 with the help of the cloud platform of ancient and modern medical records, then summarized the syndrome patterns, four qi and five flavors, and thus preliminarily acquired a core Chinese herbal formula. Meanwhile, a further search was conducted to determine the active components and action targets of the core Chinese herbal formula by the Tra-

ditional Chinese Medicine System Pharmacology Analysis Platform (TCMSP).<sup>79</sup>

Molecular docking, as a method of direct drug design, is relatively mature in computer-aided drug design. The actual material method uses computer technology to simulate the geometric structure and intermolecular interactions of molecules through chemical quantitative methods, to study the particle size between molecules and to find small particles. The low-energy mode between molecules (or ligands) and macromolecules (or binding) of known structures is determined in this process.<sup>80</sup> For example, researchers performed molecular docking verification on the active ingredients obtained by screening the crystal structures of SARS-COV-2 3CL hydrolase and ACE2. SYBYL-X.v1.3 software was used to optimize proteins and small molecules, and the SurflexDock module was used for molecular docking. According to the Total-Score scoring function, the interaction between the active ingredient and the target protein was scored. The larger the TotalScore value is, the better the matching and binding effect of the small-molecule compound and the large-molecule protein. With a total score >5 as the threshold, the two groups with the lowest binding energy for each protein were plotted using PyMOL software to plot the best results.<sup>81</sup>

The results from data analysis are of importance to the clinical application of TCM. Studies have faster access to summarize a certain amount of knowledge on classic drugs and screen potential drugs by using data analysis. However, the internal regulation of the body has a more complicated regulatory mechanism than a simple concatenation of targets and signaling pathways. Therefore, the actual effect of TCM cannot be identified with direct targeting but is affected by indirect regulation, such as bypass regulation and cross-talk. This means that there is a need to give treatments based on syndrome differentiation and modifications according to symptoms in terms of the actual situation.

## 6. Challenges and perspective

### From single internal treatment to multimode combination.

External TCM treatment is a TCM method other than internal Chinese medicine. The main mechanism of the therapy is the application of noninternal Chinese medicine to the human body through the special effect of Chinese medicine, meridian and acupoint. The therapy takes effect from the outside to the inside, unblocks meridians and collaterals, and adjusts the viscera, with the same effect as the internal Chinese medicine treatment of diseases, and even the efficacies of some external treatment methods are better than the efficacy of internal Chinese medicine. The main types of applications in the epidemic are acupuncture, moxibustion, massage, pain compliance, auricular pressure, acupoint patching, TCM and health and wellness methods,<sup>82</sup> which have a solid theoretical foundation, simple practical operation, definite clinical curative effect and easy acceptance by patients. External therapy is mainly used in the rehabilitation treatment and prognosis recovery, which can enhance the body's immunity, support healthy qi, and promote recovery.

### From curing COVID-19 to sequela treatment and prevention.

COVID-19 has been raging around the world for more than a year, and reports about sequelae are not uncommon, especially in some overseas countries. It was once mentioned that after the treatment of COVID-19, the probability and severity of sequelae is higher in European and American countries than in China.<sup>83</sup> One of the reasons is the difference in treatment methods. China mainly adopts the mode of integrated traditional Chinese and Western medicine, and TCM accounts for a relatively large proportion of this fight against the epidemic. Without specific drugs, European and American countries that adopt modern medical methods can only use antiviral drugs, antibiotics and hormones.<sup>84</sup> These drugs can ag-

gravate some long-term symptoms, mainly sequelae. The sequelae of COVID-19 manifest in multisystem damage and may have symptoms such as long-term weight loss, general fatigue, and abnormal liver and kidney function,<sup>16</sup> which may be caused by the use of hormonal drugs, the patient's underlying diseases and the influence of psychological factors. The second reason is the difference in treatment methods during the rehabilitation period and its degree of emphasis. Academician also proposed a plan attaching importance to the rehabilitation of COVID-19 and hopes that it will be implemented, which reflects China's attention to this issue. Additionally, TCM has its own unique advantages for treatment during the rehabilitation period, such as the combination of multiple modalities, combining Chinese patent medicine with physical therapy, eliminating lingering pathogenic factors and supporting healthy qi.<sup>85</sup>

**From the primary virus to the Delta variant.** At the end of July 2021, Nanjing Lukou International Airport experienced epidemic leakage under the influence of the Delta variant, with higher contagiousness, resulting in an increase in confirmed cases in China, including Nanjing, Jiangsu, Sichuan and 6 other provinces, as well as over 20 cities. At this moment, local health commissions invited outstanding TCM experts to set up a task force for COVID-19. As early as July 24<sup>th</sup>, 2021, many TCM experts adopted video conferences to carry out preliminary diagnosis and then exchanged ideas to develop specific and workable therapeutic regimens. Moreover, considering the changing features of the Delta variant, TCM experts propose that the immediate concern is now to give syndrome differentiation and treatment in TCM, prevent worsening of the condition, and help patients achieve a full recovery. The 'Prevention proposal of TCM for COVID-19 in Sichuan' was released to effectively manage the outbreak and its continued spread. Furthermore, although body temperature and inflammatory indicators have dropped to normal, symptoms have improved in many patients with Delta variant infection. TCM experts require that patients continue to take CHMs to strengthen body resistance, resolve toxins and prevent recurrence or progression.

**From China to the whole world.** According to many historical documents, TCM has historical origins in the prevention and treatment of epidemic diseases.<sup>86</sup> Currently, a large number of clinical practices have once again confirmed that early intervention with TCM and adherence to the integration of traditional Chinese and Western medicine can achieve relatively definite curative effects.<sup>87,88</sup> At present, based on the domestic epidemic being under control, Chinese medical experts have brought many medical supplies, including Chinese patent medicines Lianhua Qingwen and Jinhua Qinggan, to Italy and other countries in need.<sup>89</sup> In the future, first, TCM experts can be sent abroad for consultation and assistance to provide TCM ideas for the treatment of diseases and to directly and concretely prove the effectiveness of TCM and its curative effects. Second, TCM schools in China can recruit foreign students to study TCM. Regarding the content of promotion, the first is to move the intervention forward, which the aim to achieve 'two early'. One is early intervention, mainly for close contacts and susceptible people, through the use of TCM to improve health, prevent and reduce infection. The other is early treatment, and early interventional treatment with TCM can effectively prevent mild cases from turning into severe cases.<sup>90</sup> Second, the integration of Chinese and Western medicine means promoting the consultation system of Chinese and Western medicine abroad, using the internet and other media to conduct remote consultations, exerting the advantages of TCM syndrome differentiation and choosing syndrome differentiation or disease differentiation according to the actual situation. Third, categorized treatment means using different treatment plans for the three stages of prevention, treatment and rehabilitation. Treatment of these three stages with TCM should also be extended to foreign countries, as the COVID-19 diagnosis and treat-

ment plan has been updated to the eighth edition and classification of the stages and the corresponding treatment methods have become more detailed.

**Transformation between clinical and basic.** From clinical to basic research, at present, after the clinical efficacy of many Chinese patent medicines or compound prescriptions has been verified, basic research has been used to explore potential effective ingredients, targets and pathways to provide ideas for the development of specific drugs. From basic research to clinical application, basic research on the symptoms of COVID-19 shows that in the process of development, it will go through stages such as immune function decline and cytokine storm syndrome, and clinical treatments can be formulated based on this.<sup>91</sup> In TCM, in the early stage, the combination of internal and external TCM treatment can be used to support the body's healthy qi and improve immunity, and cytokine storms can be treated with heat-clearing and detoxifying drugs.<sup>92</sup>

## 7. Conclusions

Taken together, existing policies or regulations, clinical data, basic research and in silico studies have confirmed that TCM has made or is making great efforts in fighting the epidemic. Nevertheless, evidence supporting the use of TCM remains insufficient because TCM-related clinical trials are not progressing smoothly, and the current understanding of the mechanisms of TCM is mainly from molecular docking and network pharmacology analysis rather than in vitro and in vivo studies. Therefore, there is an urgent need for large-sample, multicenter and parallel controlled RCTs, as well as well-designed in vitro cell experiments and in vivo animal studies based on potential ingredients or extracts from CHMs, Chinese formulas, Chinese patent medicine, etc. Moreover, it is also important for the government to improve TCM recognition and acceptability at home and abroad with a series of efforts, such as perfecting education, cultivating talent, developing characteristics, inheriting experience, carrying out basic research, improving quality and normalizing the processing of CHMs (Table 1).

## Conflict of interests

The authors declare that they have no conflicts of interest.

## CRediT authorship contribution statement

**Tieying Dai:** Methodology, Formal analysis, Writing – original draft. **Leyin Zhang:** Software, Formal analysis, Writing – original draft, Visualization. **Xinyang Dai:** Investigation. **Beibei Lu:** Investigation. **Yuxi Zheng:** Investigation. **Deyi Shen:** Writing – review & editing. **Yici Yan:** Writing – review & editing. **Congqi Ji:** Writing – review & editing. **Jieru Yu:** Conceptualization, Validation, Project administration, Funding acquisition. **Leitao Sun:** Conceptualization, Validation, Supervision, Funding acquisition.

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**Table 1**  
Intervention effect of TCM treatments at different stages of CoV infection based on multiple viral targets.

	Targeted viral components	Chinese herbal medicine (or its extract)	IC <sub>50</sub> (or EC <sub>50</sub> )	
Viral entry	Viral spike protein (S)	Tanshinones	–	
		Fangchinoline	1.01 $\mu$ M	
		Tetrandrine	0.33 $\mu$ M	
		Cepharanthine	0.83 $\mu$ M	
		Caffeic acid	3.54 $\mu$ M	
		Baicalin	–	
Viral replication	Angiotensin-Converting Enzyme 2 (ACE-2)	Emodin	200 $\mu$ M	
		3C-like protease (3CLpro)	Tanshinones	14.4–226.7 $\mu$ M
			Rheum palmatum	13.76 $\mu$ g/mL
	Isatis indigotica root		217–1210 $\mu$ M	
	Houttuynia cordata		–	
	<sup>1</sup> Rhizoma Cibotii		8.42 $\mu$ g/mL	
	<sup>2</sup> Rhizoma Cibotii		>10 $\mu$ g/mL	
	Papain-like protease (PLpro)	Torreya nucifera	8.3–280.8 $\mu$ M	
		Tanshinones	0.8–30 $\mu$ M	
		Nucleocapsid protein (N)	Resveratrol	–
	Fangchinoline		1.01 $\mu$ M	
	Tetrandrine		0.33 $\mu$ M	
Host immune response	SNE-encoded accessory 3a protein	Cepharanthine	0.83 $\mu$ M	
		Emodin	–	
		Cytokine storm syndrome (CSS)	Shuang Huang Lian	0.6–6 mg/mL
	Curcumin		–	
	Scutellariae Radix		–	
	Immune response	Ma Xing Shi Gan decoction	–	
Tan Re Qing injection		–		
Sheng Jiang San		–		

## Ethical statement

No ethical approval was required, as this study did not involve human participants or laboratory animals.

## Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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