Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Contribution of traditional Chinese medicine to the treatment of COVID-19

Wan-Ying Wang, Ying Xie, Hua Zhou, Liang Liu

Abstract

COVID-19 as an epidemic disease has spread across the planet since December 2019. The somber situation reminds each country to take actions in preventing the spreading of the virus. China as one of the early affected countries has been fighting against the novel coronavirus with the achievements of nearly 80,000 cured confirmed patients. Traditional Chinese medicine (TCM) has made contributions to the treatment of COVID-19 because of its efficacy and comprehensive therapeutic theory. In this commentary, the advantage, etiology and mechanism of TCM therapy were discussed in the aspect of its functions in reducing the harms brought by COVID-19 to human beings.

Introduction

The rapid spreading of the 2019 novel coronavirus (SARS-COV-2) has resulted in an outbreak of coronavirus disease 2019 (COVID-19) in over 200 countries globally. As of the World Health Organization (WHO) situation report on May 24, 2020, there were 5204,508 confirmed cases all over the world, among them, 84,525 cases in China and 5119,983 cases in locations outside China (World Health Organization, 2020). The extensive attention to such an epidemic disease originated from several patients with severe pneumonia in Wuhan, China in January 2020. Although the situation in China has almost reached steady since March, the number of confirmed cases outside China has boosted in other regions, with 2338,124 confirmed cases in Americas and 2006,984 confirmed cases in Europe. (Fig. 1). The unique features of COVID-19 are the fast transmission, difficulty to cure and a lack of proper methods of preventing its infection. Common clinical features of confirmed COVID-19 patients are fever and cough (Guan et al., 2020). The diagnosis is confirmed by their clinical, laboratory, and radiological features and then further divided into mild, severe and critically ill according to their symptoms (Huang et al., 2020; Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020). Currently, anti-virus drugs, human immunoglobulins, corticosteroids and intestinal microecological regulators targeting virus infection or focusing immunomodulation are characterized as principal chemical therapies for COVID-19 in China (General Office of the National Health Commission, 2020; Zhu et al., 2020). These drugs are recommended and prescribed by the doctors empirically because of their efficacy in defending other coronavirus-caused infections including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (Li and De Clercq, 2020). However, COVID-19 has killed more people than the combined number of cases with SARS and MERS (Mahase, 2020).

In China, traditional Chinese medicine (TCM) is concurrently playing an important role in the treatment of COVID-19, integrated with modern imaging system, first-aid facility and ordinary chemical therapy (Yang, 2020). The national percentage of treating confirmed cases of COVID-19 patients with TCM-integrated therapy is over 90% with the support from over 4900 TCM practitioners all over China. Each mobile cabin hospital is equipped with 2–3 TCM experts and a team of 12 national TCM masters are accompanied with severe patients in Wuhan (Liu, Ruiche, 2020). Currently, the national treatment guidance of COVID-19 (7th edition) (General Office of the National Health Commission, 2020) and more than 20 provinces and regions have released modified treatment
guidance inclining TCM integration according to their geographical and weather conditions, which is an unique methodology in TCM therapy based on the perspective of harmonization between environment and human body. Each guidance has emphasized in detail that TCM therapy should be integrated with chemical therapy and TCM practitioners should be involved in the consultation system with no exception (Wang et al., 2020).

The advantages of TCM-integrated therapy

Based on the clinical data from the TCM practitioners treating patients in Wuhan, the dominant advantages of TCM-integrated therapy include shortening rehabilitation period and decreasing the transferring rate from the mild to severe or critically ill cases (Yang, 2020). In a clinical experiment (first batch of clinical data involving TCM treatment) of 52 confirmed cases, of which 34 cases were treated with TCM-integrated therapy with chemical. It was reported that the length of treatment of COVID-19 patients would be 5.15 days in TCM-integrated treatment group, which is 2 days shorter than that in chemical drugs therapy. TCM-integrated therapy could also increase around 30% clinical cure rate. The rate of mild patients transferred to severe patients of TCM-integrated treatment is 29% less than that of group treated by chemical drugs only (Wu, 2020). As reported from Prof. Tong, the total effective rate of Qingfelpaidu formula could reach 97.78% in a statistics of 1261 COVID-19 patients and no patients transferred to severe or critically ill cases (Zhao, 2020). For those severe COVID-19 patients, TCM-integrated therapy could shorten the duration of virus nucleic acid test from positive to negative, which means the patients could be discharged from hospital 2 days earlier. Technically, the clinical indexes including oxyhemoglobin saturation, lymphocyte percentage and lactate dehydrogenase are all improved substantially when patients are treated with TCM-integrated therapy (Wang, 2020).

In addition, the combinational TCM formulae could also help alleviate the adverse drug reactions induced by anti-virus drugs and corticosteroids, especially in gastrointestinal and hepatic related systems. Therefore, an early and full-dimensional intervention of TCM therapy could achieve a better outcome of the treatment.

The etiology of COVID-19 in TCM theory

Since COVID-19 could be infected through droplet from human to human in a diverse age range, this disease could be included as “pestilence” in TCM theory. January is the coldest month over a year and the rainfall of Wuhan in January is nearly 5 times of the mean rainfall during the same period in the past 20 years (Weatheronline, 2020). Low fever, dry cough, debilitation, whole-body sore, nausea, diarrhea and diarrhea are common symptoms of COVID-19 patients which correlate with “cold and damp” symptoms in TCM theory. Therefore, a qualitative definition of COVID-19 in TCM theory is a “cold and damp” pestilence because of the symptoms and the weather conditions of Wuhan, China (Tong et al., 2020). Historically, Chinese people have been fighting against epidemics adopting TCM along with the development of Chinese civilization. In the course of fighting the epidemics, Chinese medicine has developed theory and effective prescriptions for the prevention and treatment of epidemics, which have been recorded in many classic TCM books, such as the Treatise on Acute Epidemic Febrile Diseases (Wu, 1642), the earliest existing and famous treatise on the treatment of acute infectious diseases written by Youxing Wu in 1642. A number of mortal epidemics including smallpox, malaria, leprosy etc. have been cured and prevented from further transmission by TCM diagnosis and treatment theory. Smallpox vaccination has been invented in Song dynasty in China through smallpox scabs (Deng, 2006). More recently, TCM also played an important role during the fight with SARS in 2003 which benefited mainland China with the lowest death rate (Chen and

![Fig. 1. Number of confirmed COVID-19 cases, by date of report and WHO region, 30 December 2019 through 24 May 2020](Derived from Coronavirus disease 2019 (COVID-19) Situation Report – 125) (World Health Organization, 2020).
Nakamura, 2004; Jia and Gao, 2003). Using a different idea from the microbiology-oriented knowledge of the etiology of the disease or the mechanism of novel drugs, TCM emphasizes on the relief of symptoms so as to cure infected patients and control the spreading of epidemics.

The mechanism of TCM-integrated therapy in modern medical theory

COVID-19 was defined as a self-limited disease and severe immune injury is one of the characterized pathological features of reported cases (Xu et al., 2020). The enhancement of patients' immunity is therefore a crucial contributor of their recovery (Stebbing et al., 2020), which highly correlates with TCM theory. The mechanism of TCM-integrated therapy starts from the diagnosis of the disease. The criteria of confirming COVID-19 cases is unified according to their serum samples and CT images from mild patients to critically ill cases (General Office of the National Health Commission, 2020). However, over 20% of the patients might have at least one coexisting disease with COVID-19 (Guan et al., 2020). Patients are then further classified by their personal symptoms and high specificity treated with TCM-integrated therapy. In this way, TCM patent medicine or TCM combinational formulae could be prescribed to corresponding patients with different symptoms.

Locally in the organs, invigorating the circulation of blood in lung is the main issue but the balance between lung, spleen and organs in the gastrointestinal system is also emphasized in TCM theory. According to the national guidance of COVID-19 treatment, a number of TCM patent medicine were recommended during medical observation period including Jinhuaqinggan granules (12 herbs including Lonicerae Japonicae Flos, Gypsum Fibrosum, Ephedrae Herba, etc.), Lianhuaqingwan capsule (13 herbs, including Pogostemonis Herba, Forsythiae Fructus, Lonicerae Japonicae Flos etc.), Shufengji capsule (8 herbs, including Polygoni Cuspidati Rhizoma et Radix, Forsythiae Fructus, Isatidis Radix, etc.) etc. Jinhuaqinggan granules were found to be associated with multiple signaling pathways treating COVID-19 through in silico analysis, such as TNF signaling pathway, MAPK signaling pathway, T cell receptor signaling pathway and so on (Lin et al., 2020). Lianhuaqingwan granules could significantly relieve clinical symptoms in COVID-19 patients by inhibiting the release of inflammatory mediators so as to regulate the immune response of virus infection (Ding et al., 2017; Dong et al., 2014; Hu et al., 2020). Similarly, Shufengji capsule could also ameliorate upper respiratory tract infection via the ERK pathway and modulate anti-inflammatory and immunomodulation activity (Li et al., 2017; Tao et al., 2017).

For those severe COVID-19 patients, the holistic perspective of TCM could be responsible for the virus-induced lymphocytopenia. The acute respiratory distress syndrome and multiple organ failure are common clinical features of severe COVID-19 patients, which are assumed to be caused by cytokine storms (Liu et al., 2016). Over-action of T cells and an increased plasma concentrations of cytokines and chemokines (IL1B, IL1RA, IL-6, IL7, IL8, IL9, IL10, basic FGF, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF etc.) were observed clinically in COVID-19 patients (Huang et al., 2020; Wan et al., 2020; Xu et al., 2020). More importantly, most critically ill patients are gerontic with comorbidities who require a protection of most affected organs (Yang et al., 2020). Therefore, targeting cytokine storms and oxidative stress are assumed as the main tasks of TCM formulae. The recommended TCM formulae mainly focus on reducing inflammatory cytokines and endogenous pyrogen to control exacerbation. Regionally, Toujiegwan (Fever & inflammation clearance) granule recommended in Guangdong and Feiyian No.1 (COVID-19 NO.1) recommended in Hubei also exhibited great efficacy in concurrent treatment of COVID-19, which include the essential ingredients of classical prescriptions Xiaoaozhai decoction (7 herbs including Bupleuri Radix, Scutellariae Radix, Ginseng Radix et Rhizoma etc.) and Dayuanxin (7 herbs including Arecae Semen, Magnoliae Officinalis Cortex, Anemarrhenae Rhizoma etc.) (Xinhua Net, 2020a). Nationally, the efficacy of Qingfeipai (Lung clearance and detoxification) decoction integrated therapy recommended by the State Administration of Traditional Chinese Medicine of China has been evaluated in 4 provinces including Shanxi, Hebei, Heilongjiang and Shaanxi, which has critical effective rate (People’s Daily, 2020.; Xinhua Net, 2020b). This decoction is a combination of 4 classical TCM formulae including Maxingshigan decoction (4 herbs including Ephedrae Herba, Armeniacae Semen Amarum, Glycyrrhizae Radix et Rhizoma etc.), Sheganmauhuang decoction (9 herbs including Belamcandae Rhizoma, Ephedrae Herba, Zingiberis Rhizoma Recens etc.), Xiaoaohai decoction and Wuling San (5 herbs including Poly polysor, Alismatis Rhizoma, Atractylodis Macrocephalae Rhizoma etc.) (Jiang and Chen, 2020). Experiments have been conducted to confirm that the mechanism of Xiaoaozhai decoction and Sheganmauhuang decoction includes down-regulating IL-17 and TNF-α and inhibiting NF-κB signaling pathway (Cao and Tang, 2014; Liu et al., 2013, 2017; Sui et al., 2017). The active compounds in Qingfeipai decoction such as licorice flavonoids and glycyrrhizin (from Glycyrrhiza Radix et Rhizoma Praeparata Cum Melle), saikoside (from Bupleuri Radix), baicalin (from Scutellariae Radix) and amygdalin (from Armeniaca Semen Amarum) etc. all demonstrate functions in immunology disorders. Licorice flavonoids could effectively attenuate LPS-induced pulmonary inflammation through inhibition of inflammatory cells infiltration and inflammatory mediator release (Xie et al., 2009). Glycyrrhizin is evaluated by computational docking as a potential compound binding ACE2 to block the virus’s access gate and could ameliorate acute lung injury through inhibiting proinflammatory cytokines (Chen and Du, 2020; Yao and Sun, 2019). Saikoside could improve perturbations in liver molecules related to lipid metabolism, lipid peroxidation, and inflammation (Ge et al., 2012). Baicalin could limit NF-κB dependent inflammatory responses as potent antioxidants ameliorating various inflammatory disorders (Dinda et al., 2017; Patwardhan et al., 2016). Amygdalin could Inhibit IFN-γ, NF-κB and NLRP3 signaling pathways so as to reduce the inflammatory response (Paoletti et al., 2013; Zhang et al., 2017). These reports provided the scientific ground of integrating TCM therapy from the aspects of their compositions’ potential targeting proteins and signaling pathways in the treatment of COVID-19.

There are still no effective countermeasures to defeat COVID-19 from the understanding of the pathology to the development of drugs or vaccines. Currently, the number of newly confirmed COVID-19 patients is largely decreasing and the number of cured patients is increasing in China attributing to the effective therapeutic regimen which cannot ignore the integration of TCM therapy. In the future, more clinical cases of COVID-19 could be concluded in the statistics to decipher the pathology of the disease. Meanwhile, the mechanism of existing or novel drugs for COVID-19 treatment could be further evaluated. The clinical experience of treating COVID-19 could hopefully be adopted as a reference by other affected countries, especially the TCM-integrated therapy to address current crisis.

CRediT authorship contribution statement

Wan-Ying Wang: Writing - review & editing. Ying Xie: Writing - review & editing. Hua Zhou: Writing - review & editing, Supervision. Liang Liu: Writing - review & editing, Supervision.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgment

This research was funded by the Science and Technology Development Fund of Macao SAR (Project No: 0053/2020/A, 0057/2020/A, and 0040/2020/A).
Cao, F., Tang, A., 2014. Effect of Xiao-Chai-Hu decoction with different doses of Mahase, E., 2020. Coronavirus covid-19 has killed more people than SARS and MERS Liu, X., Hu, X., Xu, H.-X., Zeng, X.-Y., 2013. Xiao-Chai-Hu decoction attenuates the vicious
Liu, Ruiche, 2020. All the mobile cabin hospitals in Wuhan are equipped with TCM
Jiang, Q., Chen, X., 2020. On the basis of syndrome differentiation considering the rapid
Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X.,
Dong, L., Xia, J.W., Gong, Y., Chen, Z., Yang, H.H., Zhang, J., He, J., Chen, X.D., 2014.
Ding, Y., Zeng, L., Li, R., Chen, Qianyuan, Zhou, B., Chen, Qiaoian, Cheng, P leng,
Yatao, W., Zheng, J., Yang, Z., Zhang, F., 2017. The Chinese prescription lianhuaqingsuan capsules exert anti-inflammatory activity through the inhibition of viral propagation and impacts immune function. BMC Complement. Altern. Med. 17, 130.

References

Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhejiang Sci. Technol. Univer. Publ. 41, 145–151. https://doi.org/10.37676/j.issn.0254-6540.2020.02.003.
Piolatti, I., De Gregorio, V., Baroni, A., Tufano, M.A., Donnarumma, G., Perez, J.J., 2013. Amygdalin analogues inhibit IFN-γ signalling and reduce the inflammatory response in human epidermal keratinocytes. Inflammation 36, 1316-1326. https://doi.org/10.1007/s10753-013-9670-7.
Patwardhan, R.S., Sharma, D., Thob, M., Cheekr, R., Sandur, S.K., 2016. Balsaine exhibits anti-inflammatory effects via inhibition of NF-κB transactivation. Biochem. Pharmacol. 108, 75–89. https://doi.org/10.1016/j.biopha.2016.03.015.
People’s Daily, 2020. In the treatment of COVID-19, why is traditional Chinese medicine effective? [WWW Document]. People’s Dly. URL http://www.scm.gov.cn/hd2010/zwgk/202005/t20200512_727194.htm

Novel Coronavirus Pneumonia Emergency Response Epidemiology Team, 2020. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 41, 145–151. https://doi.org/10.37676/j.issn.0254-6540.2020.02.003.
PiolettI, I., De Gregorio, V., Baroni, A., Tufano, M.A., Donnarumma, G., Perez, J.J., 2013. Amygdalin analogues inhibit IFN-γ signalling and reduce the inflammatory response in human epidermal keratinocytes. Inflammation 36, 1316-1326. https://doi.org/10.1007/s10753-013-9670-7.

4