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Discuss about the application of *Artemisia annua* prescriptions in the treatment of COVID-19

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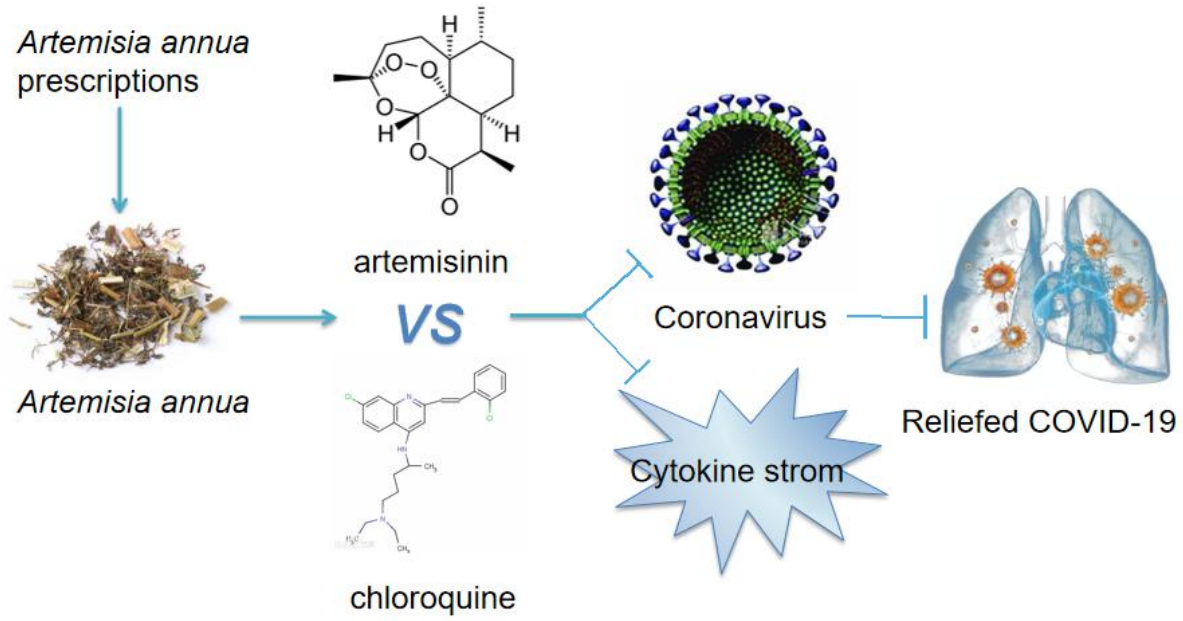
Highlights

Based on the effect of clearing dampness and heat, *Artemisia annua* prescriptions receive good results in treating the Novel Coronavirus Pneumonia patients. Exploring the possible mechanism of *Artemisia annua* prescriptions in treating new coronavirus pneumonia is conducive to the popularization of this prescription and has important clinical value. This review will discuss the possible mechanism that *Artemisia annua* prescriptions treat new coronavirus pneumonia by comparing the similar protective effect of artemisinin and chloroquine in epidemic diseases.



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Abstract

The applications of traditional Chinese medicine (TCM) have been playing an important role in treating the epidemics of Coronavirus Disease 2019 (COVID-19), which is now prevalent all over the world. Exploring the mechanisms of TCM compound prescriptions might be difficult though, pharmacological studies on elucidating the effective components of TCM could serve as the experimental basis in the application of TCM compound prescription in treating COVID-19. As the critical active ingredients of Qinghao (*Artemisia annua*), artemisinin was initially used as antimalaria drug. *Artemisia annua* prescriptions take significant effect against pneumonia. Sharing similarities in pharmacology with artemisinin, chloroquine has been confirmed effective in inhibiting Severe Acute Respiratory Syndrome coronavirus 2 (SARS-Cov-2) both in vitro and practically. In this context, we discussed the application of *Artemisia annua* prescriptions against COVID-19 along with the antiviral effect of chloroquine.

Keywords: COVID-19, Chloroquine, Artemisinin, *Artemisia annua*

Abbreviations: TCM,Traditional Chinese Medicine; COVID-19, Coronavirus Disease 2019; SARS-Cov-2, Severe Acute Respiratory Syndrome Coronavirus 2; MERS-Cov, Middle East Respiratory Syndrome Coronavirus; HIV, Human Immunodeficiency Virus; ZIKV, Zika Virus; DENV, Dengue Virus; H5N1, Avian Influenza A; TNF-α, tumor necrosis factor; IL-6, interleukin-6.

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Background

The Coronavirus Disease 2019 (COVID-19) has been rapidly spreading in many countries and regions throughout the world, posing a major public health threat. Impossible as it is in developing new antiviral drugs in a short time span, the new usage of old drugs has become an essential approach in drug screening. Chloroquine was the most widely used antimalarial drug before artemisinin was discovered. It has later been found to exert antiviral effects against many infectious diseases [1]. On February 19, 2020, chloroquine phosphate has been listed as antiviral drug in *the COVID-19 diagnosis and treatment Plan* (trial version 6) issued by the National Health Commission of China. Artemisinin became the drug of choice after plasmodium develops resistance to chloroquine. Recently, artemisinin has been reported to inhibit RNA viruses [2], with the facts that Qinghao (*Artemisia annua*) prescriptions have been widely used in effectively treating COVID-19 and achieved good curative effect. Based on the anti-viral effect of artemisinin and chloroquine, this paper sought to discuss the possible underlying mechanism of *Artemisia annua* prescriptions in treating COVID-19.

From chloroquine to artemisinin

In 1820, the first antimalarial drug quinine was extracted from cinchona bark by French pharmacists Pelletier and Caventou. In the 1940s, limited by the raw materials for quinine extraction, German scientists synthesized chloroquine, which is similar to natural quinine in chemical structure. Its derivate hydroxychloroquine was also synthesized with higher effectiveness and less toxicity. By the mid-20th century, the malaria was gradually controlled in China. However, there broke out a local epidemic in 1960s, which spread rapidly in Southeast Asia and South America. Besides, *plasmodium falciparum* developed a strong resistance to chloroquine. Inspired by ancient books of TCM, Youyou Tu, a Chinese scientist, successfully extracted artemisinin from *Artemisia annua*. With a 100% inhibition rate against plasmodium, artemisinin has gradually replaced chloroquine as the vital antimalarial drug since then. Youyou Tu became the laureate of Nobel Prize in Physiology or Medicine in 2015 for this accomplishment.

Discovery of chloroquine in the treatment of COVID-19

Chloroquine has been confirmed to be effective during the epidemics of various infectious diseases, especially Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome Coronavirus (MERS). In 2003, SARS broke out in China with a total 5327 infection, of which 349 died. In 2004, MarcVanRanst and his colleagues found that chloroquine effectively inhibited SARS coronavirus replication in vitro [3]. In 2005, Nichol ST found that chloroquine suppressed SARS virus replication both before and after infection, suggesting a preventive and therapeutic role of chloroquine against SARS [4]. Eric J. Snijder's team successfully inhibited MERS coronavirus replication by chloroquine in monkeys, with similar suppressive effect against SARS and human coronavirus [1]. Additionally, Chloroquine has also been reported to inhibit Human Immunodeficiency Virus (HIV), Zika virus (ZIKV), and dengue virus (DENV) [5]. Chloroquine phosphate was also reported to alleviate lung autophagy induced by avian influenza A (H5N1) and reduce alveolar injury in mice [6].

COVID-19 has been rapidly spreading in many countries and regions throughout the world. Further sequencing of the patient's lower respiratory secretions revealed that the disease was associated with a coronavirus, which was first named 2019 novel Coronavirus (2019-nCOV) by World Health Organization. SARS-Cov-2 belongs to β-coronavirus and shares 85% homology with SARS-Cov and was later named SARS-Cov-2 by International Committee on the Classification of Viruses [7-8]. On February 11, 2020, the pneumonia caused by SARS-Cov-2 infection was tentatively named as the Coronavirus Disease 2019 (COVID-19) by the World Health Organization. COVID-19 is highly contagious, with propagation by respiratory droplets, direct contact and aerosol transmission, people are highly susceptible to this disease. COVID-19 has been spreading in more than 100 countries around the world so far, raising great threat to people's physical and mental health.

SARS-Cov-2 infection causes fever, dry cough, fatigue and chest tightness, although some patients exhibit no or mild symptoms. The majority of patients are associated with a favorable prognosis whereas some severe individuals would eventually die of respiratory distress, sepsis or multiple organ failures [9]. With no viral-specific drug available, COVID-19 is currently treated symptomatically. Considering the long turnover of drug development, screening for potential anti-SARS-Cov-2 activity from approved drugs has become a crucial means in this scenario.

On February 6, 2020, Wuhan Virus Research Institute of Chinese Academy of Sciences and other

units jointly published the research results on cell research, which showed that chloroquine phosphate effectively inhibited SARS-Cov-2 and such inhibition was superior as compared to Redsevir [10]. The preliminary results of a subsequent clinical study involving more than 100 patients conducted jointly by more than 10 hospitals including Beijing and Shanghai, showed that chloroquine phosphate was superior to the control group in terms of a series of indicators, such as the rate of severe illness, antipyretic phenomenon, lung image improvement time, viral nucleic acid negative conversion time and rate, and shortening the course of disease [11]. Considering the urgent needs of current clinical treatment, *COVID-19 diagnosis and treatment Plan* (trial version 6) was released in February 19, 2020 by National Health Commission of the People's Republic of China, in which chloroquine phosphate (adult 500mg, 2 times daily) was added as effective anti new-type coronavirus treatment. A recent study in France involving 36 patients stated that hydroxychloroquine combined with azithromycin significantly reduce respiratory viral load in COVID-19 patients [12].

The antiviral mechanisms of chloroquine phosphate on SARS-Cov-2 might come as follows: 1) To weaken the binding of the virus to the receptor by interfering with the terminal glycosylation of the receptor protein angiotensin 2 receptor invertase of coronavirus; 2) As an alkaline drug, chloroquine increase pH value inside endosomes which was not conducive for virus-cell fusion; 3) Inhibit cell autophagy and regulate host immune reaction to suppress virus infection and replication; 4) Suppress transcription and translation of virus protein by binding to viral protease; and 5) Alleviate cytokine storm through inhibiting the production and release of TNF-α and IL-6 [13].

Application and thinking of *Artemisia annua* prescriptions in the treatment of COVID-19

The applications of clearing heat, removing dampness and resolving phlegm approaches in treating COVID-19

According to TCM theory, COVID-19 can be categorized as "plague" with the cause of suffering from "distemper". Practical treatment plan based on syndrome differentiation is put forward according to medical staging. The primary initial symptoms of most COVID-19 patients included cough, fatigue, poor anorexia, and thick greasy tongue coating. According to the theory of TCM, the pathogenic factor of COVID-19 is dampness, with the core pathogenesis being dampness obstructing lung and repressing the motion of Qi. The pathological features of COVID-19 can be summarized as "dampness, toxin, blockage and deficiency". The disease is located in the lung, sometimes affecting spleen and stomach, and in severe patients the heart and kidney can also be attacked [14]. The damage of dampness varies. It can mix with cold and impair yang Qi, or mix with dryness and impair yin Qi, or even mix with heat and turn into damp-heat. The transformation trend is associated with many factors, such as the patient's physique, eating habits, living environment, early medication and so on. With the progress of COVID-19, the damp-toxin usually goes interior and turns into heat, which wrap with each other, and lie in the lung, membranes, and Sanjiao, resulting in chest tightness and shortness of breath which aggravates after activity, or fever and loss of appetite, bitter taste, palpitations, poor sleep, fatigue, diarrhea and thick greasy tongue coating [15]. As documented in *Shire Tiaobian* written by Shengbai Xue, one famous doctor of TCM in Qing Dynasty, since the heat is one Qi from the sky and the dampness is another Qi from the earth. The heat grows more incandescent when it comes with dampness and the dampness will be more outrageous when it comes with heat. The disease will get better and slow down when heat and dampness is divided. Otherwise, it will be on the contrary. During the invasion of damp-heat epidemic toxin, Shaoyang gallbladder meridian and Sanjiao meridian are obstructed by these pathogenic factors, in which the motion of gas in Sanjiao jing has been damaged, and its function of ascending, descending, entry and exit are blocked, *Xianghuo* is incandescent, so that the Qi will not work well.

The meridian of gallbladder and Sanjiao are equally important in treatment, one is to reconcile the exterior and interior, and clear dampness and heat of gallbladder meridian, and the other one is to dispel the evil of Sanjiao. Haoqin Qingdan decoction, an important prescription for the treatment of dampness-heat, show effect on clearing the dampness of gallbladder's and reliving the stomach. Haoqin Qingdan decoction mainly targets on suppressed dampness and heat and help dredge the obstructed Qi of Shaoyang gallbladder meridian and Sanjiao meridian. The prescription consists of Qinghao (*Artemisia annua*) 4.5-6.0g, Huangqin (*Scutellariae radix*) 4.5-9.0g, Zhuru (*Bambusae caulis taenias*) 9g, Banxia (*Pinelliae rhizoma) 4.5g*, Zhiqiao (*Aurantii fructus*) *4.5g*, Chengpi (*Citri reticulatae pericarpium*) 4.5g, Fulin (*Poria)* 9g, Biyu decoction(*Talcum, Glycyrrhizae radix et rhizoma, Indigo naturalis*) 9g. In the prescription, *Artemisia annua* and *Scutellariae radix* are used as monarch medicine, with the former

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clearing away the evil heat of Shaoyang meridian, and the latter clearing gallbladder heat and drying dampness. *Bambusae caulis taenias* and *Pinelliae rhizoma* match as courtier medicine, clearing phlegm and relieving stomach to stop vomiting. *Aurantii fructus* and *Citri reticulatae pericarpium* are used as adjuvants, the former leading retained Qi down the body, the latter regulating Qi and resolving phlegm; the two drugs are used for excreting dampness and resolving phlegm. Therefore, dialectical addition and subtraction on the basis of Haoqin Qingdan decoction can be applied to treating COVID-19. Previously, we have successfully cured a severe patient with Haoqin Qingdan decoction in combination with other Chinese and western medications [16]. With the progress of the epidemics, the role of Chinese medicine application in the treatment of COVID-19 is becoming more and more prominent. While participating in the treatment of COVID-19, the Chinese Academy of TCM also applied Haoqin Qingdan decoction to mild and critically ill patients and achieved promising prognosis [15].

Thoughts and Application of *Artemisia annua* and its analogous prescription in treating COVID-19

Artemisia annua possesses functions of eliminating hectic heat, removing bone steaming, relieving summer heat, preventing malaria, and retreating jaundice. *Artemisia annua* is bitter in taste and cold in property, with meridian tropism in liver and gallbladder. According to the theory of TCM, Shaoyang gallbladder meridian is connected with Jueyin liver meridian and is the place where yangqi is originated. As a result, Shaoyang gallbladder meridian is often the target in treating fever diseases. Echoed with the orthodox principle in treating dampness-heat syndrome that treating dampness with bitterness and curing heat by cold, *Artemisia annua* has always been regarded as a reference to clear heat and eliminate dampness. *Artemisia annua*-based prescriptions include Haoqin Qingdan decoction and Qinghao Biejia decoction. The former is used for dampness-heat syndrome with pathogen invading Shaoyang, whereas the latter is often applied in patients with malaria involving Shaoyang meridian. Due to its contribution in clearing heat and eliminating dampness, *Artemisia annua* acts as a pivotal medicine in the two prescriptions. SARS is manifested by high fever, exhaustion of yin and fluid injury. Treatments for SARS have been focused on heat clearance with dampness elimination as an aid. Thanks to its aforementioned characteristics, *Artemisia annua*-based prescriptions have played a significant role in the treatment of SARS [17]. Similar to SARS, COVID-19 is also a coronavirus that causes respiratory syndromes, which starts with dampness, with a long latency and courses. The pathogenesis of COVID-19 is mainly characterized by the inward invasion of dampness towards the transformation into heat. Therefore, COVID-19 treatment should focus on clearing heat, removing dampness and resolving phlegm. Considering the initial clinical manifestations of COVID-19 characterized by pathogen invading Shaoyang gallbladder meridian, *Artemisia annua* is expected to be an essential drug for the treatment of COVID-19.

Clinicly, *Artemisia annua* prescriptions played an important role in treating COVID-19. Jinhua Qinggan granule, which is made from Yinqiao powder and Maxing Shigan decoction, is composed of 12 medicinal materials: Jinyinghua (*Lonicerae japonicae flos*), Shigao (*Gypsum fibrosum*), Zhimahuang (*Ephedare herba*), Zhimu (*Anemarrhenae rhizoma*), lianqiao (*Forsythiae fructus*), Kuxingren (*Armeniacae semen amarum*), Huangqin (*Scutellariae radix)*, Niubangzi (*Arctii fructus*), Bohe (*Menthae haplocalycis herba*), Qinghao (*Artemisia annua)*, Zhebeimu (*Fritillariae thunbergh bulbus)*, and Gancao (*Glycyrrhizae radix et rhizoma*). Two studies on the treatment of COVID-19 with Jinhua Qinggan granule led by Dr. Boli Zhang show that Jinhua Qinggan granule is effective for mild and ordinary patients, which shortens the antipyretic time, increases the normalization rate of lymphocytes and leukocytes, and significantly reduces the possibility of disease progression [18]. From the fourth edition to the seventh edition of *COVID-19 diagnosis and treatment Plan*, Jinhua Qinggan granule has been recommended as a Chinese patented medicine for patients with fatigue and fever during the medical observation period. In another research, through the preliminary observation on the use of Xuanfei Baidu granule in 280 mild patients by Dr. Boli Zhang in Jiangxia Fangcang Hospital, no one turned to severe patients. Xuanfei Baidu granule was adjusted by adding *Artemisia annua* on the basis of Maxing Shigan decoction, Maxing Yigan decoction, Tingli Dazao Xiefei Decoction, and Qianjin Weijing decoction [19]. It can be seen that *Artemisia annua* prescriptions play an important role in the treatment of COVID-19.

Extracted from *Artemisia annua* by ether, artemisinin is a first-line antimalarial drug recommended by the World Health Organization. Its main derivatives include artemether, artesunate, dihydroartemisinin, etc. As antimalarial drugs, artemisinin and chloroquine have similar therapeutic effects in many diseases. With the research going on, artemisinin and its derivatives have been found to

have curative effects on leishmania, schistosoma japonicum, toxoplasma gondii and some other infectious diseases.

Artemisinin can directly suppress virus replication. Artemisinin and its derivatives were shown to restrain both DNA virus (such as cytomegalovirus, human herpesvirus 6, herpes simplex virus 1 and 2, hepatitis B virus) and RNA virus (such as human immunodeficiency virus 1 and 2, hepatitis C virus, influenza virus) [2]. After modeling RNA-dependent RNA polymerase (RdRp) of SARS-Cov-2 with the protein crystal structure of that in SARS-Cov, it was found that artesunate could dock at the active center of RdRp model of SARS-Cov-2, which can partly explain the mechanism that artesunate suppresses virus [20].

In addition to direct suppression on virus, Jun et al reported that artesunate reduced the expression of inflammatory factors in septic mice induced by bacterial deoxyribonucleic acid and lipopolysaccharide in a dose-dependent manner [21]. Yajie Wang et al also showed that the cellular inflammatory factors in macrophage RAW264.7, the wet/dry mass ratio of lung tissue, the infiltration of inflammatory cells, the activity of myeloperoxidase, and the expression level of inflammatory factors in lung homogenate in LPS treated mice were all reduced by artesunate [22]. Therefore, the anti-inflammatory effect might also be one of the important mechanisms of *Artemisia annua* prescriptions in the treatment of COVID-19. Clinical studies have found that cytokine storm syndrome can be observed in severe patients with COVID-19 [23]. In view of the resistance of plasmodium to chloroquine, chloroquine and its derivatives are mainly used to treat autoimmune diseases in recent years. Experimental research revealed that artemisinin is also expected to be used in the treatment of systemic lupus erythematosus, rheumatoid arthritis, tumors and other diseases. The main mechanisms involve inhibiting T cells proliferation and activation, inhibiting B cells activation and antibody production, increasing regulatory T cells and reducing the release of inflammatory cytokines [24]. The study of dihydroartemisinin in the treatment of lupus erythematosus is currently in phase II clinical trials. Artemisinin and its derivatives have clear anti-inflammatory and immunomodulatory effects, and thus are able to reduce the level of a variety of cytokines, so they can alleviate the tissue and organ damage caused by cytokine storm in coronavirus pneumonia.

Conclusion

With similar pharmacological effects between chloroquine and artemisinin in treating infectious diseases, this paper discusses the modern scientific basis for the application of *Artemisia annua* prescriptions in COVID-19. Except for antimalarial, most of the other pharmacological studies on artemisinin and its derivatives are still on the bench or at animal level, with only a few in clinical trials. Artemisinin treatment on COVID-19 has not been reported yet. As a treasure of TCM, compound prescription has played an important role in plagues in history. The main cause of COVID-19 in Wuhan is damp-heat according to TCM theory. The prescription for clearing heat and eliminating dampness based on *Artemisia annua* is widely used in this epidemic. Based on the antiviral and anti-inflammatory effects of artemisinin and its derivatives, *Artemisia annua* prescriptions have great value to dig into and are promising to be used in more infectious diseases. But more in vitro experiments need to be carried out to provide more evidence, such as the influence of *Artemisia* or *Artemisia annua* prescriptions on inflammatory factors expression and lung injury in acute infectious diseases.

References

1. Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East Respiratory Syndrome Coronavirus replication in cell culture. Antimicrob Agents Chemother 2014, 58: 4875-84.
2. Efferth T. Beyond malaria: The inhibition of viruses by Artemisinin-type compounds. Biotechnol Adv 2018, 36: 1730-1737.
3. Keyaerts E, Vijgen L, Maes P, et al. In vitro inhibition of Severe Acute Respiratory Syndrome Coronavirus by Chloroquine. Biochem Biophys Res Commun 2004, 323: 264-8.
4. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS Coronavirus infection and spread. Virol J 2005, 22: 69.
5. Al-Bari MAA. Targeting endosomal acidification by Chloroquine analogs as a promising strategy for the treatment of emerging viral diseases. Pharmacol Res Perspect 2017, 5: e00293.
6. Yan Y, Zou Z, Sun Y, et al. Anti-malaria drug Chloroquine is highly effective in treating Avian Influenza A H5N1 virus infection in an animal model. Cell Res 2013, 23: 300-2.

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doi: 10.12032/TMRmhm202003075

7. Ding Q, Lu P, Fan Y, et al. The clinical characteristics of pneumonia patients co-infected with 2019 Novel Coronavirus and Influenza Virus in Wuhan, China. J Med Virol 2020, in press.
8. Ralph R, Lew J, Zeng T, et al. 2019-nCoV (Wuhan Virus), a novel Coronavirus: human-to-human transmission, travel-related cases, and vaccine readiness. J Infect Dev Ctries 2020, 14: 3-17.
9. General Office of the State Health Commission [Internet]. COVID-19 's diagnosis and treatment Plan (trial sixth Edition) [Cited 2020 February 19]. Available from: www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2.shtml.
10. Wang M, Cao R, Zhang L, et al. Remdesivir and Chloroquine effectively inhibit the recently emerged Novel Coronavirus (2019-nCoV) in vitro. Cell Res 2020, 30: 269-271.
11. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020, 14: 72-73.
12. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and Azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020, in press.
13. Che KK, Liu XM, Hu CH. Retrospective analysis and pharmaceutical care of anti-Coronavirus drugs in the latest diagnosis and treatment plan. Journal of Southwest University (Natural Science Edition) 2020, 42: 1-9 +886. (Chinese)
14. Pang WT, Jin XY, Pang Bo, et al. Analysis on pattern of prescriptions and syndromes of Traditional Chinese Medicine for prevention and treatment of Novel Coronavirus Pneumonia. China Journal of Chinese Materia Medica 2020, 6:1242-1247 +886. (Chinese)
15. Li B, Cong X, Miao Q, et al. Analysis of medical cases of Corona Virus Disease 2019 treated with Haoqin Qingdan Decoction. Chinese Journal of Experimental Traditional Medical Formulae 2020, in press +886. (Chinese)
16. Hu M, Dong R, Chen G, et al. Clinical case of severe New Coronavirus Pneumonia treated by combination of traditional chinese and western medicine. Chinese Journal of Integrated Traditional and Western Medicine 2020, 40: 228-230 +886. (Chinese)
17. Peng SQ. Syndrome differentiation and treatment of SARS. Shanghai Journal of Traditional Chinese Medicine, 2003, 05: 3-4. (Chinese)
18. Duan C, Xia W, Zheng C, et al. Clinical observation on the treatment of COVID-19 with Jinhua Qinggan Granule. Journal of Traditional Chinese Medicine 2020, in press +886. (Chinese)
19. Wang Y, Li X, Zhang JH, et al. Mechanism of Xuanfei Baidu Tang in treatment of Novel Coronavirus Pneumonia based on network pharmacology. China Journal of Chinese Materia Medica 2020, in press +886. (Chinese)
20. Tian JH [Internet]. Artesunate may be a drug with dual treatment for COVID-19. China Biotechnology Network Cited 2020 February 17. https://www.chemsrc. com/news/367.html
21. Wang J, Zhou H, Zheng J, et al. The Antimalarial Artemisinin synergizes with antibiotics to protect against lethal live Escherichia Coli challenge by decreasing proinflammatory cytokine release. Antimicr Ag Chemother 2006, 50: 2420-2427.
22. Wang YJ. The therapeutic efficacy of PEGylated Artesunate prodrug on rodent acute lung injury induced by Lipopolysaccharides. Chinese Academy of traditional Chinese Medicine 2019. +886. (Chinese)
23. Wan S X, Yi Q J, Fan S B, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 Novel Coronavirus Pneumonia (NCP). BMJ-British Medical Journal 2020, in press.
24. Jiang WW, Qian Y. Advances in the mechanisms of anti-inflammation, immune-regulation and the safety researches of Artemisinin and its derivatives. Immunological Journal 2019, 35: 630-636 +886. (Chinese)