

Potential Effects of Traditional Chinese Medicine on COVID-19 and Cardiac Injury: Mechanisms and Clinical Evidence

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Abstract: Coronavirus disease 2019 is a “Public Health Emergency of International Concern” from 30 January 2020 to 5 May 2023. While battling Coronavirus disease 2019, the Chinese government has actively promoted the collaborative treatment model of Western medicine and traditional Chinese medicine, and clinical and scientific research has applied appropriate and rigorous methodology. Severe acute respiratory syndrome coronavirus 2 infection may damage the cardiovascular system via an unclarified pathogenic mechanism. The National Health Commission of China recommends ‘three formulas and three medicines’ for the treatment of coronavirus disease 2019, which have been shown to be most effective in the treatments. Data from randomized controlled trials of ‘three formulas and three medicines’ suggested that the traditional Chinese medicine is safe and can alleviate the symptoms of cardiac injury. Therefore, we further evaluate the benefits and safety of traditional Chinese medicine treatment for Coronavirus disease 2019 patients with cardiac injury across the care continuum.

Keywords: traditional Chinese medicine, coronavirus disease 2019, cardiac injury

Introduction

Coronavirus disease 2019 (COVID-19) is a “Public Health Emergency of International Concern” from 30 January 2020 to 5 May 2023.¹ According to the current data, 20–36% of patients with COVID-19 develop acute myocardial injury and have a higher mortality rate than those without cardiac injury, associated with the degree of elevation of the serum cardiac troponin (cTn) concentration.^{2–4} Although the morbidity of cardiovascular disease (CVD) has decreased in recent years, it remains a major healthcare challenge, especially for the elderly.⁵ Patients with COVID-19 and type 1 myocardial infarction have more symptoms and higher cardiogenic shock and mortality compared with the pre-COVID-19 population.⁶ Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes overproduction of inflammatory cytokines, leading to systemic inflammation and multi-organ dysfunction syndrome that severely affect the cardiovascular system. Furthermore, in patients with heart failure (HF), monocytes produce more tumor necrosis factor (TNF)- α and less interleukin (IL)-10 than healthy subjects.⁷ A higher incidence of HF has been observed in patients hospitalized with COVID-19 and in intensive care units (ICU).^{8,9}

Traditional Chinese medicine (TCM) has profound theoretical basis and cultural heritage, and under the guidance of TCM theory, herbal medicines have been used effectively to combat epidemics' infections and save many lives. TCM and conventional Western medicine are both considered mainstream medicine, with the support and promotion of the government of China. In China, there are thousands TCM hospitals and many well-trained TCM practitioners provide TCM treatments and services to patients. TCM service network has been established with the framework of comprehensive Chinese medicine hospitals, specialized Chinese medicine hospitals, Chinese medicine departments of general hospitals, community health service institutions, and community-oriented Chinese medicine outpatient departments and Chinese

medicine clinics. The above measures form a complete traditional medical management system. As an effective means of prevention and treatment of diseases, TCM is consistent with the changes in current health concept and medical mode.

Formulated Chinese medicine has been used in managing previous pandemics, such as SARS-CoV, MERS-CoV, and seasonal epidemics caused by influenza viruses.¹⁰ During the epidemic of COVID-19, the use of herbal medicines for prevention and treatment of various ailments is rising around the world because they are safe and effective, while the demand for medicinal plants has increased significantly.¹¹ According to the literature, three TCM drugs and three herbal formulas Chinese medicines were recommended in the treatment of COVID-19 patients, including Jinhua Qinggan granule, Lianhua Qingwen capsule, Xuanfeibaidu granules, Huashibaidu granules, Xuebijing and Detoxifying Decoction, for these formulated showed the most significant efficacy for COVID-19 patients.¹²

In this article, we reported the possible mechanism and effects of TCM on cardiovascular injury in patients with COVID-19 infection.

Methods

We performed a comprehensive literature search in June 2023 of PubMed, EMBASE, Medline, and “Chinese National Knowledge Infrastructure” focusing on human studies published in English. The main search terms were “coronavirus disease 2019”, “cardiovascular injury”, “SARS-CoV”, “traditional Chinese medicine”, “angiotensin converting enzyme 2”, “inflammation”, “cardiovascular disease”, “chronic heart failure”, “arrhythmia”, and “acute cardiac injury”. The highest quality studies were included in the review, including cohort studies, interventional studies, and meta-analyses. Unpublished and noncommercial publications were excluded.

Possible Mechanism of Cardiovascular Damage in Patients with SARS-CoV-2 Infection and the Effect of TCM

Angiotensin converting enzyme 2 (ACE2) is a functional receptor on cell surfaces, through which virus, including SARS-CoV and SARS-CoV-2, enters the host cells and is highly expressed in the heart.¹³ SARS-CoV-2 causes an intense systemic inflammatory response, and the release of proinflammatory cytokines leads to a diffuse endotheliitis and procoagulant activity, which contributes significantly to both immune and cardiovascular mechanisms behind myocardial injury.^{8,14} SARS-CoV-2 disrupts the balance of ACE/ACE2, cardiovascular tissues, or cells that express ACE2, which ultimately leads to COVID-19 progression, especially in patients with CVD and may exacerbate cardiovascular disease in the short and long term.

Prescription mining and molecular dynamics simulations have shown that the main active component of *Eriobotrya japonica*, 23-trans-p-coumarylformic acid, has the best binding affinity for the recognition interface between SARS-CoV-2 S protein and ACE2. Upon binding with 23-trans-p-coumarylformic acid, the key interactions between the SARS-CoV-2 S protein and ACE2 are almost completely interrupted, and thus, it can play a role in the prevention or treatment of COVID-19,¹⁵ similar effects are also seen after the administration of the TCM Lianhuaqingwen, emodin, and glycyrrhizin acid.^{16–18} Furthermore, network pharmacology has shown that Yinhua Qinggan granules regulate multiple signaling pathways by binding ACE2 to prevent COVID-19.¹⁹ Fifty studies have demonstrated that glycyrrhizin and licorice extract exhibit antiviral activity by disrupting viral uptake into the host cells and destroying the SARS-CoV2 and ACE2 receptor-binding domain.²⁰

Pathological examination of adults who died of COVID-19 shows a large number of inflammatory cells in their organs and tissues and inflammatory infiltration of interstitial monocytes in the myocardium.²¹ Inflammatory cells infiltration increases myocardial cell apoptosis and the release of pro-inflammatory factors causes heart injury.²² Virus-induced cellular autoimmune response results in myocarditis, which lead to myocardial interstitial edema with myocardial and interstitial connective tissue necrosis. Myocarditis may progress to dilated cardiomyopathy.^{23,24} Moreover, approximately 20–30% of patients with COVID-19 develop myocarditis.²⁵ Reducing the number and severity pro-inflammatory cell infiltration and reducing associated edema may help prevent the development of COVID-19 induced heart disease and HF (Figure 1).

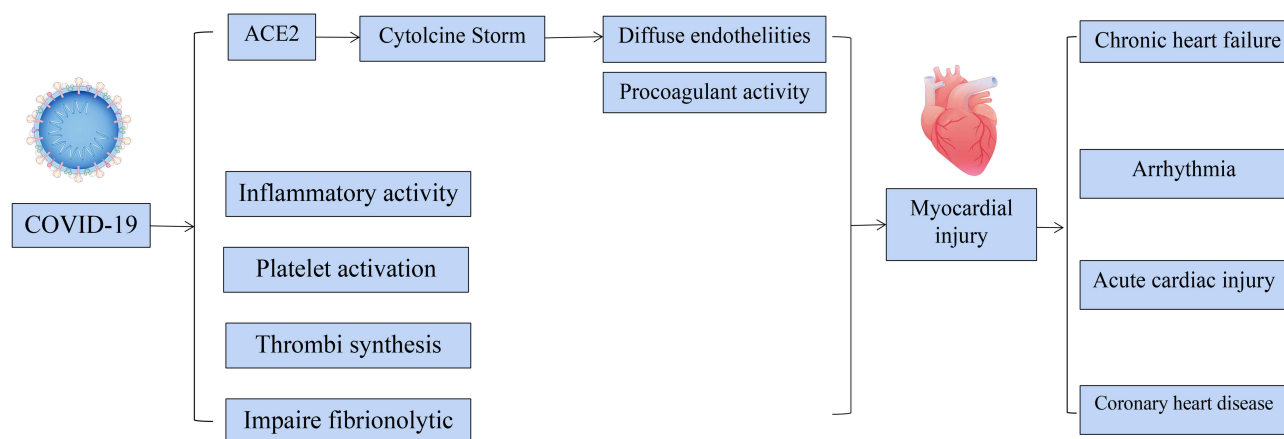


Figure 1 Etiology and Symptoms of Acute Effects of Viral Infection on the Cardiovascular System.

Abbreviation: ACE2, angiotensin converting enzyme 2.

Based on previous literature, after acute infection, inflammatory activity increases, platelet activation, increased thrombi synthesis, and impaired fibrinolytic function have increased myocardial damage.²⁶ In patients with COVID-19, an imbalance in T-helper 1 (Th1) and Th2 responses contributes to the cytokine storm as the most aggressive response to COVID-19, interleukin (IL)-1, IL-6, and IL-17, TNF- α , elevated levels of inflammatory mediators in tissue samples.^{27–29} Cytokines can adversely affect cardiac function by promoting myocardial expression of monocytes, neutrophils, and lymphocytes. The accumulation of inflammatory cells in the heart muscle may impair the heart function, which can lead to HF. In addition, the effects of cytokines may also directly affect cardiac function. Cytokine storms may be related to disease severity and observed effects on the cardiovascular system and cause myocardial damage.^{30,31} Preventing inflammation caused by COVID-19 can help prevent pathological events leading to heart damage.

Administration with “three formulas and three medicines” reduce the level of IL-6 in each clinical stage of COVID-19, which include active ingredients including quercetin, ursolic acid, and rutin.^{32,33} Furthermore, the production of pro-inflammatory cytokines (TNF- α , IL-6, CCL-2, and CXCL-10/IP-10) is markedly reduced by the administration of Lianhuaqingwen³⁴ and Shufengjiedu.³⁵ Computational modeling has shown that berberine significantly inhibits the expression of ACE2, in patients infected with SARS-CoV-2.³⁶ Keguan-1 and Huashi Baidu prescriptions significantly inhibit the severe progression of COVID-19 by decreasing the production of proinflammatory factors.^{37,38}

Possible Effects of TCM on COVID-19 Patients with Cardiovascular Disease

Recent decades have seen remarkable progress in TCM research, and TCM has been shown to play an important role in the treatment of cardiovascular disease. The use of TCM to restore cardiac function has been increasingly studied as a therapeutic strategy for cardiovascular disease (Table 1). Furthermore, there is a correlation between the regulation by TCM and the prevention and control of prevention and control of cardiovascular disease with COVID-19.

Chronic Heart Failure

Patients with chronic heart failure (CHF) are prone to develop acute decompensation after infection with SARS-CoV-2, and the progression is often accompanied by high mortality and disability rates.⁵⁶ Chen et al²⁹ reported that among 99 adult patients with COVID-19, one 61-year-old man with no prior chronic underlying disease died after developing severe HF during treatment. Peng et al⁵⁷ reported that among 112 adult patients with COVID-19 who had CVD, 40 patients developed HF and 13 patients died, indicating that patients with CVD and COVID-19 had a worse prognosis than those without CVD. TCM has many advantages in treating CHF. TCM can regulate the patient as a whole, enhance the physical and immune functions, improve clinical symptoms and quality of life, and prevent re-hospitalization or death from acute episodes of CHF.^{58,59}

Table 1 Mechanism of TCM Treatment of Cardiovascular Disease

Type of Disease	TCM Formulae	Method	Possible Efficacy	Possible Mechanism
Chronic heart failure	Ginseng ³⁹	Vivo model	Enhance cardiac contractility	Increase peroxisome proliferator-activated receptors expression
	Scleroderma of Poria cocos(Hoelen) ⁴⁰	Mice model	Exert diuretic effect and improves cardiac function	Suppress renal aquaporin-2 expression
	Shengmai San-derived ⁴¹	Mice model	Prevent the myocardial infarction induced vulnerable substrate for atrial fibrillation	Inhibit left atrial fibrosis and increase the expression of connexin
	Qi-shen-yi-qi ⁴²	Mice model	Ligation-induced left ventricular remodeling	Attenuate inflammation and fibrosis via STAT3 and NF-κB signaling pathway
	Qili qiangxin ⁴³	Mice model	Inhibit cardiomyocyte apoptosis	Reduce reactive oxygen species and depress the expression of Fas and caspase 3.
	Notoginseng and safflowe ⁴⁴	Metabolomics and pharmacodynamics	Anti-myocardial Ischemia	Attenuate the NF-κB signaling pathway, depress the expressions of TNF-α, IL-6, IL-1β, and PLA2.
Arrhythmia	Que ^{45,46}	Mice model	Inhibit atrial tissue fibrosis	Inhibit the TGF-β/Smads pathway, decrease TLR4 and NF-κB expression
	Pueraria lobata ⁴⁷	Mice model	Maintain the electrical balance on both sides of myocardial cell membrane.	Improve Na ⁺ -K ⁺ -ATPase activity, reduce the damage of oxygen free radicals
	Zhigancao Decoction ⁴⁸	Mice and rabbit model	Reverse the atrial electrical remodeling, lowering the degree of myocardial fibrosis.	Reduce the maximum ascent rate (Max dV/dt) and plateau potential, shorten the action potential duration, reduced COL1A1, COL1A2, COL3A1, and TGF-β1 in myocardial fibrotic tissue and interfere with the expression of COL1A1, COL1A2, COL3A1, and TGF-β1
	Wenxin Keli ⁴⁹	Systems Pharmacology and in vivo	Reduce arrhythmias and shortened RR, PR, and the QT interval	Inhibit p-CaMKII and intracellular Ca ²⁺ transients and overexpressing CNCA1C
	Anlv capsule ⁵⁰	Mice model	Reduce arrhythmias and blocking effect on ion channels in ventricular myocytes	Block effect of L-type calcium channel current
Coronary heart disease	Xuefu Zhuyu Decoction ⁵¹	Metabolomics, network pharmacology and mice model	Reduce the level of autophagy, improving energy metabolism, and maintaining mitochondrial homeostasis	Regulate the expression levels of autophagy-related proteins LC3-B and P62/SQSTM1
	Zhishi Xiebai Guizhi Decoction ⁵²	Network pharmacology and clinical trials.	Anti-inflammatory and treat cardiovascular diseases	Activate PPARγ, regulate TNF, AMPK, PI3K-Akt signaling pathway
	Si-miao-yong-an Decoction ^{53,54}	Network pharmacology, vitro study and mice model	Reduce inflammation, protect the cell injury	Regulate AKT/VEGFA pathway, inhibit TLR4/NF-κB signaling pathway
	Tongmai Yangxin Pill ⁵⁵	Clinical trial, microarray study, bioinformatics analysis and the vitro assays.	Anti-inflammatory, attenuate macrophage foam cell formation	Regulate NF-κB signaling pathway activity

Abbreviations: TCM, traditional Chinese medicine; STAT3, signal transducer and activator of transcription 3; NF-κB, nuclear factor kappa-B; Fas, factor-related apoptosis; TNF, tumor necrosis factor; IL, Interleukin; PLA2, phospholipase A2; TGF-β, transforming growth factor-β; TLR4, Toll like receptor 4; Na, sodium; K, potassium; ATPase, adenosine triphosphatase; TGF-β1, transforming growth factor-β1; PPARγ, peroxisome proliferator activated receptor γ; AMPK, adenosine-monophosphate activated protein kinase; PI3K, phosphatidylinositol 3-kinase.

Qili Qiangxin (QQQX) capsule is a traditional Chinese herbal remedy that is listed by the China Food and Drug Administration as a treatment for CHF that reduces heart rate and reverses ventricular remodeling. QQQX capsule is also reported as a potentially effective treatment in the “Chinese Heart Failure Diagnosis and Treatment Guidelines 2018”.⁶⁰ A randomized trial of 512 patients with CHF who received either placebo or QQQX capsule in addition to their standard medications for the treatment of CHF showed that a reduction in the NT-proBNP concentration of at least 30% was achieved by 47.95% of patients in the QQQX group compared with 31.98% of patients in the placebo group at the 12-week follow-up.⁵⁸ Another randomized trial reported that 90 patients with CHF with a heart function of grade III and IV who were treated with Lixin pill, Lixin pill plus a small dose of digoxin, or an ordinary dosage of digoxin showed total effective rates in improving heart function of 83.3%, 93.3%, and 90.0%, respectively.⁶¹ To observe the effect of Zhuangshenling combined with Western medicine (WM) on cardiac function, 140 patients with CHF were randomly divided into two groups at a 1:1 ratio, all patients received WM therapy, and treatment group additionally received Zhuangshenling. After 12 weeks of treatment, the effective rate of improved cardiac function grading and the BNP concentration were better in the treatment group.⁶² Many Chinese herbs, including *Salvia miltiorrhiza*, *Panax notoginseng*, and *Poria cocos*, can enhance myocardial contractile force, dilate blood vessels, diuresis, and inhibit ventricular remodeling.^{39,40,44,63}

Arrhythmia

Arrhythmia is a potentially life-threatening complication of COVID-19 infection, arrhythmia in 44% of ICU patients.⁶⁴ Drug therapy and artificial pacemaker implantation are two main Western methods to treat tachyarrhythmia. However, there is insufficient evidence for the efficacy of certain drug, and the expenditure of artificial pacemakers is too high to fully meet the clinical needs.⁶⁵ Therefore, it is important to determine timely and effective measures for arrhythmia prevention and economic treatment. There is a high incidence of arrhythmias in COVID-19 patients due to electrolyte and hemodynamic disturbances and high levels of inflammatory stress.^{66–68} The total prevalence of arrhythmia in patients with COVID-19 in China is 16.7%. Recently, many studies have reported that the advantages of TCM in preventing and treating arrhythmia and can reduce the incidence of complications.

Hua et al⁶⁹ conducted an RCT trial to evaluate the efficacy and safety of a TCM called Wenxin Keli (WXKL) for the treatment of premature ventricular contractions (PVCs). A total of 1200 eligible participants were randomly assigned to receive WXKL or placebo in a 1:1 ratio. After the four-week treatment period, the frequency of PVCs was significantly reduced in the WXKL group ($P < 0.001$).

Xin Su Ning (XSN) is the first TCM approved for arrhythmia in accordance with TCM theory in China. A double-blind, placebo-controlled, multicenter clinical trial of XSN involving 861 patients showed that XSN significantly inhibited PVCs.⁷⁰ Another TCM, Shensong Yangxin (SSYX) capsule, has been proven to improve myocardial infarction and arrhythmia.⁷¹ A randomized study of 465 patients with congestive HF showed that SSYX capsule combined with standard treatment suppresses ventricular premature complexes and improves cardiac function.⁷² SSYX capsule inhibits a variety of myocardial ion channels and improves ventricular remodeling and the electrophysiological channel current, thus improving arrhythmia.

Acute Cardiac Injury and COVID-19

COVID-19 can cause acute myocardial damage and chronic damage to the cardiovascular system, which might be related to severity of the disease and the patient’s prognosis.³⁰ Proposed mechanisms of myocardial injury include direct myocardial cell damage, systemic inflammation, myocardial interstitial fibrosis, interferon-mediated immune response, and hypoxia.⁷³

It has been reported that 62.3% (190/305) of patients with COVID-19 had myocardial injury, and that patients with myocardial injury had more electrocardiographic abnormalities and higher concentrations of inflammatory biomarkers than those without.⁷⁴ It is essential to identify patients with COVID-19 combined with myocarditis due to the increased mortality in patients with myocardial inflammation and acute respiratory distress syndrome.⁷⁵ cTnI concentrations are significantly increased in patients with serious COVID-19, research shows that 34.6% of patients with COVID-19 had cardiac injury indicated by an increased cTnI concentration during hospitalization.²⁸ The incidence of acute cardiac

injury is reportedly about 13-fold higher in patients with severe COVID-19 requiring ICU admission compared with patients with milder forms of COVID-19, and at least 8.0% of patients with COVID-19 develop acute cardiac injury.⁷⁶

Tanshinone IIA combined with puerarin can inhibit inflammatory cell concentration and improve hemodynamics by improving cardiac function and reducing myocardial cell destruction.⁷⁷ Network pharmacology and experimental studies have shown that dried ginger-aconite decoction can ameliorate myocardial apoptosis, myocardial ischemia, and reperfusion injury.⁷⁸

Coronary Heart Disease

Patients with COVID-19 with hypertension have a poor prognosis.⁷⁹ The mortality rate is as high as 10.5% in patients with COVID-19 and heart disease in China.⁸⁰ An increasing number of people in China are taking TCM as an adjuvant treatment for CHD because it is economical and readily available. TCM protects the heart from ischemic injury, improving patient quality of life.^{79,81,82}

Tongxinluo (TXL) was registered with the China State Food and Drug Administration.⁸³ TXL has been shown to significantly increase the ejection fraction, promote angiogenesis in the peri-infarct region, protect against pressure overload-induced HF, and substantially decrease fibrosis and the size of the infarcted area.^{84,85} TXL significantly promotes cardiac repair through a novel mechanism involving exosomal transfer of miR146a-5p targeting the IRAK1/NF- κ B p65 pathway. Pretreatment with a single low loading dose of TXL 1 hour before myocardial ischemia attenuates no-reflow and ischemia-reperfusion injury by regulating endothelial nitric oxide synthase via the PKA pathway.⁸⁶ In addition, TXL protects human cardiomyocytes from ischemia/reperfusion injury.⁸³

Wang et al⁸⁷ assessed the clinical efficacy of danlou tablet on angina pectoris of CHD. Sixty-six patients with CHD angina were assigned to the treatment group (treated with danlou tablet + WM, n=33) or the control group (treated with WM, n=33). After 28 days of treatment, the total effective rate in the treatment group (81.2%) was significantly higher than in the control group (43.3%, $P < 0.05$).

Ge et al⁸⁸ performed a multicenter, double-blind, randomized clinical trial to determine the effects of Shexiang Baoxin pill (SXBX) as an aid to optimal drug therapy in patients with stable CAD. From China's 97 hospitals, 2674 patients with stable CAD according to the proportion of 1:1 randomized to the SXBX or placebo group. Both groups received optimal medical therapy in accordance with local tertiary hospital protocols. After 24 months of treatment, the occurrence of major adverse cardiovascular events was reduced by 26.9% in the SXBX group compared with the placebo group. Furthermore, the frequency of angina was significantly reduced in the SXBX group at 18 months ($P=0.0362$). The authors concluded that SXBX is safe and significantly reduces the frequency of angina in patients with stable CAD.

Conclusion

During the novel COVID-19 epidemic, there have been many patients with CVD complicated by COVID-19, viral infection may damage the cardiovascular system via an unclarified pathogenic mechanism. Based on the available investigation, there is a paucity of data on the treatment of SARS-CoV-2 infection in people with cardiac injury by TCM. In this review, based on the available evidence and the latest research, we comprehensively evaluated the impact of TCM in people with SARS-CoV-2 infection and cardiac injury, as well as the possible mechanisms of each process. TCM had a role to play at all stages of viral infection, and the core principles and practices of TCM remain the same, with treatment being adjusted according to different patterns on the basis of the national protocol. Early TCM intervention helped to reduce progression to serious disease, especially for the elderly. For patients with mild or moderate, TCM intervention including TCM medicines combined with specific acupuncture, moxibustion, transdermal therapy, and Tai Chi exercises can shorten the time to resolution of symptoms and viral clearance. For patients with severe disease and in a critical condition, TCM intervention was applied as an accompaniment to conventional medicine, it was noted that the proportion of patients progressing to severe disease appeared to be reduced among those receiving TCM. During the convalescence stage, TCM interventions were reported to improve the quality of life and clinical symptoms, such as anorexia and fatigue. Patients with CVD may be at greater risk of severe complications after infection with SARS-CoV-2. Patients with CVDs, such as congestive HF and hypertension, should pay particular attention to virus prevention and avoid infection while adhering to the treatment of basic

diseases. TCM plays an important role in the prevention, treatment, and recovery of CVDs, but it still needs high-level evidence to support.

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Disclosure

The authors declare that there are no competing interests in this work.

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