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Review article

Therapeutic options of TCM for organ injuries associated with COVID-19 and the underlying mechanism

Jia-Li Zhang a, Wen-Xiong Li a, Yue Li a, Man-Sau Wong b,c, Yong-Jun Wang a,d, Yan Zhang a,d,*

a Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
b Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China
c State Key Laboratory of Chinese Medicine and Molecular Pharmacology (Incubation), Shenzhen 518057, China
d Key Laboratory of Theory and Therapy of Muscles and Bones, Ministry of Education, Shanghai 200032, China

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ABSTRACT

Background: Coronavirus disease-2019 (COVID-19) caused by infection with severe acute respiratory coronavirus-2 (SARS-CoV-2) has been spreading rapidly throughout China and in other countries since the end of 2019. The World Health Organization (WHO) has declared that the epidemic is a public health emergency of international concerns. The timely and appropriate measures for treating COVID-19 in China, which are inseparable from the contribution of traditional Chinese medicine (TCM), have won much praise of the world.

Purpose: This review aimed to summarize and discuss the essential role of TCM in protecting tissues from injuries associated with COVID-19, and accordingly to clarify the possible action mechanisms of TCM from the perspectives of anti-inflammatory, antioxidant and anti-apoptotic effects.

Methods: Electronic databases such as Pubmed, ResearchGate, Science Direct, Web of Science, medRxiv and Wiley were used to search scientific literatures.

Results: The present review found that traditional Chinese herbs commonly used for the clinical treatment of organ damages caused by COVID-19, such as Scutellaria baicalensis, Salvia miltiorrhiza/Salvia miltiorrhiza, and ginseng, could act on multiple signaling pathways involved in inflammation, oxidative stress and apoptosis.

Conclusion: TCM could protect COVID-19 patients from tissue injuries, a protection that might be, at least partially, attributed to the anti-inflammatory, antioxidant and anti-apoptotic effects of the TCM under investigation. This review provides evidence and support for clinical treatment and novel drug research using TCM.

Abbreviations: ACE2, angiotensin converting enzyme-2; Ang-(1-7), angiotensin (1-7); AS-IV, Astragaloside IV; AMPK/Nrf2, adenosine 5′-monophosphate (AMP)-activated protein kinase/nuclear factor(NF)-erythroid-derived 2(E2)-related factor 2; ARDS, acute respiratory distress syndrome; Bax, BCL2-associated X protein; Bcl-XL, recombinant human B-cell leukemia/lymphoma 2 XI; Bcl-Xs, recombinant human B-cell leukemia/lymphoma 2 Xs; caspase-3, cysteine aspartate specific proteinase-3; COVID-19, Coronavirus disease-2019; COX-2, cyclooxygenase-2; CP, Codonopsis pilosula polysaccharide; CAT, catalase; DOX, doxorubicin; ERK 1/2, extracellular signal-regulated kinase 1/2; Fox/Fasl, factor associated suicide/factor associated suicide ligands; GCSF, granulocyte colony stimulating factor; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase-1; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HUVEC, human umbilical vein endothelial cell; IL-1β, interleukin-1β; IL-17, interleukin-17; IL-8, interleukin-8; IFN-γ, interferon-γ; IP10, 10 kDa interferon-gamma-induced protein; IL-6, interleukin-6; JAK2, just another kinase 2; JNK, c-Jun N-terminal kinase; KLF4, Kruppel-like factor 4; LPS, lipopolysaccharide; LT, Lonicerajaponica Thunb; NLRP3, NLR family pyrin domain 3; NF-eB, nuclear factor-kappa B; NO, nitric oxide; NQO-1, NADPH dehydrogenase quinone-1; Nox4/Smad2, NADPH oxidase 4/Smad-mad 2; MARCH5, membrane-associated RING-CH5; MERS, Middle East Respiratory Syndrome Coronavirus; MCP1, monocyte chemotactic protein 1; MIP-1α, macrophage inflammatory protein-1α; MDA, malondialdehyde; PTEN-PDK1-Akt-mTOR, gene of phosphate and tension homology deleted on chromosome ten-3-phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; PGE2, prostaglandin E2; P38K/Akt/FoxO3a, phosphatidylinositol 3-kinase/protein kinase B/Forkhead box O3a; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory coronavirus-2; SARS, severe acute respiratory syndrome; STAT3, signal transducer and activator of transcription signaling 3; SOD, superoxide dismutase; TCM, traditional Chinese medicine; TNF-α, tumor necrosis factor-α; TAK-1, tanhoshine IA; TLR4-MD8β, toll like receptor 4-myeloid differentiation primary response gene 88; WHO, World Health Organization; XST, Xuesaitong; 8-OHdG, 8-hydroxy-2′-deoxyguanosine.

* Corresponding author: Room 908, #12 Building, 725 South Wanping Road, Shanghai 200032, China
E-mail address: medicineyan.aliyun.com (Y. Zhang).

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1. Introduction

A novel coronavirus infection in severe acute respiratory syndrome (SARS), named coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) (World Health Organization, 2020a), has been spreading rapidly to the whole of China and other countries since the end of 2019. Data from the WHO show that there are more than 83000 confirmed cases in 49 countries/regions, and 78959 confirmed cases, including 2791 deaths by February 28, 2020 in China (World Health Organization, 2020b). The total number of COVID-19 cases worldwide has already far outnumbered that of SARS in 2003, clearly showing the present epidemic is a major global threat to public health (Roosa et al., 2020).

The source of infection and intermediate host of COVID-19 are not yet identified. Studies found that severe acute respiratory coronavirus-2 (SARS-CoV-2) is 96% identical at the whole-genome level to the Chinese horseshoe bat coronavirus, thus, they conjectured that the Chinese horseshoe bat might be the natural host of the novel coronavirus (Zhou et al., 2020). Pangolins (Li et al., 2020c), snakes (Ji et al., 2020), mink (Guo et al., 2020) and turtles (C. picta bellii, C. mydas, and P. sinensis) (Liu et al., 2020) are all potentially considered as intermediate hosts.

SARS-CoV-2 infects lung alveolar epithelial cells by binding the spike protein (S) to angiotensin-converting enzyme-2 (ACE2) (Huang et al., 2020; Li et al., 2020; Li et al., 2019; Zhou et al., 2020), reducing the level of ACE2 and the production of active peptide angiotensin-(1-7) [Ang-(1-7)] in the lung and the whole body to induce lung injury and multiple organ damage, which are attributed to the possible pathological mechanisms such as inflammation, oxidative stress and apoptosis. Since there are not yet any vaccines or drugs approved to fight against SARS-CoV-2, the Chinese government has decided to apply complementary and alternative medicine to treat COVID-19 by using TCM, which functions effectively in organ protection via anti-inflammatory, antioxidant and anti-apoptotic actions (Li et al., 2018; Liu et al., 2018a; Yang et al., 2019a). Preliminary clinical studies showed the beneficial effects of TCM decoction on COVID-19 (Ling, 2020) as indicated by the shortening of hospitalization duration and the reduction in the number of mild and moderate cases developed into severe ones (Luo et al., 2020).

A study has shown that serious complications are more likely to occur in COVID-19 patients who simultaneously suffer from other chronic diseases (Cao et al., 2020). The high incidence of acute organ injury closely contributed to the increased mortality rate (Cao et al., 2020; Wang et al., 2020a). Inflammatory storm, oxidative stress, and apoptosis are important hallmarks of the transition of COVID-19 patients from mild to severe or even critical periods, and these mechanisms greatly increase the risk of organ damage, especially for patients with chronic diseases (Qin et al., 2020). Therefore, this review will discuss the protective effect of TCM recommended in China on visceral from the perspectives of inflammatory storm, oxidative stress and apoptosis.

2. Medication recommended in China

Monoclonal antibodies, interferon therapies, and small molecule drugs are commonly used in Western medicine to combat HIV, HBV, and MERS (Li and Clercq, 2020), but the long-term usage of these drugs is often accompanied by low selectivity and adverse side effects. A report recently published in The Lancet demonstrated no significant clinical improvement in severe COVID-19 patients treated with remdesivir as compared with the placebo-controlled group, indicating the limitation of the application alone with western medicine (Wang et al., 2020b). The Chinese National Health Commission has figured out an essential strategy, a combination of TCM and Western medicine, to combat COVID-19, and successively published seriate versions of the diagnosis and treatment protocol. This section will start with the latest version (Trial Version 7) of the Diagnosis and Treatment Protocol for COVID-19 (in short "the Protocol") (National Health Commission of the People’s Republic of China, 2020), and introduce TCM formulas and Chinese patent medicine recommended for each developing stage of COVID-19 in the Protocol (Table 1). COVID-19 can be roughly divided into three stages, the medical observation stage, the clinical treatment stage and the stage of convalescence. The treatment stage is further subdivided into mild, moderate, severe and critical based on the severity of the disease.

In the medical observation stage, patent Chinese medicine such as Huoxiang Zhengqi capsules (symptom with fatigue and gastrointestinal upset) or Lianhua Qingwen capsules (symptom with fever and weakness) are administered to suspected COVID-19 patients. In the clinical medication stage, patients of mild COVID-19 often have mild fever and respiratory symptoms. The recommended decoction mainly includes single Chinese herb such as Magnolia officinalis, Scutellaria baicalensis, and licorice. Patients of moderate COVID-19 with mild fever and exacerbated respiratory symptoms are recommended to be prescribed with medicine such as licorice, Magnolia officinalis and Astragalus membranaceus. Patients of severe COVID-19 with respiratory symptoms manifested as respiratory distress are recommended to take TCM and herbal decoction including Rheum officinale, Salvia miltiorrhiza, Astragalus membranaceus, Lonicera japonica Thunb, Magnolia officinalis, and licorice. For the critically ill patients who are characterized by respiratory failure, auxiliary ventilation is required. At this stage, the joint use of TCM decoction and patent Chinese medicine will achieve better therapeutic efficacy (National Health Commission of the People’s Republic of China, 2020).

In accordance with the clinical observations of doctors in various locations, the Qingfei Paidu decoction recommended by the Protocol is applicable to mild, moderate and severe cases, and could also be used in critically ill patients in consideration with their actual conditions. Qingfei Paidu decoction is a combination of Chinese prescriptions that include Maxing Shigan decoction, Shegan Mahuang decoction, Xiao Chaihu decoction, and Wuling powder. Its broad application in different stages of COVID-19 stems not only from the combination of various Chinese prescriptions, but also from its acting on multiple potential targets through distinct intervention pathways. Patients who had repeated fever and cough with obscure respiratory rules of both lungs before receiving this treatment had their body temperature returned to normal on the night of the administration of Qingfei Paidu decoction and chest CT scan showed improvement after 6 days of treatment (Zhang and Zhu, 2020). The total effective rate for confirmed COVID-19 patients using this prescription in the 4 pilot provinces of China is over 90% by February 6, 2020 (National Administration of Traditional Chinese Medicine, 2020).

Convalescence is a period when a patient has just recovered from illness and is recuperating while the body is still weak. Intervention of TCM at this point could help patients speed up their recovery. The Protocol recommends the application of Salvia miltiorrhiza, licorice and so on in this stage (National Health Commission of the People’s Republic of China, 2020).

TCM and Chinese patent medicine have contributed a lot in combating with the SARS-CoV in 2003 by their antiviral and immunomodulatory effects (Luo et al., 2020). Some of the traditional herbs recommended in the Protocol possess antiviral property, such as Lonicera japonica Thunb, Scutellaria baicalensis, Astragalus membranaceus, and Salvia miltiorrhiza (Chen et al., 2020b). The underlying antiviral mechanisms can be roughly divided into the following two: (1) direct interaction with viruses. Based on TCM principles, most of the herbs exert heat-clearing and detoxifying properties, such as Lonicera japonica Thunb and Scutellaria baicalensis; (2) indirect antiviral effect or inhibition of virus-mediated inflammatory response via modulating immune function, such as Astragalus membranaceus and Salvia miltiorrhiza. However, the use of antiviral herbal medicine only could not effectively prevent tissue injuries due to inflammatory storm, oxidative stress or apoptosis caused by excessive immune response associated with COVID-19. Thereafter, we will discuss the protective effects of TCM on...
organ damages from the anti-inflammatory, antioxidant and anti-apoptosis perspectives.

TCM theory demonstrates that traditional herbal medicine pays special attention to the overall regulation of the body and the differentiation of clinical syndromes (Fan et al., 2020). The decision which particular TCM formula and/or Chinese patent medicine is to be used is based on the specific Chinese medicine syndrome associated with disease. Therefore, compared with the use of single TCM compound, TCM special attention to the overall regulation of the body and the differentiation of clinical syndromes associated with cytokine storm begins at a local site and spreads to the whole body via the systemic circulation (Medzhitov, 2008).

3. Mechanisms of TCM function in treating COVID-19

3.1. Anti-inflammatory effect of TCM

The inhibition of lymphocytes by TCM in severe COVID-19 patients was shown by the lowered CD4+ T and CD8+ T, both of which are closely associated with the inflammation (Wan et al., 2020). Patients infected with SARS-CoV-2 had higher concentrations of IL-1β, IL-7, IL-8, IFN-γ, IP10, and MCP1 than those in healthy adults. Moreover, severe COVID-19 patients showed higher circulating levels of GCSF, IP10, MCP1, MIP1A, and TNF-α, suggesting that cytokine storm had occurred during the development of COVID-19 (Huang et al., 2020). Inflammation associated with cytokine storm begins at a local site and spreads to the whole body via the systemic circulation (Medzhitov, 2005).

According to the Protocol, Chinese herbs with anti-inflammatory activity such as Rheum officinale, Scutellaria baicalensis, patchouli, ginseng, Salvia miltiorrhiza, and gypsym, are clinically applied to treat COVID-19 (Table 2) (National Health Commission of the People’s Republic of China, 2020). The Lianhua Qingwen capsule recommended in the Protocol could dose-dependently inhibit the mRNA expression of the inflammatory cytokines, such as TNF-α, MCP 1 and IL-6, in host cells infected by SARS-CoV-19 (Li et al., 2020).

Many herb-derived natural products are excellent anti-inflammatory agents. The anti-inflammatory activity of emodin, the biologically active constituent of the Chinese herb Rheum officinale, has been reported using in vitro and in vivo models (Shrimali et al., 2013). It could attenuate IL-1β secretion via the inhibition of the activation of the NLR family pyrin containing domain 3 (NLRP3) inflammasome, a member of the NOD-like receptor family (Xia et al., 2019), and alleviate lipopolysaccharide (LPS)-triggered liver cell inflammatory injury by suppressing NF-κB pathway (Xie et al., 2019). Baicalein, another herbal monomer isolated from the root of Scutellaria baicalensis, possesses many pharmacological effects including anti-inflammatory activity (Dinda et al., 2017) as shown by its repressing of caerulein-induced pancreatic injury and macrophage infiltration through inhibiting the phosphorylation of TLR4-MyD88-NF-κB pathway and regulating production of cytokines, including NO, PGE2, TNF-α, and IL-6, in an intervertebral disc degeneration model (Jin et al., 2019). In addition, ginsenoside Rf1, one of the active saponins found in ginseng, significantly decreased the level of IL-1β, IL-6 and TNF-α in an incisional pain model (Kim et al., 2018). Furthermore, tanshinone IIA (Tan IIA), a well-known flavonoid ingredient of Salvia miltiorrhiza, elicited an important therapeutic effect by inhibiting inflammatory response (Zheng et al., 2014). An early study indicated that Tan IIA exerted anti-inflammatory effect by deactivating TLR4-MyD88-NF-κB signaling pathway and regulating production of cytokines such as TNF-α, IL-1β and COX-2 in LPS-induced RAW264.7 cells (Pan et al., 2016).

3.2. Antioxidant effect of TCM

The balance between oxidation and antioxidation plays an important role in the regulation of signal transduction, cell proliferation and apoptosis (Forrester et al., 2018). When the balance is destroyed by stress, virus or other factors, oxidative stress response will be stimulated (Forrester et al., 2018). The excessive immune response associated with COVID-19 might largely promote the production of free radicals, consequently the over-accumulation of oxidative free radicals, leading to tissue injury and organ damage. The Protocol recommends the application of kinds of traditional Chinese herbs to inhibit oxidative stress stimulated by SARS-CoV-2, as many herbs such as Codonopsis pilosula, Glycyrrhiza glabra roots, Astragalus membranaceus, Lonicera japonica Thunb, and Forsythiae Fructus contain naturally-occurring bioactive components that exert anti-oxidative effects (National Health Commission of the People’s Republic of China, 2020).

Astragaloside IV (AS-IV), an active compound from Astragalus

### Table 1
Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7).

| Patient type       | Period               | Syndrome differentiation                              | Main medication                                           |
|--------------------|----------------------|-------------------------------------------------------|-----------------------------------------------------------|
| Confirmed patients | Medical observation  | Fatigue with gastrointestinal discomfort Fatigue with fever | Huaxiang Zhengy Capsule (Pill; Liquid; Oral liquid)        |
|                    | Clinical treatment   | Cold-damp constraint in the lung pattern Damp-heat accumulation in the lung pattern | Magnolia officinalis, Licorice, etc.                       |
|                    | Mild                 | Damp-heat blocking the lung pattern                   | Scutellaria baikalensis, Magnolia officinalis, etc.        |
|                    | Moderate             | Damp-toxin constraint in the lung pattern              | Licorice, Semen lepidil, Ephedra herb, etc.                |
|                    | Severe               | Cold-damp obstructing the lung pattern                 | Magnolia officinalis, Atractylodes rhizome, etc.           |
|                    | Critical             | Epidemic toxin blocking the lung pattern               | Licorice, Rhexum officinale, etc.                         |
|                    | Blazing of both qi and ying pattern | Internal blockage and external desertion pattern | Salvia miltiorrhiza, Captis chinesis, etc.                  |
|                    | Convalescence        | Lung-spleen qi deficiency pattern                      | Codonopsis pilosula, Astragalus membranaceus, etc.        |
|                    |                      | Deficiency of both qi and yin pattern                  | Salvia miltiorrhiza, Salvia miltiorrhiza, Ophiopogonis radix, etc. |

### Table 2
Potential active components in traditional Chinese herbs used for treatment of COVID-19.

| No. | TCM                          | Active component                          |
|-----|------------------------------|-------------------------------------------|
| 1   | Rheum officinale             | Emodin                                    |
| 2   | Scutellaria baikalensis      | Baicalein                                 |
| 3   | Ginseng                      | Ginsenoside Rf                            |
| 4   | Salvia miltiorrhiza          | Tanshinone IIA                            |
| 5   | Magnolia officinalis         | Magnolol                                   |
| 6   | Astragalus membranaceus      | Astragaloside IV, Astragalus polysaccharide |
| 7   | Codonopsis pilosula          | Codonopsis pilosula polysaccharide         |
| 8   | Lonicera japonica Thunb      | Neohelvogenic acid                        |
| 9   | Pseudo-ginseng               | Panax notoginseng saponins                 |
| 10  | Rhodiola crenulata           | Rhodiola polysaccharide                   |
membrane, pharmacologically displays anti-oxidative stress effects (Qiu et al., 2010). A research study found that AS-IV (20 mg/kg) effectively attenuated the expression of 8-hydroxy-2’-deoxyguanosine (8-OHdG) (a maker of oxidative damage in intact DNA) in both glomeruli and tubules, decreased the malondialdehyde (MDA) level and enhanced the superoxide dismutase (SOD) activity associated with indoxyl sulfate-induced tubulointerstitial injury (Ji et al., 2018), as well as displayed therapeutic potential in prevention of dementia caused by cerebral hypoperfusion, suggesting that the ameliorating effect of AS-IV on learning and memory deficits might be attributed to its suppressive effect on neuronal apoptosis and oxidative damage in the hippocampus (Kim et al., 2015). Moreover, AS-IV possessed antioxidant properties, including increasing SOD activity and reducing reactive oxygen species (ROS) generation and lipid peroxidation, consequently protecting against ischemic brain injury (Li et al., 2012; Qu et al., 2009). Codonopsis pilosula polysaccharide (CP), a bioactive component in Codonopsis pilosula, enhanced the content of SOD and glutathione peroxidase (GSH-Px) in the liver and reduced the level of TNF-α in serum of mice with hepatic injury induced by baclelle-calmette-guerin/LPS (Liu et al., 2015). In addition, the effective chemicals in Salvia miltiorrhiza (Wang et al., 2016) and Loniceraja japonica Thunb (LJT) (Guo et al., 2018) could increase activities of SOD, catalase (CAT) and GSH-Px in serum, and decrease the generation of ROS in doxorubicin (DOX)-induced acute cardiotoxicity animals and hyperlipidemia rats. In brief, TCM may improve organ injury by activating the activity of antioxidant enzymes and inhibiting oxidative stress caused by various inducers.

Furthermore, pretreatment with Tan IIA induced the nuclear accumulation of Nrf2 and triggered the expression of its downstream gene heme oxygenase-1 (HO-1) and NADPH dehydrogenase quinone-1 (NQO-1) in both mice cardiac tissue and H9c2 cells (Guo et al., 2018). Nrf2/HO-1 signaling was also affected by the water extract of Forsythiae Fructus which suppressed inflammation and disrupted inflammatory signaling cascade (Lee et al., 2018). Baiacalin protected against LPS-induced severe lung injury by activating an antioxidant system and reducing both the number of inflammatory cells and expression of mediators via the Nrf2/HO-1 signaling pathway (Meng et al., 2019). Moreover, it exerted beneficial effect on lung function as shown by anti-airway remodeling through regulating the release of proinflammatory cytokine in long-term cigarette smoke-induced chronic obstructive pulmonary disease model (Wang et al., 2018). Neochlorogenic acid isolated from LJT, an activator of AMPK/Nrf2 signaling, prevented excessive macrophage-mediated responses associated with acute and chronic inflammatory disorders (Park et al., 2018). Thus, previous studies revealed that the Nrf2-mediated HO-1 signaling pathway might be a crucial antioxidant target. Collectively, activation of the antioxidant enzymes activity and Nrf2/HO-1 signaling pathway is potentially recognized as one of the anti-oxidant mechanisms involved in the treatment of COVID-19 using TCM.

### 3.3. Anti-apoptotic effect of TCM

A study on clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan (China) indicated that among the 710 patients with COVID-19, most patients had organ function damages, including 35 with acute respiratory distress syndrome (ARDS), 15 with acute kidney injury, 12 with cardiac injury, and 15 with liver dysfunction (Yang et al., 2020b). Recently multiple lines of evidences pointed to the idea that renal impairment was common in COVID-19 patients, a condition that might lead to multi-organ failure and death eventually (Li et al., 2019b). Studies have shown that the progression of various diseases such as ARDS, heart failure, chronic kidney disease and liver injury are closely related to apoptosis.

The apoptosis of pulmonary capillary endothelial cells and alveolar epithelial cells worsened the structural integrity and function of the alveolar-capillary barrier, and eventually resulted in pneumonia and ARDS (Hu, 2018). Apoptosis was also in the pathogenesis of heart failure (Sabbah and Sharov, 1998). Apoptosis of podocytes could lead to proteinuria and the development and progression of glomerulosclerosis and renal fibrosis (Cao et al., 2016; Chuang et al., 2011). Liver injury was also associated with dysregulation of hepatocyte apoptosis (Wang, 2015). Current research studies have found that 3 signaling pathways (Fig. 1) are involved in apoptosis, they are the exogenous apoptosis pathway induced by death receptors, endogenous apoptosis pathway mediated by mitochondria, and endoplasmic reticulum stress (Marriott et al., 2006; Zhao et al., 2013).

Among the various intervention guidelines on the use of TCM issued in different Chinese regions after the spread of COVID-19, Astragalus membranaceus is recommended in 13 prevention programs with the aim to reinforce vital Qi. Scutellaria baicalensis, Magnolia officinalis, Pseudo-ginseng, and Rhodiola crenulata are also usually used in different prescriptions (Xu et al., 2020).

It was found that Astragalus membranaceus and its active component (Astragalus polysaccharide, AP) and compound (AS-IV) could protect against multiple-organ damages induced by apoptosis. AP could inhibit mitochondrial-mediated apoptosis and reduce cell damage by mediating the PI3K/Akt/FoxO3a signaling pathway (Li and Yang, 2017); it could also decrease hepatocytes apoptosis caused by oxidative stress (Li, 2018b). AS-IV dose-dependently inhibited the rise in apoptosis induced by oxidative stress in renal podocytes (Xiao et al., 2013), and prevented human umbilical vein endothelial cell (HUVEC) apoptosis by inhibiting Nox4 expression through the Nox4/Smad2 pathway (H2O2-induced cell apoptosis) (Ma et al., 2015; Zhang et al., 2020b). Baicalein protected cardiomyocytes by decreasing oxidative stress, myocardial inflammatory responses and apoptosis associated with LPS-induced sepsis (Lee et al., 2011). It could also stabilize MARCH5 expression by upregulating expression of KLF4, and in a sequence promote mitochondrial fusion, stabilize mitophagy and reduce apoptosis, suggesting that baicalein could significantly attenuate apoptosis induced by oxidative damage (Li et al., 2020a). Additionally, studies showed that triptolide exerted its protective effect via inhibiting apoptosis and restoring of survivor, on podocytes with exposure to puromycin aminonucleoside, which could induce apoptosis by increasing protein expression of caspase-3 and Bax (Yang et al., 2019). Magnolol, a purified single compound from Magnolia officinalis, showed anti-apoptotic effect by protecting the liver from warm ischemia-reperfusion injury through upregulation of mRNA expression of the anti-apoptotic factor Bcl-XL and suppression of gene expression of Bcl-Xs (Jawan et al., 2003). Taken together, the active ingredients from TCM recommended in the Protocol could inhibit mitochondrial pathway-involved apoptosis.

AS-IV could suppress apopotic and inflammatory responses in HUVECs upon to the stimulation with high glucose by inhibiting the JNK signaling pathway (You et al., 2019). Xuesaitong (XST), a TCM pharmacological preparation consisting of total saponins from the root of Pseudo-ginseng, could effectively treat patients with cerebrovascular diseases by inhibiting the overload of Ca2+ in brain cells, stabilizing cell membrane and protecting the brain from ischemia/reperfusion damage (Zhong et al., 2005). XST attenuated ischemic stroke in mice through regulating microglial phenotypes and decreasing apoptosis of neuronal cells (Li et al., 2019a). Moreover, treatment with XST ameliorated podocyte apoptosis in diabetic rats partly through modulation of PTEN-PDK1-Akt-mTOR pathway and Nox4 expression, which might point to a novel natural therapeutic way to cure diabetic nephropathy (Xue et al., 2020). Thus, inhibition of endoplasmic reticulum stress is one of the mechanisms by which TCM exerts its anti-apoptotic actions.

Study indicated that aging induced by D-galactose could trigger marked neuronal apoptosis through activation of extrinsic-dependent apoptotic pathways. Intriguingly, Rhodiola crenulata protected against neurotoxicities which could stimulate the apoptotic pathways in aging brain (Chen et al., 2020a). Furthermore, Rhodiola polysaccharide could reduce the apoptosis of bone marrow cells and promote the recovery of its hemopoietic function by affecting Fas/FasL-caspase-3 apoptosis signal pathway (Li et al., 2008a), which was also involved in apoptosis.
associated with jaundice hepatitis. Rhubarb exerted its therapeutic efficacy in patients with jaundice hepatitis by regulating the Fas/FasL system (Huang et al., 2008). Ligustrazine could repress Fas/FasL axis to inhibit hepatocyte apoptosis, consequently improving CCl₄-induced liver fibrosis in rats (Li et al., 2008b). Additionally, polysaccharide from lycium barbarum modulated the apoptosis of brain cells by inhibiting the expression of Fas; it also played a role in improving brain functional memory (Cai et al., 2005). Therefore, traditional Chinese herbs and active components recommended in the Protocol could suppress apoptosis through mediating the death receptor pathway.

4. Outlook

Since 2003, TCM has played a significant role in combating viruses such as SARS-CoV, MERS-CoV and Ebola virus (Chen and Nakamura, 2004). TCM has received much attention due to its multi-component, multi-target properties, and multi-pharmacological effects. The National Health Commission of the People’s Republic of China emphasized the concept of TCM and Western Integrative Medicine. Various herbal formulas and active components of TCM have certain potential in treating COVID-19 via differential pharmacological mechanisms (Fig. 2). Amount of evidences supported the therapeutic efficacy of TCM in improving the clinical symptoms of COVID-19, while, the underlying mechanisms behind the antiviral effects, especially in models infected with SARS-CoV-2, the immunomodulatory response in host cells, and the inhibitory effects on cytokine inflammatory storm, etc., remain elusive. Moreover, the screening for candidate naturally-occurring component from TCM should be further carried out and the novel compatibility with active components will be further developed based on the exploration of substance basis and the clarification of pharmacological mechanism. Importantly, multicenter studies with rigorous randomized controlled trials need to be performed to provide more clinical evidences of the clinical effectiveness of TCM.

Author contributions

Zhang Jia-li: Methodology, Writing-Original draft and image preparation. Li Wen-xiong: Investigation and drafting. Li Yue: Writing-Original draft. Wong Man-sau: Reviewing and Editing. Wang Yongjun: Conceptualization and Supervision. Zhang Yan: Conceptualization, Writing-Reviewing and Editing.

All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.
Fig. 2. Therapeutic mechanisms of TCM on organ damages associated with COVID-19. The bioactive compounds and components of TCM, baikaline, ginsenoside Rf, Tan-IIA, emodin, water extract of FF, neochlorogenic acid, CP, AS-IV, puerarin, magnolol and PNs, are presented to illustrate the therapeutic mechanisms of TCM.

Declarations of Competing Interest

None.

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