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Multi-effective characteristics and advantages of acupuncture in COVID-19 treatment

Lifen Wang[1], Xiyou Hu[1], Lianqi Geng[2], Ningcen Li[1], Yong Chen[1], Jingyu Zhang[1], Xinru Yuan[1], Lihong Huang[1], Dongsheng Ba[1], Jinyu Lian[1], Xiaoyan Lyu[1], Zelin Chen[1,3,4], Yue Zhang[5,*], Bo Chen[2,3,*]

Abstract

Coronavirus disease 2019 (COVID-19) is a major disease that threatens human life and health. Its pathogenesis is complex and still not fully clarified. The clinical treatment is mainly supportive and lacks specific treatment methods. Acupuncture treatment can inhibit immune inflammatory reactions, neuroinflammatory reactions, oxidative stress levels, and hypothalamus-pituitary-adrenal (HPA) axis activity, improve lung function, and relieve migraine, fatigue, anxiety, and depression. However, whether acupuncture treatment is suitable for treating these symptoms in patients with COVID-19 still needs to be investigated. For this review, the literature was systematically searched for multiple databases to summarize the mechanisms of acupuncture treatment for COVID-19-related symptoms and complications. A complex network analysis of acupoints and symptoms was also performed to clarify acupoint selection in the acupuncture treatment of symptoms related to COVID-19. The evidence indicates that acupuncture can improve the respiratory, digestive, nervous, and mental and psychological symptoms related to COVID-19 by inhibiting immune inflammatory reactions, regulating intestinal flora, mitochondrial function, oxidative stress level, cardiomyocyte apoptosis, neurotransmitter release, and HPA axis activity, and alleviating basic diseases such as diseases of the vascular system. Acupuncture can improve various clinical and concomitant symptoms of COVID-19; however, its mechanism of action is complex and requires further study.

Keywords: Acupuncture, COVID-19, Inflammatory factor storm, Multi-efficiency

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Introduction

Coronavirus disease 2019 (COVID-19) is an acute infectious pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly contagious and universal susceptibility in the population. Most infected individuals have mild symptoms and recover well, whereas those with severe disease develop severe pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), or multiple organ failure and death[1]. According to official data from the World Health Organization, as of December 18, 2022, the cumulative number of confirmed COVID-19 cases worldwide exceeded 649 million, with more than 6.6 million deaths and a mortality rate of 1.02%. Therefore, the COVID-19 pandemic has become a public health emergency of international concern[2]. In many cases, patients with COVID-19 do not die of the infection, but from the inflammatory disease that follows the infection. An "inflammatory factor storm," also known as "cytokine storm syndrome," is an important factor in the rapid deterioration and even death of patients with COVID-19[3]. Following the invasion of the body, the virus causes a loss of the negative feedback of immune regulation and abnormal elevation of multiple cytokines, which activate and recruit more immune cells, causing diffuse damage to pulmonary capillary endothelial cells and alveolar epithelial cells and massive exudate obstruction of the airway, finally resulting in ARDS. Subsequently, cytokines enter the bloodstream and circulate throughout the body, causing further single-organ or multiple organ damage and failure[4]. As the pandemic progresses, several countries around the world have issued treatment guidelines or guidance for COVID-19. *The COVID-19 Treatment Guidelines* issued by the National Institutes of Health on January 26, 2023[5], and *the COVID-19 Diagnosis and Treatment Plan (Trial Version 10)* issued by the Health Commission of China[6] are consistent in terms of overall treatment principles and improving

Lifen Wang and Xiyou Hu contributed equally to this work.

[1] Research Center of Experimental Acupuncture Science, Tianjin University of Traditional Chinese Medicine, Tianjin, China; [2] School of Acupuncture & Moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, Tianjin, China; [3] Fourth Teaching Hospital of Tianjin University of TCM Binhai New Area Hospital of TCM Tianjin,Tianjin, China; [4] National Clinical Research Center of Traditional Chinese Medicine and Acupuncture, Tianjin, China; [5] Department of Neurosurgery, University of Pennsylvania, Philadelphia, the United States of America

**Corresponding author: Bo Chen, School of Acupuncture & Moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; Fourth Teaching Hospital of Tianjin University of TCM Binhai New Area Hospital of TCM Tianjin, Tianjin 300451, China, E-mail: tjutcmchenbo@163.com; Yue Zhang, Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA 19104, USA, E-mail:yue.zhang@pennmedicine.upenn.edu.*

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patients' symptoms through antiviral, immunosuppressive, and hormonal therapy, as well as corresponding organ supportive therapy. Currently, clinical treatment mostly involves symptomatic supportive treatment, as long-term medication could aggravate immunosuppressive conditions, toxic side effects on the heart, and the burden on the liver and kidneys in the later stages of the disease[3,7]. There is no suitable Western medicine for injuries to multiple organs caused by cytokine storm, nor for anxiety, depression, insomnia, and other symptoms after the disease. Re-administration of medication may cause secondary injury to patients owing to side effects[8–9]. Therefore, it is necessary to seek new treatment strategies, especially for high-risk groups such as older patients with cardiovascular and other basic diseases.

Since the outbreak of the COVID-19 pandemic, long COVID has become widespread globally. According to World Health Organization statistics, the incidence rate of long COVID is 10%–20%[10]. The pathogenesis of long COVID is extremely complex, including inflammatory reactions[11], immune disorders[12], intestinal flora disorders[13], endothelial dysfunction[14], and other pathophysiological processes caused by SARS-CoV-2. In addition to the respiratory system, the digestive, nervous, and mental systems of patients with long COVID are affected to varying degrees, with cough, dyspnea, headache, diarrhea, anxiety, depression, fatigue, and other sequelae[15].However, extensive and effective treatment methods for long COVID are lacking. Leukotriene receptor antagonists, antiviral drugs, non-steroidal anti-inflammatory drugs, antihistamine famotidine, low-dose naltrexone, coenzyme Q10, and antidepressants are often used in the treatment of long COVID; however, the efficacy of these treatments is uncertain, and long-term use of these drugs will increase the burden on the liver and kidneys, cause gastrointestinal reactions, and aggravate diarrhea, nausea, vomiting, and other symptoms[16–17].

As a non-drug therapy, acupuncture regulates the body's surface have essential characteristics and advantages for preventing and treating long COVID. A systematic review and meta-analysis of 12 randomized controlled trials (RCTs) involving 597 people with advanced dyspnea [347 chronic obstructive pulmonary diseases (COPD), 190 advanced cancer] showed that acupuncture improved dyspnea and quality of life in people with advanced disease[18]. A multi-center RCT involving 150 patients with migraine showed that acupuncture safely reduced the severity of migraine[19]. Other studies found that acupuncture treatment can inhibit immune inflammatory reactions, neuroinflammatory reactions, oxidative stress levels, and hypothalamus-pituitary-adrenal (HPA) axis activity; improve lung function, and relieve migraine, fatigue, anxiety, and depression[20–23].However, whether acupuncture treatment is suitable for the treatment of these symptoms in patients with COVID-19 still needs to be investigated. Therefore, we reviewed the literature to summarize the mechanisms of acupuncture treatment for COVID-19-related symptoms.

We systematically searched for articles published up to July 2022 in PubMed, Web of Science, and Embase, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang Database. The search terms were ("acupuncture" OR "electroacupuncture" OR "auricular points" OR "fire needling" OR "transchannel electrical nerve stimulation" OR "TENS" OR "acupoint injection") AND ("novel coronavirus pneumonia" OR "COVID-19" OR "2019-nCOV" OR "coronavirus release 2019"). Seventeen clinical studies and case reports of acupuncture treatment for COVID-19 were included. See Supplementary Digital Content 1, http://links.lww.com/AHM/A52, for the detailed retrieval strategy. Using Cytoscape 3.6.0 software for the visual display, a complex network analysis was performed of acupuncture points and symptoms related to the respiratory, digestive, nervous, and cardiovascular systems and psycho-psychological disorders of patients with COVID-19. The rules of acupoint selection in the acupuncture treatment of symptoms related to COVID-19 were summarized, and the mechanism of acupuncture treatment was explored. The findings of this review are expected to serve as a reference for clinical decision-making and the application of acupuncture in the prevention and treatment of COVID-19-related symptoms and long COVID sequelae.

Therapeutic role of acupuncture in COVID-19-related symptoms

Acupuncture treatment for COVID-19-related symptoms related to the respiratory, digestive, and nervous systems

COVID-19 is an infectious disease caused by SARS-CoV-2, with the lung as the main target organ. In addition to the typical clinical manifestations of respiratory infections such as fever, cough, expectoration, pharyngalgia, chest tightness, and dyspnea. COVID-19 causes other atypical symptoms such as diarrhea, nausea and vomiting, anorexia, headache, dizziness, and fatigue[24].

Acupuncture for respiratory symptoms related to COVID-19

SARS-CoV-2 mainly infects alveolar epithelial cells and induces a high local inflammatory state. Persistent inflammation can lead to lung tissue injury and a series of respiratory symptoms[25]. Ten systematic reviews/meta-analyses including 134,222 patients demonstrated that the most common symptoms experienced by patients with COVID-19 were fever (78.0%–91.3%)[26–35], cough (52.0%–72.2%)[26–35], dyspnea (10.4%–45.6%)[29–30,32,34–35], expectoration (21.3%–41.8%)[26,30,34], chest distress (31.2%), and sore throat (13.1%)[26,32]. Clinical guidelines such as the *American Clinical Practice Guidelines* recommend acupuncture for the clinical treatment of allergic rhinitis and acute pharyngitis[36–37]. A randomized clinical study including 32 patients with asthma showed that acupuncture treatment could increase forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC and improve the respiratory function of the patients[38]. Several systematic evaluations have shown that acupuncture can relieve symptoms

such as cough, expectoration, and dyspnea in patients with COPD and cough variant asthma and improve lung function[39–40].

Several studies have demonstrated that acupuncture can improve respiratory function by regulating the balance of helper T cells, promoting macrophage polarization, and modulating inflammatory signaling pathways and cytokines. Imbalances in between helper T cells (Th1/Th2) and regulatory T cells (Treg/Th17) play a key role in the inflammatory immune response of respiratory diseases[41–44],and acupuncture can increase the levels of IFN-γ in bronchoalveolar lavage fluid (BALF), reduce the levels of interleukin (IL)-4, IL-17, and transforming growth factor beta (TGF-β), regulate the balance of $CD4^+$ T lymphocyte subsets (Th1/Th2 and Treg/Th17), and improve airway inflammation[45]. Acupoint catgut embedding promotes macrophage polarization, reduces BALF tumor necrosis factor(TNF)-α and IL-6 levels, upregulates IL-10 levels, reduces local inflammatory responses, and improves respiratory function[46]. Additionally, EA downregulates the JAK/STAT pathway to inhibit IL-6 and TNF-α, thereby improving COPD[47–48].A study has shown that EA can reduce the levels of TNF-α and IL-1β in BALF in rats with COPD, as well as improve pathological lung damage[49].

Acupuncture for digestive symptoms related to COVID-19

With continuous research on COVID-19, digestive system symptoms were found to occur during the course of treatment. Some patients report digestive system symptoms as the first symptoms of COVID-19, and they are more likely to develop severe COVID-19[50]. Four systematic reviews/meta-analyses including 19,007 patients showed that the pooled prevalence of digestive symptoms was 9.8%–17.6%[51–53], with diarrhea (7.8%–12.9%)[26,51–52,54], nausea or vomiting (5.5%–10.2%)[26,51–52,54], abdominal discomfort/pain (3.0%–6.9%)[51–52], and loss of appetite (11%)[52] being the most common symptoms. Although acupuncture for COVID-19 digestive symptoms has not been evaluated in a clinical trial, there is abundant evidence of its effect on digestive symptoms. The American Society of Clinical Oncology (ASCO) recommends acupoint pressing and acupuncture to alleviate nausea and vomiting after chemotherapy. ASCO also suggests that EA can be used as a supplement to antiemetic drugs during chemotherapy (level B)[55]. Several clinical trials have shown that acupuncture can improve the symptoms of diarrhea, abdominal distension, nausea and vomiting, and improve the quality of life of these patients[56–57]. Several systematic evaluations and meta-analyses have shown that acupuncture can improve nausea, vomiting, anorexia, and other symptoms without adverse events[58–59].

An imbalance in the intestinal microbiota changes the intestinal mucus layer, destroys the tight connections, increases intestinal permeability, and promotes bacterial translocation[60]. Destruction of the intestinal barrier leads to the transfer of intestinal bacteria or harmful antigens to the host's immune system and promotes the development of intestinal inflammation[61]. Acupuncture can reduce intestinal bacterial translocation, protect the intestinal mucosal barrier, regulate visceral hypersensitivity, and improve gastrointestinal function by inhibiting inflammatory reactions and mast cell activity and reducing intestinal permeability. Research has shown that EA can increase the numbers of *Lactobacillus* sp. and *Trichospiraceae* in the intestine, reduce the numbers of *Clostridium bifurcans*, and improve the diversity and number of beneficial flora to correct intestinal flora disorders[62]. EA can reduce colon tissue TNF-α, IL-1β, IL-6, and inducible nitric oxide synthase levels; increase IL-10 levels; upregulate the expression of ZO-1, occludin, E-cadherin, and mucin 2 (MUC2) in the colon tissue; inhibit intestinal epithelial cell apoptosis; and reduce intestinal permeability[63]. Visceral hypersensitivity is the main pathogenesis of functional dyspepsia[64], and mast cell activation is closely related to visceral hypersensitivity. EA can inhibit the activity of degranulated mast cells in colon tissue and reduce serum IL-1 and IL-8 concentrations to regulate visceral hypersensitivity[65].

Acupuncture nervous system symptoms related to COVID-19

Autopsy, animal, and organoid studies have shown that SARS-CoV-2 can reach and infect central nervous system cells and neurons and produce neuroinflammation[66]. According to statistics, 36% of patients with COVID-19 have nervous system symptoms[67], with headache (12.1%–42%), dizziness (12.1%), and fatigue (35.5%–51.0%)[30,32,35] being the most common symptoms. The results of a cohort study showed that acupuncture could effectively improve dizziness, vertigo, and other symptoms[68]. In 2017, the American Cancer Society published a guide on complications during treatment for breast cancer, recommending acupuncture to improve fatigue after cancer treatment (level C)[69]. Subsequently, a systematic review and meta-analysis including 31 RCTs with 2,255 patients for chronic fatigue syndrome (CFS) showed that acupuncture was better than traditional Chinese medicine, Western medicine, or sham acupuncture in alleviating fatigue[70]. A randomized clinical trial including 150 patients with migraine without aura showed that acupuncture could significantly improve the number of attacks and pain intensity in patients with migraine[19]. A recent meta-analysis of 13 RCTs with 1,559 patients with migraine found that EA is more effective for reducing the severity of headaches than sham acupuncture[71].

The analgesic and anti-fatigue effects of acupuncture are closely related to the downregulation of neurotransmitters and neuropeptides, such as glutamate, substance P (SP), and calcitonin gene-related peptide (CGRP), as well as anti-oxidative stress. Glutamic acid is the most common excitatory neurotransmitter in the central nervous system[72]. In addition, EA can inhibit the expression of glutamic acid in the hippocampus to reduce neuropathic pain in the higher regions of the brain[73]. EA can reduce the concentration of serum CGRP, reduce the mRNA expression of SP and CGRP in the dorsal cervical root ganglion, inhibit hyperalgesia, and relieve migraine[74]. Oxidative stress and lipid peroxidation are important factors in the occurrence of pain and fatigue[75]. A study on the analgesic effect of EA on paclitaxel-induced neuropathic pain showed

that under oxidative stress, EA upregulated the expression of Nrf2 antioxidant response element (Nrf2-ARE) and superoxide dismutase (SOD) in the dorsal cervical root ganglion enhanced the antioxidant signal pathway, and inhibited the oxidative stress products NOX4 and 8-iso-prostaglandin F2α (8-iso PGF2 α) to reduce neuropathic pain[22]. In addition, a study showed that acupuncture intervention can affect the level of malondialdehyde and the activities of SOD and glutathione peroxidase, improve the antioxidant capacity of CFS rats, and alleviate fatigue[76].

Acupuncture for the treatment of mental and psychological disorders secondary to COVID-19

After the outbreak of the COVID-19 pandemic, the atmosphere of fear led to depression, anxiety, and sleep disorders among hospitalized patients, isolated people, and front-line medical staff[77]. A web-based survey of 4,283 participants from 101 countries found that the rates of depression and of anxiety, as well as insomnia caused by COVID-19 were 32.8% and 30.8%, respectively, and that the psychological effects were long-term[78]. A recent cohort study published in *The Lancet* showed that patients with COVID-19 mainly experienced sleep difficulties, anxiety, or depression 6 months after discharge[9]. The clinical practice guidelines for non-drug treatment and drug treatment of adult patients with major depression developed by the American College of Physicians in 2016 suggested that acupuncture treatment for major depression has fewer adverse reactions than drug treatment. Moreover, acupuncture combined with second-generation antidepressants is better than using second-generation antidepressants or acupuncture alone[79]. In 2018, ASCO proposed that acupuncture can be used to improve emotional disorders, anxiety, and depression in patients with breast cancer (level C)[55]. In 2022, a randomized clinical trial including 247 patients with depression and insomnia showed that EA could significantly improve anxiety, depression, and sleep quality[80]. Several meta-analyses have shown that acupuncture can effectively relieve anxiety and depression in patients and that it is very safe[81–82].

Acupuncture can play a role in relieving anxiety and depression and promoting sleep by regulating neurotransmitters, immune inflammatory reactions, and HPA axis activity. Neurotransmitter and immune inflammatory reaction disorders are increasingly considered key factors in depression[83–84]. A study found that acupuncture has an antidepressant effect by upregulating the levels of neurotransmitters such as 5-hydroxytryptamine

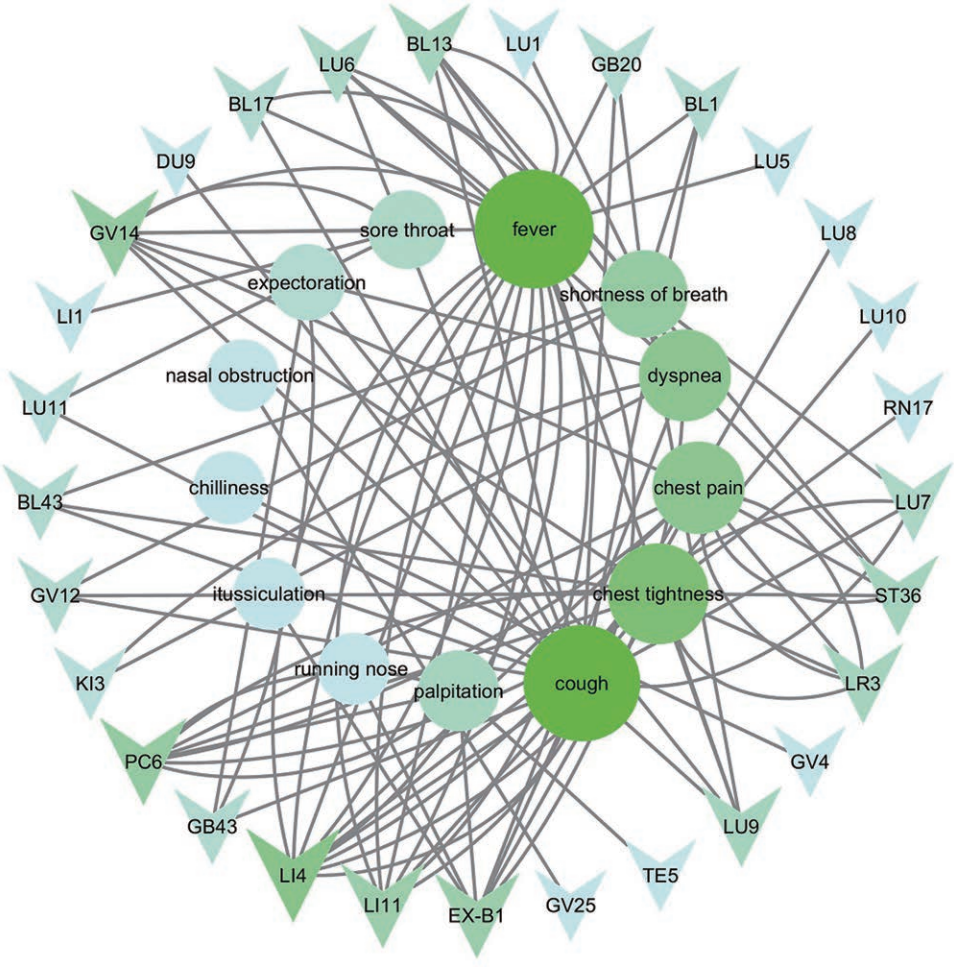

Figure 1. Network topology of acupoints and respiratory symptoms. Circles represent common respiratory symptoms, and arrowheads present acupoints. Green represents the largest value, and blue is the smallest value. The larger the shape, the greater the value, and the closer the connection between the two nodes.

(5-HT), dopamine (DA), and norepinephrine (NE) in the hippocampus[85]. Acupuncture inhibits the expression of inflammatory factors such as IL-1β, IL-18, high mobility group box 1 (HMGB1), IFN-γ, IL-6, and TNF-α in serum and the hippocampus and improves depressive-like behavior[86]. In addition, the HPA axis is closely related to anxiety, depression, and insomnia. EA can reduce the concentration of corticotropin-releasing hormones (CRH) in the hypothalamus and pituitary, as well as the concentrations of CRH, adrenocorticotropic hormone (ACTH), and cortisol (CORT) in the serum, indicating that acupuncture can relieve anxiety, depression, and sleep difficulties by inhibiting the activity of the HPA axis[23,87].

Acupuncture for the treatment of COVID-19 combined with cardiovascular and other underlying diseases

Among patients with COVID-19, those with cardiovascular and other basic diseases are more likely to develop severe pneumonia, ARDS, or multiple organ failure owing to their decreased immunity, weak defense system, and reduced ability to withstand systemic cytokine storms, which will lead to an increase in the incidence rate and mortality[1,88]. A study shown that 46.4% of 138 inpatients with COVID-19 had one or more basic diseases. The most common were hypertension (31.2%), cardiovascular disease (14.5%), and diabetes (10.1%)[50]. Another epidemiological survey of 257 patients with severe COVID-19 from a tertiary hospital showed that 82% had at least one chronic disease, of which the most common were hypertension (63%) and diabetes (36%)[89]. A systematic review and meta-analysis including 13 RTCs with 797 patients showed that the clinical efficacy of acupuncture for the treatment of paroxysmal supraventricular tachycardia (PSVT) was not lower than that of oral antiarrhythmic drugs[90]. A systematic review including 22 RCTs with 1,744 patients with primary hypertension showed that acupuncture had better immediate hypotensive effects than drug treatment[91]. A multiple centers large sample RCT report included 404 patients with chronic stable angina pectoris. The results showed that acupuncture as an auxiliary intervention method has a better effect in alleviating the frequency of angina attacks[92]. In addition, in 2019, a systematic review of 12 RCTs involving 974 patients with stable angina pectoris showed that acupuncture plus medication or acupuncture alone was more effective than medication alone in relieving angina pectoris and improving

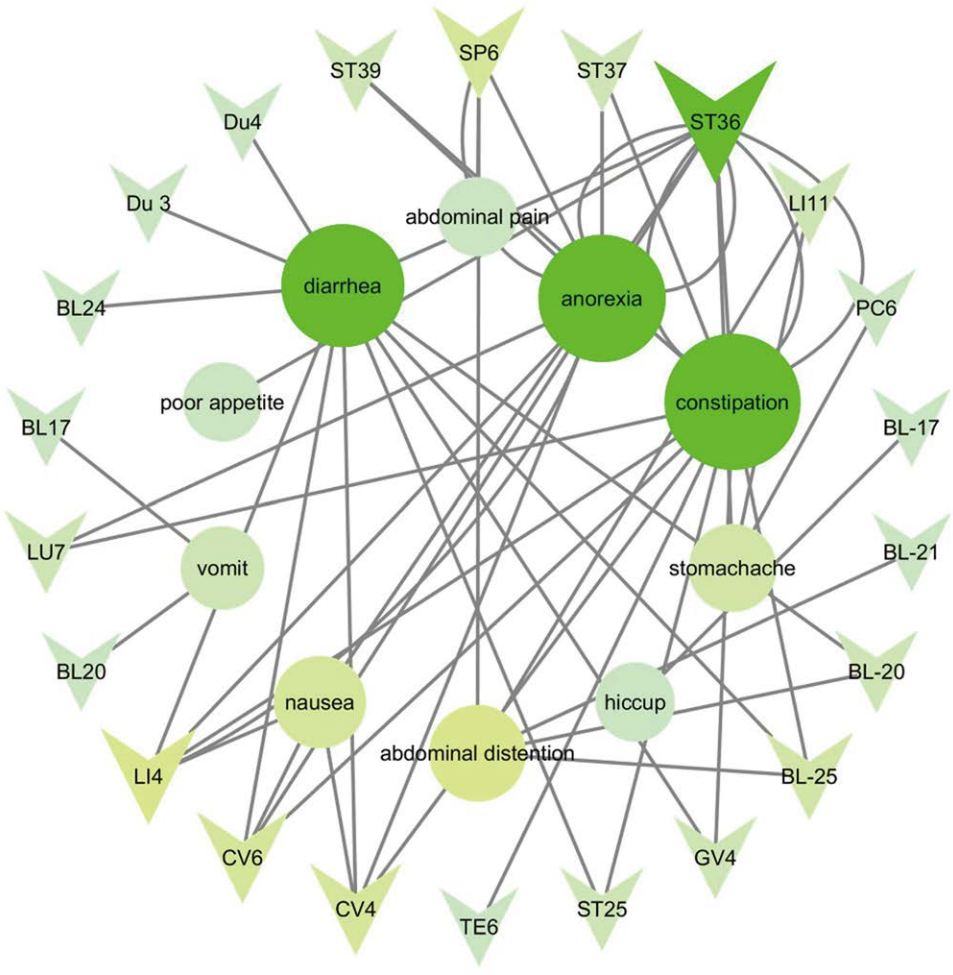

Figure 2. Network topology of acupoints and digestive symptoms. Circles represent common digestive symptoms, and arrowheads represent acupoints. Green represents the largest value, and yellow is the smallest value. The larger the shape, the greater the value, and the closer the connection between the two nodes.

electrocardiogram ischemia markers[90,93]. In April 2021, the Chinese Medical Association officially released the *Guidelines for the Prevention and Treatment of Type 2 Diabetes in China* (2020 Edition), in which "acupuncture combined with basic treatment to control blood glucose synergism" was included in the treatment recommendation[94].

The mechanism of acupuncture in treating cardiovascular diseases is complex. Acupuncture can reduce cardiomyocyte apoptosis and improve cardiac function by inhibiting inflammatory reactions and improving mitochondrial functions. The mechanism of acupuncture in treating arrhythmia and hypertension is related to the renin-angiotensin-aldosterone system (RAAS). Studies have found that EA pretreatment can reduce myocardial caspase-1 and IL-1β, inhibit the activation of NLRP3 inflammatory bodies, and play a protective role in the heart[95]. EA pretreatment can promote the synthesis of adenosine triphosphate (ATP), inhibit the expression of ROS, upregulate the level of anti-apoptotic protein Bcl-2, improve mitochondrial dysfunction, reduce cardiomyocyte apoptosis, and improve myocardial injury[96]. EA can also significantly inhibit the degree of ST-segment elevation, improve left ventricular dysfunction, and reduce systolic and diastolic blood pressure by reducing the release of cardiac norepinephrine[97]. RAAS plays a role in causing vasoconstriction and raising blood pressure[98]. EA can reduce the concentrations of angiotensin II (AngII) and endothelin-1 (ET-1) in plasma and the levels of angiotensin II type 1 receptor (AT1R) and endothelin-1 type A receptor (ETAR) in the aorta and myocardium and reduce blood pressure[99]. Hyperglycemia is related to insulin resistance and endothelial dysfunction. EA upregulates the expression of insulin receptor substrate 1 (IRS-1), PI3K, Akt2, and eNOS in vascular endothelium by activating the PI3K/Akt signal pathway, improves insulin sensitivity, improves endothelial dysfunction, and reduces blood glucose[100].

Complex network analysis of acupuncture treatment for COVID-19-related symptoms

Based on extracting the application characteristics of acupoints, complex network analysis was used for the acupoint-symptom analysis. Acupoint-symptom analysis reflects the close relationship between acupoints and symptoms through a complex network of acupoints and symptoms. The results showed that the most frequent respiratory symptoms related to COVID-19 were fever, cough, chest tightness, chest pain, dyspnea, and other symptoms, and the most frequently selected acupoints were Hegu (LI4), Dazhui (GV14), Neiguan (PC6), Quchi (LI11), and Dingchuan (EX-B1). The network topology of symptoms and acupoints related to the respiratory system is shown in Figure 1. The most frequent digestive

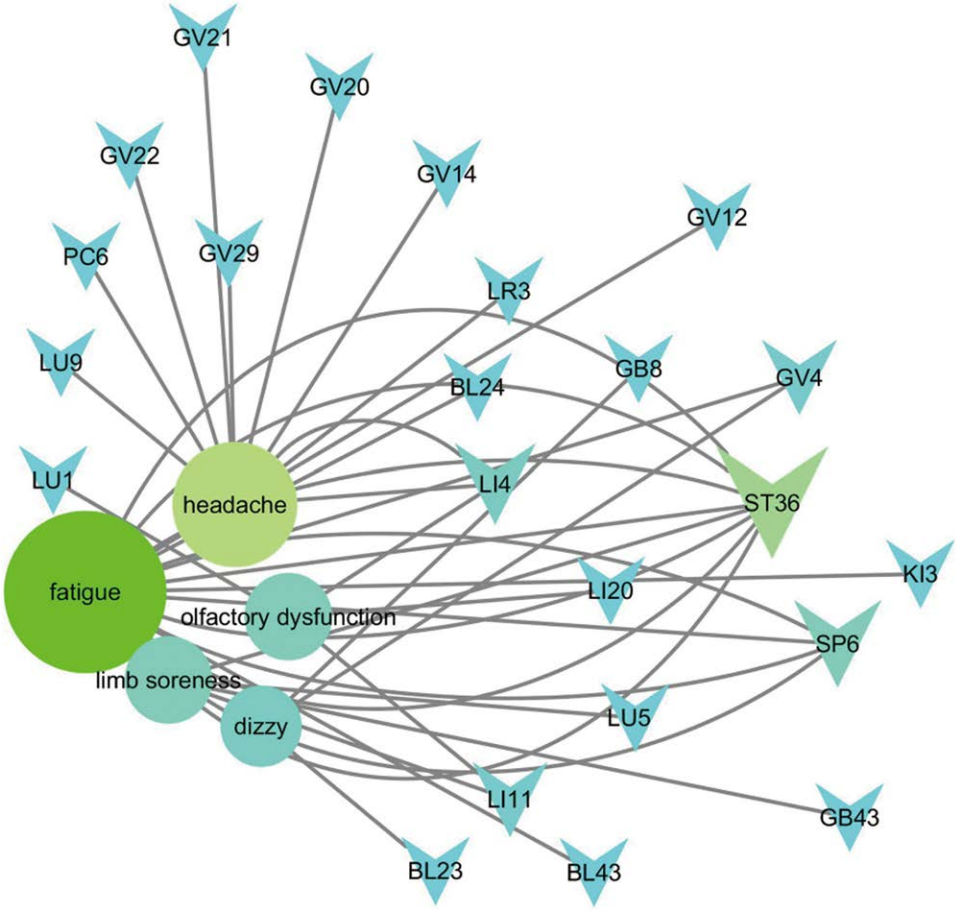

Figure 3. Network topology of acupoints and nervous system symptoms. Circles represent common nervous system symptoms, and arrowheads represent acupoints. Green represents the largest value, and blue is the smallest value. The larger the shape, the greater the value, and the closer the connection between the two nodes.

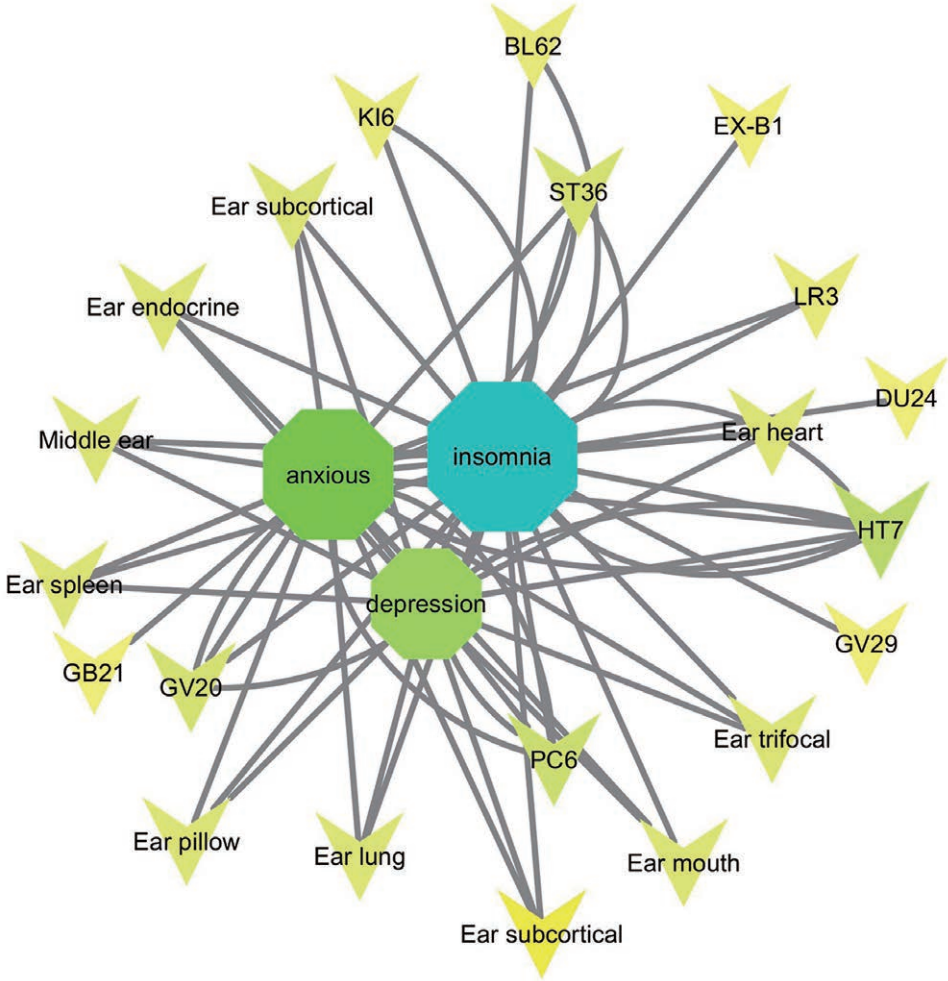

Figure 4. Network topology of acupoints and symptoms of mental disorders. Circles represent common symptoms of mental disorders, and arrowheads represent acupoints. Blue represents the largest value, and yellow is the smallest value. The larger the shape, the greater the value, and the closer the connection between the two nodes.

symptoms related to COVID-19 were constipation, anorexia, diarrhea, abdominal distension, nausea, vomiting, abdominal pain, and other symptoms, and the most frequently used acupoints were Zusanli (ST36), LI4, Qihai (CV6), Guanyuan (CV4), and Sanyinjiao (SP6). The network topology of symptoms and acupoints related to the digestive system is shown in Figure 2. The most frequent neurological symptoms related to COVID-19 were fatigue, headache, olfactory dysfunction, limb pain, and dizziness, and the most frequently used acupoints were ST36, SP6, LI4, LI11, and Mingmen (GV4) The network topology of symptoms and acupoints related to the nervous system is shown in Figure 3. The most frequent symptoms of mental and psychological disorders related to COVID-19 were insomnia, anxiety, depression, and other symptoms, and the most frequently used acupoints were Shenmen (HT7), PC6, ST36, Baihui (GV20), and Ear trigcal. The network topology of symptoms and acupoints related to mental and psychological disorders is shown in Figure 4.

Methods of acupuncture for the treatment of COVID-19-related symptoms were mainly manual acupuncture, followed by filiform-fire needling, tube needle, thumb-tack needles, ear point pressure, intradermal needle, and acupoint injection. Manual acupuncture, filiform-fire needling, and acupoint injection were performed once daily or every other day and the needle was kept in place for 20–30 min. Thumb-tack needle and auriculopressure interventions lasted for 7h, 12h, or up to 1 day before discharge. However, owing to the varying severity of COVID-19-related symptoms and individual physical differences between patients, there is no uniform standard for the treatment period. In the analyzed literature, the shortest treatment period was 2 days, and the longest was 4 months; alternatively, acupuncture treatment was administered immediately after admission until the patient was discharged. The therapeutic role of acupuncture in COVID-19-related symptoms was shown in Table 1.

Summary and prospect

Acupuncture treatment of COVID-19-related symptoms involves multiple systems and levels. Acupuncture can improve COVID-19-related symptoms by inhibiting immune inflammatory reactions and regulating intestinal flora, mitochondrial function, oxidative stress levels, myocardial cell apoptosis, neurotransmitter release, and HPA axis activity. Acupuncture promotes the transformation of macrophages from M1 pro-inflammatory type to M2 anti-inflammatory type, regulates the balance of $CD4^+$ T lymphocyte subsets, and downregulates

Table 1.

The therapeutic role of acupuncture in related symptoms of COVID-19

Author and publication time	COVID-19 presentation/ stage	Intervention methods	Acupoints	Acupuncture parameters	Related symptoms
Bhat et al., 2022[101]	Recovery period	MA	GV20, LI20, EX-B1, H7, LI11, GB8, GB21, GV25	Four months	Olfactory dysfunction, nasal congestion, runny nose, nausea, anxiety, depression, dizziness, insomnia
Yin et al., 2021[102]	Severe disease	MA	LI11, LI4, ST40, PC6, KI3, EX-B1, SP6	Fifteen days, once a day	Fever, expectoration, chest tightness, dyspnea, cough, fatigue,anorexia
Yin et al., 2021[103]	Severe disease	MA	KI3, SP6, EX-B1	Once a day, everyday, 15–30 min for 9 days	Chest tightness, dyspnea, anorexia, fatigue
Tao et al., 2020[104]	Ordinary type	MA	KI3, SP6, EX-B1	Once a day, everyday, 10 days, no needle left	Dyspnea, fatigue, cough
Luo et al., 2022[105]	Recovery period	Filiform-fire needling	GV4, GV12, BL43, ST36, ST37, ST39, ST40, LU11, LI1	Every other day, 3 times a week, 3 times per course, 2 courses	Fatigue, cough, chest tightness, shortness of breath, chills, anorexia, constipation, expectoration, limb soreness, sore throat
Li et al., 2021[106]	Ordinary type	Acupoint injection	GV20, GV14, GV9, GV4, GV3, BL24, BL17	Once a day, everyday for 20 days	Fever, sore throat, chest tightness, cough, insomnia, diarrhea, fatigue
Wang et al., 2021[107]	Severe disease	Intradermal needle	LU6, GV14, BL13	7 days/time, twice	Dyspnea
Cheng, 2021[108]	Severe disease	MA	LU1, LU6, ST36, LU11, GV14, EX-B1	Once a day, everyday, 30 min, 2 days	Dyspnea, olfactory dysfunction, cough, fatigue, headache, chest pain
Wang et al., 2022[109]	Ordinary type	MA	GV14, GB20, BL12, BL13, BL17, BL20, LI10, SP4, ST25, CV4, TE6, LU6, LI4, CV6, CV12, ST36, LR3	Alternate use of two groups of acupoints,Once a day, 20 min 5 times/ week	Cough, sore throat, nasal congestion, fever, shortness of breath, insomnia, anorexia, headache, limb soreness, constipation, nausea, fatigue, chest tightness, diarrhea
Jania, 2021[110]	Long COVID	MA	SP6, ST36, ST40, ST44, ST25, TE5, LU7, CV6, CV12, CV15, LR3, GB41, GV20, GV21, GV22, GV29, BL25, BL23, BL20, BL21, BL17, BL13	Once a day, everyday, 25 min, 6 weeks	Diarrhea, abdominal pain, abdominal distention, constipation, migraine, fever, chest tightness, hiccup, insomnia, dizzy
Gong et al., 2021[111]	Ordinary type	MA	LU7, LI4, PC6, LI11, ST36, LR3, KI6, BL62	Every other day for 30 min. Acupuncture treatment administered immediately after admission until the patient was discharged	Migraine, shortness of breath, constipation, insomnia, fever, cough, chest tightness, chest pain, stomach ache, anorexia, fatigue, insomnia, anxiety
Shi et al., 2021[112]	Ordinary type	MA	LI4, PC6, LI11, LU7, ST36, LR3, BL62, KI6, SP6	Every other day, 30 min, 12 days or until the patient is discharged	Chest tightness, chest pain, fatigue, anxiety, anorexia, insomnia
Luo et al., 2022[113]	Recovery period	MA	CV4, ST36, LU9	Once a day, 7 days per course, 2 courses	Fever, cough, fatigue, expectoration, chest tightness, shortness of breath, anorexia, chilliness, constipation, limb soreness, dizziness, headache
Luo et al., 2021[114]	Mild disease	Ear point pressing bean	HT7, subcortical, lung, spleen, endocrine	Five times per day, 2 min, continue until 1 day before discharge	Insomnia, anxiety, depression
Yang et al., 2021[115]	Ordinary type	Auricular point sticking and pressing	HT7, subcortical, heart, pillow, middle ear, mouth, trifocal	Three times per day, 30 s, 12 days	Insomnia, anxiety, depression
Gong et al., 2020[116]	Severe disease	MA	ST36, SP6, LR3, LI4, LU7, PC6, LI11	Once a day, Everyday, 30min, 12 days or until the patient is discharged	Fever, cough, chest pain, shortness of breath, anorexia, constipation, fatigue, insomnia, anxiety
Robert et al., 2022[117]	Long COVID	MA	GV20, ST36,SP6, LR3, PC6, LI4, TE5, LI11	Everyday, 30min, 7 days	Fever, fatigue, olfactory dysfunction, anxiety, dyspnea, chest tightness, cough

Abbreviations: COVID-19, Corona Virus Disease 2019; MA, Manual acupuncture; EA, Electroacupuncture; GV20, Baihui; LI20, Yingxiang; GV25, Suliao; KI3, Taixi; EX-B1, Dingchuan; GV4, Mingmen; GV12, Shenzhu; GV3, Yaoyangguan; GV14, Dazhui; CV15, Jiuwei; GV21, Qianding; GV22, Xinhui; ST36, Zusanli; ST37, Shangjuxu; ST39, Xiajuxu; ST40, Fenglong; BL43, Gaohuang; LU11, Shaoshang; LI1, Shangyang; GV9, Zhiyang; BL24, Qihaishu; BL17, Geshu; BL13, Feishu; BL20, Pishu; LU6, Kongzui; LU2, Yunmen; GB20, Fengchi; BL12, Fengmen; LI10, Shousanli; SP4, Gongsun; ST25, Tianshu; CV4, Guanyuan; TE6, Zhigou; CV6, Qihai; CV12, Zhongwan; LR3, Taichong; LI10, Shousanli; LU7, Lieque; LI4, Hegu; PC6, Neiguan; LI11, Quchi; GV29, Yingtang; SP6, Sanyinjiao; HT7, Shenmen; CV17, Danzhong; BL62, Shenmai; KI6, Zhaohai; LU9, Taiyuan.LI; GB8, Shuaigu; GB21, Jianjing; GB41, Zulinqi; ST44, Neiting; TE5, Waiguan; BL25, Dachangshu; BL23, Shenshu; BL21, Weishu.

the JAK/STAT and PI3K/Akt pathways to improve airway and lung inflammatory responses and respiratory functions. Acupuncture inhibits intestinal inflammatory reactions and mast cell activity and decreases intestinal permeability to reduce intestinal bacterial translocation, protect the intestinal mucosal barrier, regulate visceral hypersensitivity, and improve gastrointestinal functions. Acupuncture can inhibit the release of neurotransmitters and neuropeptides, reduce oxidative stress, and exert analgesic and anti-fatigue effects. Moreover, acupuncture regulates neurotransmitter release, immune inflammatory reactions, and HPA axis activity to improve anxiety, depression, and insomnia. Acupuncture inhibits inflammatory reactions, regulates mitochondrial function and RAAS, and reduces cardiomyocyte apoptosis to improve cardiac function and hypertension. The therapeutic role and possible mechanism of acupuncture in the treatment of COVID-19-related symptoms are shown in Figure 5.

The complex network analysis demonstrated that among the most frequently selected acupoints for respiratory system-related symptoms, LI4, GV14, and LI11 were used to relieve heat and asthma, PC6 was used to regulate *qi* and relieve pain, and EX-B1 was used to relieve asthma and cough. The most frequently selected acupoints for digestive system-related symptoms were ST36 and SP6 to strengthen the spleen and stomach, LI4 to relieve static pain, LI11 to regulate *qi* to relieve pain, and CV4 and CV6 to strengthen the intestine and stop diarrhea. For nervous system-related symptoms, the most frequently used acupoints were ST36 and SP6 to replenish *qi* and strengthen the spleen, LI4 to soothe static pain, LI11 to regulate *qi* and relieve pain, and GV4 to nourish vital energy. For symptoms related to mental and psychological disorders, the following acupoints were most frequently used: HT7 to calm the mind and nerves, ST36 with PC6 to soothe the liver and regulate *qi*, GV20 to awaken the brain and open the mind, and Ear trigcal to regulate the *qi*. In general, selecting acupoints for COVID-19-related symptoms follows the treatment principle of syndrome differentiation.

In the fight against the pandemic, acupuncture therapy is widely used in the treatment of COVID-19. Acupuncture interventions are used to treat mild, moderate, and severe COVID-19, during convalescence, and for long COVID. Acupuncture combined with drug therapy has a synergistic effect and can promote recovery from COVID-19 and improve the quality of life of patients. Various acupuncture intervention methods are used, including manual acupuncture, filiform-fire needling, tube needle, thumb-tack needles, ear point pressure, intradermal needle, and acupoint injection, and there are little side effects. Different acupuncture methods can be selected for symptomatic treatment according to the condition

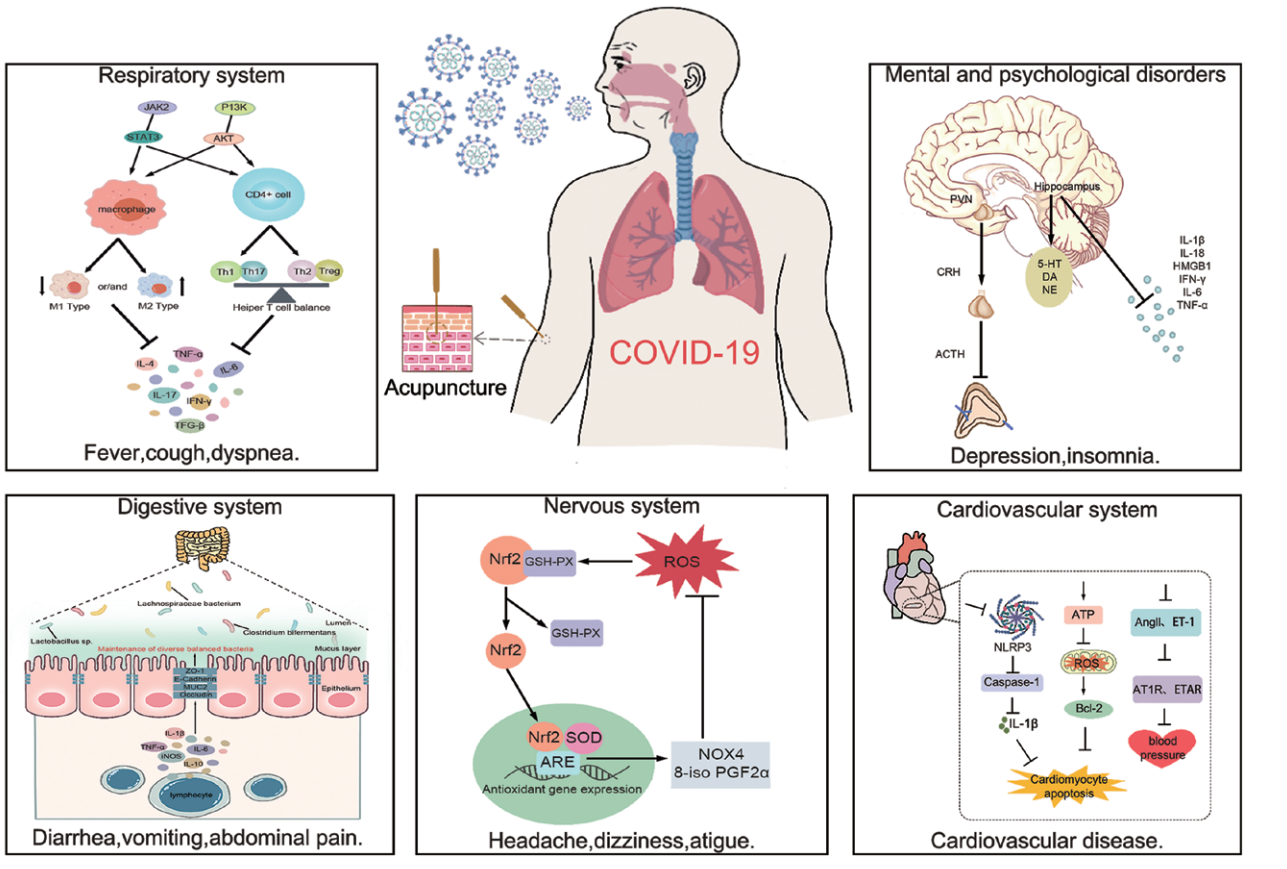

Figure 5. The role and possible mechanism of acupuncture in the treatment of COVID-19-related symptoms. 8-iso PGF2α: 8-iso-prostaglandin F2α; ACTH: adrenocorticotropic hormone; Akt: protein kinase B; ATP: adenosine triphosphate; AngII: angiotensin II; AT1R: angiotensin II type 1 receptor; CRH: corticotropin-releasing hormones; ET-1: endothelin-1; ETAR: endothelin-1 type A receptor; JAK: the Janus kinase; PI3K: phosphatidylinositol 3-kinase; PVN: paraventricular nucleus; ROS: reactive oxygen species; SOD: superoxide dismutase; STAT: signal transducer and activator of transcription.

of the patient or the symptom characteristics of COVID-19 or long COVID. In addition, a characteristic of acupuncture therapy is that it affects multiple organs from one point. For example, ST36 is used to treat common digestive symptoms of COVID-19 and common nervous system symptoms and psychosocial disorders related to COVID-19, thus, playing a multi-target and multi-system regulatory role.

This study has several limitations. First, most of the included clinical studies are case reports or small-sample studies, and the quality of evidence is low, which affects the reliability of the results. Second, owing to the lack of case reports on acupuncture treatment for COVID-19 combined with the cardiovascular system and other basic diseases, the principles of acupoint selection for acupuncture treatment of cardiovascular system-related symptoms have not been summarized, and there is no agreement on the treatment course of acupuncture for COVID-19-related symptoms. Finally, basic research on acupuncture treatment for COVID-19-related symptoms is lacking. Therefore, we could only speculate on the possible mechanisms underlying the pathological process of COVID-19-related symptoms. As a next step, we will perform further relevant experimental research by collecting and analyzing evidence data from clinical practice to improve the level of evidence and the scientific accuracy of acupuncture interventions for COVID-19-related symptoms and long COVID.

In conclusion, acupuncture has certain advantages and characteristics in the treatment of COVID-19 and long COVID. The rate of acupuncture therapy for long COVID should be increased, and the core role of acupuncture in the treatment of long COVID should be investigated in rigorous studies so that it can be applied optimally for the treatment of COVID-19-related symptoms.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

The authors contributed in the following manner: Lifen Wang and Xiyou Hu contributed to the concept design, data collection, and paper writing; Xinru Yuan, Jinyu Lian, Xiaoyan Lyu contributed to the figures and graphic abstract edit; Lihong Huang, Dongsheng Ba contributed to the data collection and analysis; Ningcen Li,Yong Chen, Jingyu Zhang contributed to the language modification and text check; and Zelin Chen, Bo Chen,Yue Zhang and Lianqi Geng contributed to the concept design and paper review. Lifen Wang and Xiyou Hu contributed equally to this work. All authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

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None.

Data Availability

All data generated or analyzed during this study are included in this published article.

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