

REVIEW

Potential therapeutic effect and methods of traditional Chinese medicine on COVID-19-induced depression: A review

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Abstract

COVID-19 (coronavirus) has spread all over the world with a high infection rate. Currently, there are no targeted therapeutic drugs for COVID-19 as well as for stress induced by COVID-19. The unpredictable events of COVID-19 can trigger feelings of fear, worry, or unease in people, leading to stress-related disorders such as depression and anxiety. It has been reported that individuals, including COVID-19 patients, medical staff, and ordinary people, are under both physical and psychological pressure, and many of them have developed depression or anxiety during this pandemic. Traditional Chinese medicine (TCM) has been widely used in treating depression with relatively better safety and efficacy and may have an important role in treating stress-related disorders induced by COVID-19. In this review, we collected the common TCM treatment methods including Qigong, Acupuncture, Five Elements Musical Therapy, Five Elements Emotional Therapy, and Chinese herbal medicine from the databases of PubMed and the China National Knowledge Internet to illustrate the effect of TCM on depression. The better knowledge of TCM and implementation of TCM in COVID-19 clinics may help to effectively improve depression induced by COVID-19, may assist people to maintain a healthy physical and mental quality, and may alleviate the current shortage of medical resources.

摘要:新型冠状病毒(COVID-19)以较高传染率在世界范围内广泛传播。目前, COVID-19的靶向治疗药物仍在研究中。因此,人们对于COVID-19引起的不可预知事件,具有明显的恐惧、担忧或不安感,导致机体产生压力相关的障碍疾病风险增加,如抑郁和焦虑。据报道,在此次COVID-19的流行中, COVID-19患者、医务人员和普通人群,都承受着生理和心理上的双重压力,已经导致许多人患上抑郁症或焦虑症。中医药治疗抑郁症具有相对的安全性和有效性,在COVID-19引起的应激障碍中可能发挥重要作用。因此,本文从PubMed数据库和中国知网数据库中收集整理了包括气功、针灸、五行音乐、五行情志、中药等在内的常用中医治疗,并阐述其治疗抑郁症的潜在作用机制。本综述旨在有效改善由COVID-19疫情引发的抑郁症流行,促进人们保持身心健康,缓解目前全球紧张的医疗资源。

KEYWORDS

COVID-19, depression, traditional Chinese medicine

1 | INTRODUCTION

Currently, COVID-19 has spread almost all over the world, and its prevalence trend has not weakened. According to the data from Johns Hopkins University in the United States, as of January 27, 2021, there were an estimated 100 million COVID-19 cases with more than 2 million 140 thousand cumulative death cases worldwide, spreading over five continents and 196 countries/regions. However, no (Huang et al. 2020) specific drug has been confirmed to cure COVID-19.

The unoptimistic situation due to the COVID-19 pandemic has not only hindered the development of the global economy but also reduced the physical and psychological quality of people's lives. With the development of the pandemic, the problem of depression has gradually emerged, but limited medical resources and the large invisible patient population have made psychological treatment difficult. Therefore, this review discusses the application of traditional Chinese medicine (TCM) in COVID-19-induced depression.

2 | THE IMPACT OF COVID-19 ON PUBLIC MENTAL HEALTH

2.1 | Potential mental hazard of the public

After serious disasters, psychological trauma is always a troubling problem, which can cause many to develop panic and stress, become depressed or suicidal, and gradually develop severe mental disorders, such as post-traumatic stress disorder (PTSD) and depression. A large number of data have found that the incidence of depression after disasters can be as high as 25%, and the victims and rescuers may also experience psychological and behavioral problems, such as anxiety, sleep disorders, substance abuse, and stigmatization (North & Pfefferbaum, 2013). The disease prevalence can engender considerable proportions of PTSD and depression among populations. Severe acute respiratory syndrome (SARS) was the first pandemic outbreak in the 21st century. The data have shown that during the SARS epidemic, both medical staff and SARS survivors have experienced mental health problems (Lee et al., 2007; McAlonan et al., 2007). In Hong Kong,

researchers investigated the psychological impact of SARS in 195 adult patients. Among the participants, 10% to 18% reported symptoms related to PTSD, anxiety, and depression (Wu et al., 2005). A cohort study about long-term psychiatric morbidities among SARS survivors showed that post-SARS cumulative incidence of diagnostic and statistical manual of mental disorders psychiatric disorders was 58.9%, and 15.6% of the survivors had depressive disorders. The study not only pointed out that SARS could cause significant prolonged psychiatric problems but also emphasized that the psychological impact of future comparable infectious diseases on survivors should not be ignored (Mak et al., 2009). Survivors of the infection with Ebola virus also faced various forms of physiological and psychological sequelae. In the exploratory study of 256 Ebola virus survivors in Guinea, 15% of survivors presented depressive symptoms for a median period of 8 months, and the clinical consultation showed that these major symptoms had significant repercussions on the survivors' capacity for social reintegration (Keita et al., 2017). Similar results have been reported in previous studies of Middle East respiratory syndrome (MERS). The researchers concluded that the MERS is similar with 2003 SARS outbreak in inducing depressive symptoms, as evidenced that between 18% and 57% of medical staff experienced severe emotional distress during and shortly after both outbreaks (Lee et al., 2018).

During the pandemic of COVID-19, a significant amount of research data have shown that depression caused by the disease has a gradually onset and affects people with various occupations. A study on surgeons from 101 countries showed that 32.8% of them felt depression, and the COVID-19 pandemic might have a long-term impact on the mental health of healthcare personnel (Tan et al., 2021). In addition to the impact on the medical staff, researchers are also aware of the impact of the pandemic on COVID-19-related unemployment, death of relatives, other stressors, and reduced access to mental health services in general population (Iob et al., 2020; Witteveen & Velthorst, 2020). The U.S. Census Bureau assessed the prevalence of anxiety and depression during the 2019 and 2020 COVID-19 pandemic, and the results showed that compared with American adults in 2019, three times more American adults in 2020 were screened for depression and anxiety (Twenge & Joiner, 2020).

2.2 | Countermeasures of public mental health

The public health events could leave a long-term traumatic effect on patient's mental health, highlighting the urgent need to improve mental health worldwide (Twenge & Joiner, 2020; Winkler et al., 2020). Therefore, available effective solutions should be utilized to overcome the limited medical resources and to treat patients with depression. Some self-guidelines such as routine physical activity and breathing exercise, sleep hygiene, and mental therapy have been advocated to relieve stress (McIntyre & Lee, 2020; Razai et al., 2020).

These methods are in line with the TCM treatment strategies, such as Qigong, Five Elements Musical Therapy, and Five Elements Emotional Therapy, which have existed for thousands of years. Compared with the above trivial treatments and conventional antidepressants, TCM has the advantages of systemic and persistent effects, low drug resistance, and fewer adverse effects. TCM emphasizes the integrity of man and nature with simple, convenient, cheap, and efficient characteristics. Therefore, TCM therapy is mild and available to most. Indeed, various TCM therapies have been proven to be effective by a large number of clinical trials. Thus, TCM might be a potential alternative treatment option for COVID-19-induced stress.

2.3 | TCM treatment methods for depression

TCM is an empirical medicine with a long history and is based on TCM theories and practical experiences. It is an integral part of Chinese traditional culture. The diagnosis, treatment methods, and guiding principles of TCM are fundamentally different from Western medicine. TCM is abstruse and difficult to be verified by modern scientific methods, so the scientific community's acceptance of TCM is limited (Jiang, 2005). TCM takes human-nature (environment)-society (psychology) as the medical model and is influenced by multiple disciplines, especially by ancient Chinese philosophy. TCM emphasizes strengthening and rebalancing the body-mind network (balance between "Yin" and "Yang"), which corresponds to the concepts of sympathetic nervous system and the parasympathetic nervous system in modern medicine (Heine, 2004; Wong et al., 2001). Therefore, TCM has an important influence on health care and disease prevention. The therapeutic methods used in TCM are herbal medicine, acupuncture, and other physical therapies. More and more evidence suggested that not only the contribution of TCM to modern medicine is appreciated, but

it is also expected to make a greater contribution to the development of modern medicine around the world (Wang et al., Wong, and Liao 2018).

TCM has a unique effect on mental illness and is known to be as effective as Western medicine. Although ketamine and related agents can rapidly cure depression, the rapid-acting agents might be beneficial only for patients with severe forms of depression. Moreover, the psychotomimetic, dissociative, and abuse potentials of these agents are troublesome to humans. For most patients with mild and moderate depression, the best treatment is the individualized therapy tailored by each patient's main cause which could implement appropriate drug therapy or psychotherapy. Thus, TCM may be an alternative treatment for this problem (Zhang & Cheng, 2019). A large meta-analysis on the effects of TCM concluded that acupuncture, Qigong, and Five Elements Musical Therapy could relieve anxiety and alleviate sleep disturbance, and may even lower the depression level (Tao et al., 2016). The present review summarized the therapeutic effects of Qigong, Acupuncture, Five Elements Musical Therapy, Five Elements Emotional Therapy, and Chinese herbal medicine on COVID-19-induced depression (Figure 1).

2.3.1 | Qigong

Qigong, as an ancient health exercise, can be traced back to as early as 2,000 BC when ancient people found that dancing could promote and strengthen human health. With the passage of time, it gradually became a popular mental and physical exercise. "Qi" is a TCM concept; it is a kind of quantitative energy in the Western sense (similar to the concept of vitality proposed in the 19th century), and it is the connection in the universe, which exists in a virtual form (Kaptchuk, 2002). Qigong achieves the overall balance of Yin and Yang through the mobilization of Qi flow (encouraging and accelerating the body's self-repair ability) throughout the body to maintain health. It consists of concentration, relaxation, meditation, breathing regulation, body posture, and exercise. It can be defined as a body and mind movement, which enhances mental focus, corresponding to the concept of mindfulness meditation movement.

Currently, Qigong has gradually evolved into various national health care activities. The most widespread are Baduanjin (八段锦), Ma Wang Dui Dao Yin Shu (马王堆导引术), Wuqinxi (五禽戏), Yijin Jing (易筋经), and Liu Zi Jue (六字诀). Many people can improve physical condition and prevent illness through Qigong activities. In addition to China, Qigong has been accepted by many other countries because of its positive effects. In America,

TCM

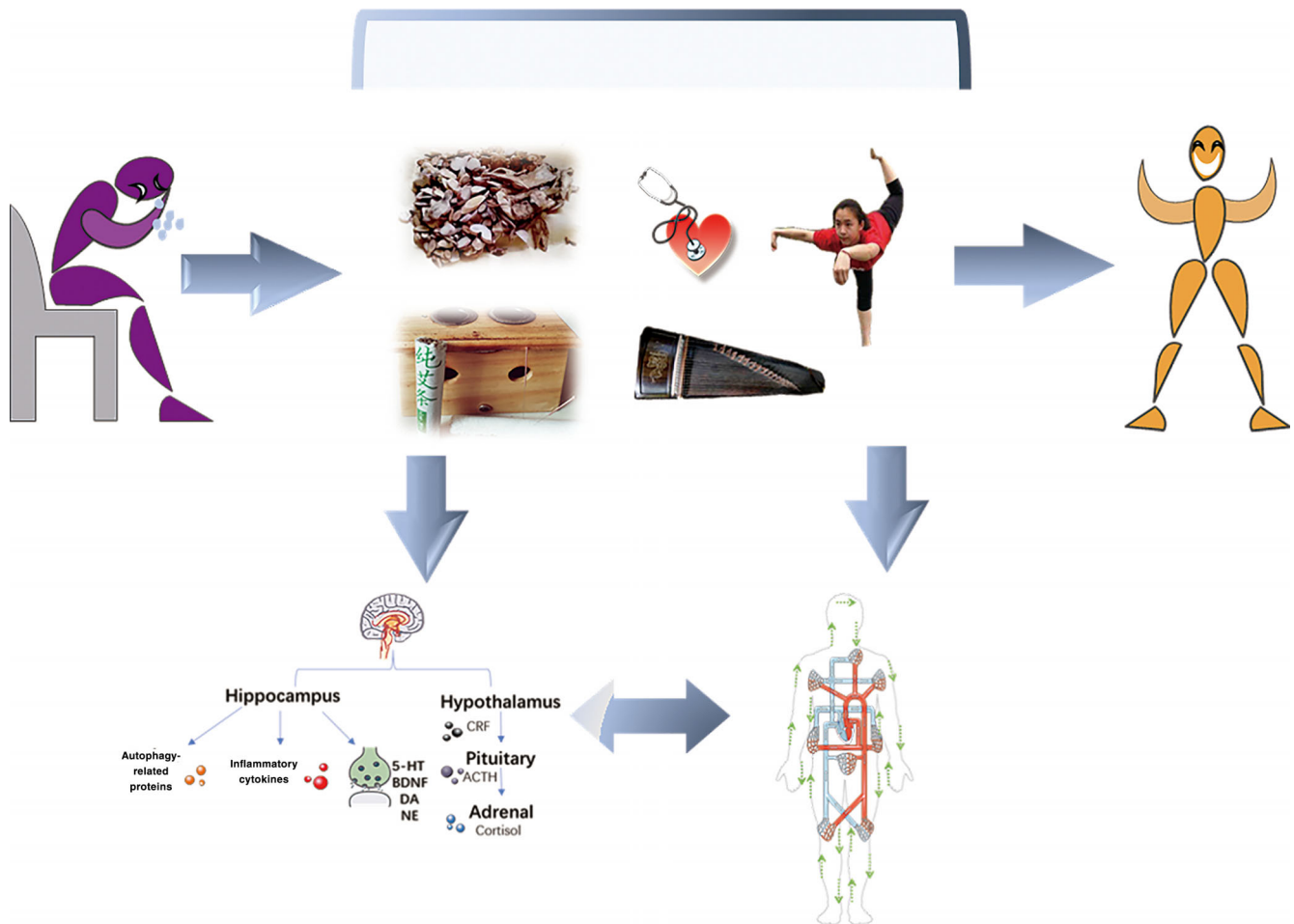


FIGURE 1 Traditional Chinese medicine (TCM) for depression

there are approximately 7.38 million adults practicing tai chi, Qigong, or both (Lauche et al., 2016), and the number is increasing. A new survey suggested that the proportion of U.S. Qigong users increased from 5.8% in 2002 to 14.5% in 2017, and only 6.6% were recommended to practice Qigong by their medical doctors; hundreds of people practiced voluntarily. There are three main reasons for the recognition and acceptance of Qigong: (a) it is beneficial; (b) the practice focuses on the whole body; and (c) the practice is natural (Wang, Zhang, et al., 2017). According to current reports, Qigong has been proven to have a positive effect on lumbar spondylosis, limb diseases, cervical diseases, heart disease, central nervous disorders, immune dysfunction, and psychological illness (Chen et al., 2019). In particular, Qigong has been shown to improve mental health.

The data showed that Qigong is beneficial for depression. A meta-analysis about the effect of Qigong on self-rating depression and anxiety scale scores of chronic

obstructive pulmonary disease (COPD) patients showed that Qigong could improve anxiety and depression symptoms of COPD patients. Moreover, it had auxiliary effects on ameliorating lung function (Wu et al., 2019). Another randomized controlled trial focused on older hospitalized patients and observed how different rehabilitation methods can change the quality of life. The results indicated that compared with usual care, structured Qigong intervention combined with usual care better alleviated depression and improved quality of life (Martinez et al., 2015). The meta-analytic review suggested that Qigong-based intervention could be significantly beneficial in improving the response and remission rate of major depressive disorder (MDD), compared with the control group ($p < .05$), indicating that Qigong could be an effective alternative therapy for MDD (Guo et al., 2019).

Obviously, the impact of Qigong on depression has been confirmed by many scholars. There are a few

hypotheses trying to clarify the effects of Qigong on depression, including (a) hypothalamic–pituitary–adrenal (HPA) axis, (b) renin–angiotensin system, (c) serotonin, (d) autonomic nervous system, (e) immune system, (f) metabolic system, and (g) psychological outcomes (So et al., 2019). Previous studies found a reduction in the cortisol levels and the occurrence of depression in the Qigong-practicing group, compared with the control group (Chan et al., 2013). In addition, some studies showed that there were significant differences in the level of C-reactive protein between the Qigong-practicing group and the control group, and there was also a significant depression reduction in the Qigong-practicing group compared with the control group (Payne et al., 2017). Tsang et al. (2013) observed that depression was remarkably correlated with self-efficacy, and Qigong was able to relieve depressive symptoms and improve physical and psychosocial wellness. The antidepressive mechanism of Qigong needs to be further explored, while the curative effect of Qigong is very practical and helpful.

Qigong is a low-cost and engaging treatment for patients. Moreover, Qigong does not have any side effects. Based on the previous studies, Qigong can be promoted as a preventive intervention, so that the public can prevent suffering from clinical depression and other chronic diseases (So et al., 2019). Particularly in the COVID-19 pandemic, Qigong is a good choice for preventing depression and can be easily performed at home. To keep the mind and body healthy, what a person needs to do is only practicing a series of simple exercise postures. In China, Baduanjin has become a national fitness and virus prevention exercise, and has been widely publicized. It can also be used to achieve positive effects in this pandemic. The previous meta-analysis results on the improvement of depression symptoms by Baduanjin showed that the scores of self-rating depression scale and the Hamilton depression scale for Baduanjin treatment groups were better than those of control groups (Dingrong et al., 2019). Thus, Qigong can be turned into a national health promotion activity that can strengthen people's physical and mental wellness.

2.3.2 | Acupuncture

Acupuncture is a unique treatment for diseases in China and is originated thousands of years ago. It is based on the concept of Qi (energy) which flows through the meridian (channels). The acupuncture points (acupoints) lie along the meridians, which are stimulated to treat various diseases. There are 365 designated acupoints on meridians, which can be stimulated to relieve the blockage of Qi and balance Yin and Yang (Uletta et al., 1998).

Acupuncture can be used to treat a wide range of diseases such as, diseases of the nervous system and musculoskeletal system, connected tissue diseases, tumors, diabetes, and digestive system diseases. Modern studies through functional magnetic resonance imaging found that acupuncture could regulate neuroendocrine and immune systems. It is believed that acupuncture can be used as a neuromodulation input to the central nervous system (Ernst, 2006; Yang et al., 2020). Additionally, acupuncture therapy has other advantages, such as rapid and obvious curative effects, simple and easy methods, relatively low medical cost, and few side effects. Therefore, Western health professionals are increasingly interested in this practice. According to the World Health Organization (WHO) report, acupuncture has been used in at least 78 countries. Among different types of TCM treatments, acupuncture is the most recognized and accepted one (García-Escamilla et al., 2017).

Acupuncture has a long history of treating depression with good therapeutic effects. Studies have shown that acupuncture could regulate the mental state and behavior of patients effectively and can improve their quality of life (Zhang et al., 2010). Clinical research about the effects of acupuncture on sleep quality and depressive symptoms in patients with depression found that the augmented acupuncture protocol had a better efficacy to treat depression and improve sleep quality of patients with depression compared with the standard protocol (Wen et al., 2018). In another clinical trial, it was found that acupuncture treatment was able to improve depression (Bosch et al., 2015). Acupuncture has been demonstrated to have positive therapeutic and preventive effects on depression caused by stroke, perimenopause, and other diseases. Meanwhile, the effectiveness and safety of acupuncture treatment have also been supported by the research data (Feng et al., 2019). These findings suggested that acupuncture can be as effective as antidepressants in reducing and alleviating depression.

Previous studies showed that acupuncture could significantly decrease the levels of pro-inflammatory cytokines in the hippocampus and prefrontal cortex, and could improve depression-like behaviors (Lu et al., 2016). Another study found that acupuncture treatment could effectively reduce depression-like behaviors in mice, and the therapeutic effect was induced by the modulation of central neural activity and 5-HT receptor expression in various brain regions (Lee et al., 2019). In addition, there are studies on the HPA axis that is closely related to the occurrence of depression. A previous study showed that acupuncture could significantly reduce the cortisol and ACTH levels in clinically depressed patients ($p < .05$), indicating that acupuncture had an effect on the HPA axis in patients with depression (Xu et al., 2004). Qiao

et al. (2014) found that acupuncture could downregulate the levels of serum CORT and ACTH in model rats suffering from chronic stress depression, and proposed that the effect was probably related to the regulatory function of acupuncture on HPA axis (Qiao et al., 2014). Apart from the above hypotheses, there are many other hypotheses, such as acupuncture could relieve depression through regulating several signaling pathways (including BDNF, CREB, PKA, JNK, and ERK pathways), by regulating brain-gut peptide hormones (including GAS, NPY, CGRP, and NT) and by inhibiting renin-angiotensin system (RAS) (Kou et al., 2017).

Generally, the effect of acupuncture on depression is excellent, but the specific mechanisms need to be explored. Compared with classical anti-depression drugs, acupuncture possesses a multilevel and multi-target regulatory effect and has fewer side effects. Therefore, acupuncture can be used to promote human health, thereby providing the possibility to improve medical care.

2.3.3 | Five Elements Musical Therapy

Musical therapy is a treatment to diseases that has become widely acknowledged in recent years, while originally emerged thousands of years ago in ancient India and Western Egypt where musical therapy was used to relieve the suffering of sick people and to relieve pain during childbirth. Data have shown that musical therapy is helpful for disease treatment. Notably, musical therapy has a good effect on patients with depression, which can regulate mood and sleep. A systematic review has shown that the combination of musical therapy and conventional therapy was superior to conventional therapy alone. Besides, musical therapy had a positive effect in reducing depression. The study reported that musical therapy should be personalized and tailored according to the characteristics of individual patients (Aalbers et al., 2017).

The history of musical therapy in China can be dated back to the Neolithic Age. Then, with the origin of TCM theory, Chinese musical therapy and Chinese medicine theory combined to form a unique set of musical therapy, namely five elements of musical therapy. The five elements of music consist of five scales, including Gong, Shang, Jue, Zhi, and Yu (宫, 商, 角, 徵, 羽), which represent the basic elements of Chinese classical music. In addition, the five elements of music not only indicate five scales but also correspond to the five elements (Earth, Metal, Wood, Fire, and Water, respectively) of TCM, which represent five different attributes and characteristics of nature and the human body. In TCM theory, five elements correspond to five organs (liver, heart, spleen,

lung, and kidney) and five emotions (anger, joy, thought, sadness, and fear). Five scales can mediate five emotions by having certain effects on five organs, so as to achieve the purpose of treating diseases (Liu et al., 2021) (Figure 2).

The earliest method of Five Elements Musical Therapy can be found in the Yellow Emperor's Internal Classic, which has related narratives. For instance, it records that "Gong is melodious and harmonious, and can help the body to digest better and increase appetite." It used the principle of mutual stimulation and restraint between the five elements, and the principle of five scales, five elements, five organs, and five emotions being interlinked. Similarly, for people with depression, there is a musical therapy. In addition to ancient records, there are many modern studies related to it. In a clinical study on nursing students with depressed mood, the data showed that depression and salivary cortisol levels decreased significantly with musical therapy over time as reflected by pretreatment and post-treatment scores. By comparing the treatment group with the control group, the depression level of nursing students was found significantly reduced, demonstrating that Chinese Five Elements Musical Therapy could improve depression (Chen et al., 2019). In another randomized controlled trial, scholars found that progressive muscle relaxation training combined with Five Elements Musical Therapy could be used to mitigate anxiety and depression symptoms in cancer patients (Liao et al., 2018). A recent study showed that Five Elements Musical Therapy could improve the behavior of rats by regulating glutamatergic and GABAergic, which provided a scientific basis for its intervention in neuropsychiatric diseases (Hao et al., 2020).

Musical therapy is a convenient and concise auxiliary treatment method and has no adverse reactions. It is a good treatment method for depression. The Five Elements Musical Therapy combined with TCM can be used for depression caused by different reasons, and can improve the mood and physical quality of patients with depression.

2.3.4 | Five Elements Emotional Therapy

Five Elements Emotional Therapy is a method in TCM for the treatment of diseases. It is a psychological therapy that uses one or more emotions to regulate, control, and overcome one or more unhealthy emotions based on the theory of TCM, so that people's mentality can reach a dynamic balance, thereby treating certain mental and physical disorders caused by emotion. The therapy is similar to the Five Elements Musical Therapy. Recorded in

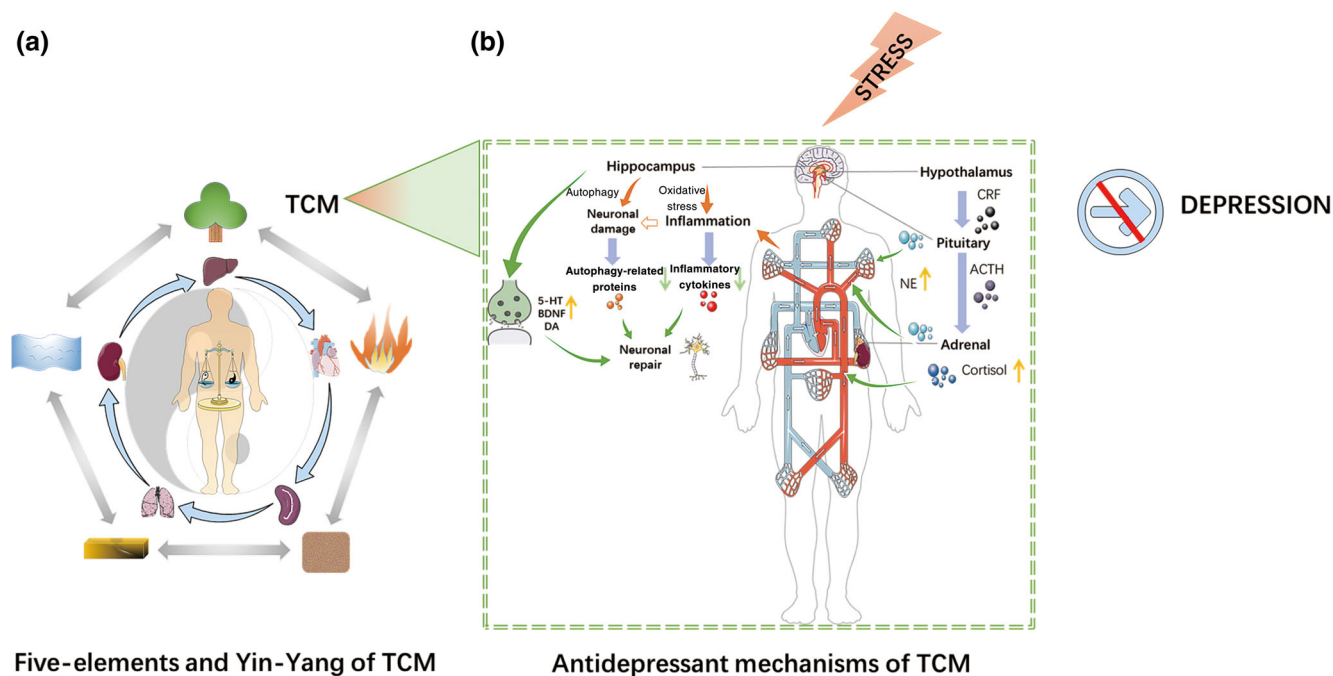


FIGURE 2 (a) Five-elements and Yin–Yang of traditional Chinese medicine (TCM) and (b) antidepressant mechanisms of TCM

the Yellow Emperor's Internal Classic: "Anger hurts the liver, sadness overcomes anger; joy hurts the heart, fear overcomes joy; thought hurts the spleen, anger overcomes thought; sadness hurts the lung, joy overcomes worry; fear hurts the kidney, thought overcomes fear" (Ye et al., 2019). In brief, it indicates that when one emotion is too excited, it can damage the organs defined in the corresponding Chinese medicine theory. Therefore, it is necessary to suppress one overexcited emotion by another emotion, so that the whole body can stay healthy.

Depression is a common emotional illness, often manifested by decreased interest and low mood. The presentations of depression resemble those of sadness, thought, and fear among the five elements of emotion. Thus, using joy to ease the excessive sadness can keep the patient temporarily away from the unhealthy mood's influence. Many modern studies have shown that when people are joyful, the secretion of vasopressin could increase, which can alleviate depression symptoms (Zhang et al., 2017). The data proved the applicability of the theory of joy and sadness to the treatment of depression. For depression caused by over-worrying, patients suppressed emotions are vented, so that their low mood is improved. For depression caused by excessive fear, patients can be guided through various ways to think about the events of fear to promote their rationality, so as to get rid of the spiritual shackles, and fear will naturally disappear.

Therefore, the method of contemplation can overcome fear, and at the same time, can improve psychological endurance.

Five Elements Emotional Therapy is simple, easy to operate, and can be performed in daily life. But for some special types of depression, it may take a longer period of treatment. A clinical study revealed that acupuncture combined with emotional therapy could effectively improve depressive symptoms in patients with alcohol dependence (Xin et al., 2016), and emotional therapy is increasingly used in combination with other antidepressive therapies. These unique Chinese ancient psychotherapy ideas can be used as references in modern psychotherapy theories. Several popular modern therapies, such as pet therapy and manual therapy are also being used as part of emotional therapies to relieve depression and anxiety.

2.3.5 | Chinese herbal medicine

Chinese herbal medicine originated thousands of years ago and has grown and matured progressively with the development of Chinese civilization. With the improvement of the theoretical system of TCM and the continuous understanding of diseases and TCM, the use of Chinese herbal medicine has started entering the medical-treatment model. Until modern civilization, Chinese herbal medicine has been explored by various

technologies, such as the biomolecular technology. At present, the methods of Chinese herbal medicine in treating depression mainly include Chinese herbal formula treatment and Chinese patent medicine treatment in clinical settings.

Chinese herbal formula

We searched through the two databases of China National Knowledge Internet and PubMed and found several Chinese herbal formulas, which had been most researched. They are Chaihu Shugan San (柴胡疏肝散), Xiaoyao San (逍遥散), and Sini San (四逆散).

- Chaihu Shugan San (柴胡疏肝散)

Chaihu Shugan San has the functions of soothing the liver, regulating Qi (疏肝理气), promoting blood circulation, and relieving pain. The efficacy of Chaihu Shugan San has been demonstrated by the clinical data obtained from treating 35 cases of depression. The total effective rate was 97.14%, and there were no serious adverse reactions (Jia, 2015). Another clinical study found that the total effective rate was 90% in 40 depression patients treated with Chaihu Shugan San for 4 weeks (Sun, 2016). Researchers have found that the antidepressant mechanisms of Chaihu Shugan San could be related to increasing the level of monoamine neurotransmitters, regulating the expression of BDNF, increasing the expression of 5-HT_{1A} receptor mRNA, and inhibiting the expression of cJun amino terminal kinase protein in the hippocampus (Gao et al., 2018)

- Xiaoyao San (逍遥散)

Xiaoyao San (XYS) has the functions of soothing liver-Qi stagnation (疏肝解郁), nourishing the blood, and strengthening the spleen (养血健脾). It is a commonly used prescription for treating depression in TCM (Hou et al., 2020). A study on the efficacy of YYS in patients with poststroke depression showed that the total effective rate in the YYS group (93.3%) was higher than that of the fluoxetine group (90.0%; Liu et al., 2017). There are some hypotheses regarding YYS antidepressant mechanisms, including its ability to increase the level of norepinephrine in the plasma, increase the level of monoamine neurotransmitters in the hippocampus, increase the 5-HT_{1A} receptor in the brain and BDNF expression, downregulate the expression of autophagy-related proteins Belin-1 and LC3 in the hippocampal CA3 region, and promote the conversion of tryptophan into 5-HT in the hippocampus region (Gao et al., 2018).

- Sini San (四逆散)

Sini San has the effects of harmonizing the liver and spleen (调和肝脾), relieving pathogenic factors, eliminating depression (除邪解郁), strengthening the spleen, and nourishing the liver (健脾养肝). It has been demonstrated that Sini San could increase the 5-HT and DA levels and increase the expression of 5-HT_{1A} mRNA in the brain. Furthermore, Sini San has also been shown to regulate monoamine neurotransmitter and protect neurons in the brain (Li et al., 2017). A clinical study showed that Sini San combined with paroxetine can significantly increase the level of 5-HT and reduce the level of cortisol, and its therapeutic effect (82.50%) was found to be better than that of paroxetine alone (67.50%) (Lili et al., 2019).

Chinese patent medicine

In order to make it convenient for people to take medicines, Chinese medicine formulas have been developed into Chinese patent medicines by a special processing method, which have the same effects as their corresponding Chinese medicine formulas. All the Chinese medicine formulas mentioned above are currently sold in the form of Chinese patent medicines. Besides the classical Chinese medicine compounds that were made into Chinese patent medicines, there are some new Chinese patent medicines, such as Shuyu capsule (疏郁胶囊) and Yixin Ningshen tablet (益心宁神片). Clinical studies showed that Shuyu capsule had a clinical efficacy equivalent to that of fluoxetine in the treatment of vascular depression (Li et al., 2010). A previous study suggested that Shuyu capsule could reverse low-level protein expression of p-ERK, p-CREB, and BDNF in stressed rats (Wang, Zhang, et al., 2017), increase 5-HT_{1A}R protein levels, and activate 5-HT_{1A}R-mediated cAMP-PKA-CREB signaling pathway in hippocampal neurons (Wang, Zhang, et al., 2017). These pathways work together to improve depressive behaviors. Yixin Ningshen tablet is a CFDA-approved TCM formula for treating depression, and the indications are heart Qi deficiency, heart “Yin” deficiency caused by insomnia, palpitations, memory loss, and neurasthenia. A recent study demonstrated that Yixin Ningshen tablet could treat depression by primarily targeting MAPT, CHRM1, and DRD1, and regulating serotonergic neurons, cholinergic transmission, norepinephrine, and dopamine reuptake (Wu et al., 2020). A clinical study on 120 patients with depression showed that Yixin Ningshen tablet combined with fluoxetine has satisfactory curative effects and no serious adverse reactions (Yan et al., 2018).

Chinese herbal medicine has more advantages than Western medicine in the prevention and treatment of depression, such as multitargeting, high efficacy, low

TABLE 1 Traditional Chinese medicine (TCM) treatment for depression

Types of TCM treatment	Representative method	Antidepressant mechanism	Strengths and limitations
Qigong	Prevent depression and keep physical and mental health by a series action of concentration, relaxation, meditation, breathing regulation, body posture and exercise. The common exercises of Qigong are Baduanjin, Ma Wang Dui Dao Yin Shu, Wuqinxi, Eijing Jing, and Liu Zi Jue	It is related to the HPA axis, renin-angiotensin system, serotonin, autonomic nervous system, immune system, and metabolic system (So et al., 2019)	Strengths: (a) easy, (b) convenient, and (c) safe Limitations: need to keep exercising long time on your own (Gouw et al., 2019)
Acupuncture	Stimulate the body's response by acupuncture at specific points, so as to achieve the effect of improving depression. Clinically, the five viscera acupoints such as Shenting, Baihui, and Shenmen are often stimulated to treat symptoms	By regulating inflammatory response and HPA axis, increasing 5-HT expression, and regulating brain-gut peptide hormone (Kou et al., 2017; Lee et al., 2019; Lu et al., 2016; Qiao et al., 2014; Xu et al., 2004)	Strengths: (a) multitarget; (b) efficient, durable; (c) less toxic effects; and (d) convenient Limitations: need professional operation (Zhang et al., 2010)
Five elements musical therapy	By listening to five elements music, that is, five scales of Chinese music (Jue, Zi, Gong, Shang, and Yu), corresponding to depression caused by different causes, so as to relieve depression	Related to cortisol secretion; regulating glutamatergic and GABAergic (Chen et al., 2020; Hao et al., 2020)	Strengths: (a) easy, (b) convenient, and (c) safe Limitations: slow effect
Five elements emotional therapy	Using emotion of joy to overcome depression caused by excessive sadness Using emotion of anger to overcome depression caused by thought Using emotion of thought to overcome depression caused by excessive fear		Strengths: (a) easy, (b) convenient, and (c) safe Limitations: need someone to guide
Chinese herbal medicine	Chinese medicine formula	Chaihu Shugan San Xiaoyao San	By increasing the monoamine neurotransmitters level in the hippocampus, and by increasing the expression of BDNF and 5-HT 1A receptor mRNA (Gao et al., 2018) By increasing the levels of norepinephrine in the plasma and monoamine neurotransmitters in the hippocampus, the 5-HT 1A receptor in the brain, and BDNF expression, downregulating the expression of autophagy-related proteins Belin-1 and LC3 in the hippocampal CA3 region and promoting the conversion of tryptophan into 5-HT in the

TABLE 1 (Continued)

Types of TCM treatment	Representative method	Antidepressant mechanism	Strengths and limitations
		hippocampus region (Gao et al., 2018)	
	Sini San	By increasing the levels of 5-HT and DA and the expression of 5-HT 1A mRNA, regulating the brain monoamine neurotransmitter and protective neurons (Li et al., 2017)	Limitations: (a) complex operation and (b) fuzzy mechanism (Li et al., 2020)
	Chinese patent medicine	Shuyu capsule	
		By increasing 5-HT _{1A} R protein levels and the expression of BDNF, and by activating 5-HT _{1A} R-mediated cAMP-PKA-CREB signaling pathway in hippocampal neurons (Wang, Zhang, et al., 2017)	
	Yixin Ningshen tablet	By targeting MAPT, CHRM1 and DRD1, and regulating serotonergic neurons, cholinergic transmission, norepinephrine, and dopamine reuptake (Wu et al., 2020)	

toxicity, minimal side effects, low drug resistance, and more stable efficacy. A systematic review proved that Chinese herbal medicine was associated with fewer adverse events than antidepressants (Yeung et al., 2014). Furthermore, much evidence has illustrated that Chinese herbal medicine could prevent depression at an early stage from different aspects (Zhang & Cheng, 2019). Therefore, Chinese herbal medicine might be considered as an alternative to antidepressants.

3 | THE PRACTICE OF TCM IN COVID-19-INDUCED DEPRESSION

Depression always follows after disasters. This warns us of an increased incidence of depression after the COVID-19 pandemic. Therefore, effective measures should be taken to prevent and cure COVID-19-induced depression. However, the spread of this pandemic could last for a long time. The number of people suffering from COVID-19-induced depression cannot be underestimated, which puts forward higher requirements for the prevention and treatment of depression.

TCM is one of the complementary and alternative treatments. It has been safely and effectively used for thousands of years. TCM has a positive role in improving the clinical practice of Chinese medicine. The clinical research supports Chinese medicine and acupuncture with the use of the dialectical theory, and demonstrates a positive effect

of TCM. Many TCM treatments, such as Qigong, Five Elements Musical Therapy, and Five Elements Emotional Therapy can be used as daily preventive and health-care methods. Chinese medicine can also be used as an adjuvant treatment for depression. As far as the research of the depression caused by COVID-19 with TCM, some studies have shown positive results. A review study on 972 patients with COVID-19 showed that acupuncture, Chinese herbal medicine, Qigong, and other TCM alternative therapy can significantly improve the psychological symptoms of patients, including depression, anxiety, stress, sleep quality, negative emotions, quality of life, and improve their physical symptoms, such as physical activity, chest pain, and respiratory function (Badakhsh et al., 2021). Another clinical study also showed the effectiveness, too. Chao Yang et al. used auricular plaster therapy (a kind of acupuncture) and Baduanjin Exercise in patients with COVID-19 combined with insomnia, and found that the combined method can significantly improve the anxiety and depression symptoms of COVID-19 patients, and the therapeutic effect of this combined treatment is better than the oral administration of estazolam (Yang et al., 2021). These studies indicate the feasibility and effectiveness of TCM in the treatment of depression caused by COVID-19, although there are few reports in this regard. In future research, TCM has a great potential in this field. In practical terms, there are still arguments regarding TCM. For example, some studies showed that compared with the placebo group, acupuncture and Qigong did not exhibit

significantly better alleviate effects in the treatment of depression (Gouw et al., 2019; Zhang et al., 2010). The complexity of TCM compounds still needs to be further studied, and other TCM therapies lack sufficient high-quality evidence (Li et al., 2020). Therefore, in-depth analysis is needed to excavate more effective and direct evidence for the treatment of depression with TCM (Table 1).

4 | CONCLUSION

In general, TCM can be used to treat depression induced by COVID-19, and has positive and effective therapeutic effects. It may help to alleviate the current shortage of medical resources and depression, so that people can maintain a healthy body and mind in order to take on the pandemic challenges. In addition, more TCM-related research should be included in the future, so as to improve the quality of the article and provide a more reliable research basis.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Xiao-li Da: Conceptualization (lead); writing – original draft (lead). **Li-feng Yue:** Data curation (equal); formal analysis (equal); supervision (equal). **Xiaojuan Li:** Project administration (equal); writing – review and editing (equal). **Jianbei Chen:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Nai-jun Yuan:** Data curation (equal); formal analysis (equal); writing – review and editing (equal). **Jiaxu Chen:** Funding acquisition (lead); project administration (lead); resources (lead); supervision (lead); writing – review and editing (lead).

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