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Review



From the perspective of Traditional Chinese Medicine: Treatment of mental disorders in COVID-19 survivors

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ARTICLE INFO

Keywords:

COVID-19
Depression
Anxiety
Post-traumatic stress disorder
Traditional Chinese medicine

ABSTRACT

Purpose: The aim of this study is to explore the possible benefits of traditional Chinese medicine on the pathogenesis of psychological and mental health of COVID-19 survivors.

Methods: A literature search was conducted to confirm the effects of COVID-19 on psychological and mental health of survivors. In addition to this, on the basis of signs and symptoms, TCM were used on treat mental disorder as per suggested clinical and animal experimental data plus relevant records in classical Chinese medicine books written by Zhang Zhongjing during Han Dynasty. A series of treatment plans were prescribed for COVID-19 survivors with psychological and mental disorders.

Results: According to previous extensive studies focusing on effects on mental health of survivors, high incidence was observed in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) survivors. During investigations of mental health of COVID-19 patients and survivors, it is observed that they also had symptoms of mental disorders and immune dysfunction. Furthermore, it was also proposed that depression, anxiety and post-traumatic stress disorder (PTSD) were most common mental disorders requiring special attention after the recovery from COVID-19. The symptoms of COVID-19 were analyzed, and the TCM syndrome of the depression, anxiety and PTSD after recovered from COVID19 was interpreted as internal heat and Yin deficiency. These three mental disorders pertains the category of “Lily disease”, “hysteria” and “deficient dysphoria” in TCM.

Conclusion: Lily Bulb, Rhizoma Anemarrhena Decoction and Ganmai Dazao Decoction were used to treat depression. Suanzaoren Decoction, Huanglian Ejiao Decoction and Zhizi Chi Decoction were suggested for anxiety. Moreover, Lily Bulb, Rehmannia Decoction and Guilu Erxian Decoction were the formula for PTSD.

1. Introduction

Coronavirus Disease 2019 (COVID-19), which broke out in Wuhan on December 31, 2019, was an emerging, rapidly developing epidemic

and a Public Health Emergency of International Concern (PHEIC) that affected people around the world [1,2]. According to latest investigations, fever, cough and fatigue are the main symptoms of patients with mild COVID-19 while patients with severe COVID-19 might present

Abbreviations: TCM, traditional Chinese medicine; COVID-19, Corona virus Disease 2019; SARS, severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; PTSD, post-traumatic stress disorder; PHEIC, Public Health Emergency of International Concern; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; TNF- α , tumor necrosis factor alpha; NE, neurotransmitters norepinephrine; 5-HT, 5-hydroxytryptamine; DA, dopamine; FST, forced swimming test; TST, tail suspension test.

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<https://doi.org/10.1016/j.bioph.2020.110810>

Received 9 July 2020; Received in revised form 19 September 2020; Accepted 25 September 2020

Available online 30 September 2020

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with respiratory distress syndrome, shock and sepsis [3]. Both post-traumatic stress disorder (PTSD) and acute stress disorder (ASD) refer to the stress response that occurs after the person suffered a fatal and catastrophic traumatic event that is beyond the individual's capacity [4,5]. The understanding about COVID-19 has been insufficient yet, and there is no effective treatment plan for it at this stage as vaccines are still testing or trial phases [1].

Most current practice to address COVID-19, Isolation and addressing symptomatic treatment is the only option at this stage, isolation and treatment measures would lead to a battery of emotional and behavioral reactions. Past evidence suggests that mental disturbance in COVID-19 cases is closely linked to symptoms coming in survivors after large infectious diseases.

Research proved that severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) survivors had a higher prevalence of PTSD [6,7]. Besides this, individuals with PTSD often suffered from depression and anxiety as well [8]. The research found that 59 percent of those who fully met the PTSD diagnosis had anxiety disorder and 34.5 % had depression [9]. According to the investigation results of Ju *et al*, nearly 50 % of COVID-19 patients in isolation ward suffered from ASD, along with anxiety, depression, insomnia and other mental and psychological symptoms [10]. Moreover, a clinical survey of 68 patients with COVID-19 showed that the anxiety score was (60.20 ± 2.04) , the incidence rate was 70.6 % (including 32 cases of mild anxiety, 20 cases of moderate anxiety and 3 cases of severe anxiety), the depression score was (64.03 ± 3.21) , and the incidence rate was 73.5 % (including 34 cases of mild depression, 15 cases of moderate depression and 1 case of severe depression) among them [11]. Therefore, patients recovering from COVID-19 are more likely to suffer from PTSD, anxiety and depression.

Unfortunately, there are many limitations to treat mental disorders. Serotonin reuptake inhibitors (SSRIs) and Norepinephrine reuptake inhibitors (SNRIs) are commonly used as antidepressants drugs for the treatment of PTSD. However, their clinical application was very limited (more or less 50 %), and this treatment regime comes with possible side effects such as headache, dizziness and increased muscle tension [12]. Although benzodiazepines had a significant anti-anxiety effects, but because of respiratory inhibition effects of these drugs are not suitable for patients with pulmonary damage related to COVID 19 [10]. On the other sides, TCM therapy has the advantages of multi-pathway and multi-target, and is comparatively safer option. In addition to this, Chinese herbs treat symptoms and deal with causes of disease, and it can

remedy the remaining symptoms of COVID-19 at the time of treating mental disorders.

In this review, we were trying to find the pathogenic factors of mental disorders in COVID-19 survivors from the perspective of both western medicine and traditional Chinese medicine theory, and trying to put forward the corresponding TCM treatment plan (Fig. 1).

2. Occurrence possibility of mental disease in COVID-19 survivors

2.1. Sudden epidemic is the cause of mental illness

Based on the researches, all of sudden and life-threatening events, people would experience the corresponding psychological stress reaction and emotions such as anxiety, fear and loneliness. A small number of people could even suffer into mental distress [13]. Studies demonstrated that the prevalence of all kinds of mental illness within 30 months after the outbreak of SARS was 33.3 %, and a quarter of the patients had PTSD, while 15.6 % underwent depression disorder [14, 15]. Besides this, a four-year follow-up of 233 SARS survivors showed that more than 40 % claimed to be suffering from mental illness, and 40.3 % reported chronic fatigue problem [16]. In addition to this, many patients and medical workers went through severe emotional stress during the outbreak period of MERS [7]. When the epidemic was controlled, many medical workers and recovered patients would be bothered with anxiety, depression and even PTSD [7]. COVID-19 is a respiratory infection caused by corona virus that similar to SARS and MERS. An investigation on the basic reproduction number of SARS-COV-2 transmission proved that the R_0 (2.8, 3.9) of SARS-COV-2 was higher than the R_0 (2.2, 3.7) of SARS-COV, but lower than the R_0 (2.0, 6.7) of MERS-COV, indicating that SARS-COV-2 was a medium-high infectious disease [17].

On January 30, 2020, the world health organization declared the outbreak of COVID-19 in Wuhan, central China as a Public Health Emergency of International Concern (PHEIC) [18]. So far, there is no treatment of covid-19 available and the number of infections continuously increasing. Until Thursday, May 31, 2020, more than 6.15 million people had been infected [19], i.e. more than the total number of people infected with SARS and MERS. Therefore, due to the fear of disease, physical discomfort, drug side effects and social isolation, COVID-19 patients might be suffering from loneliness, anger, anxiety, depression, insomnia and PTSD in the period of treatment and isolation [20]. The

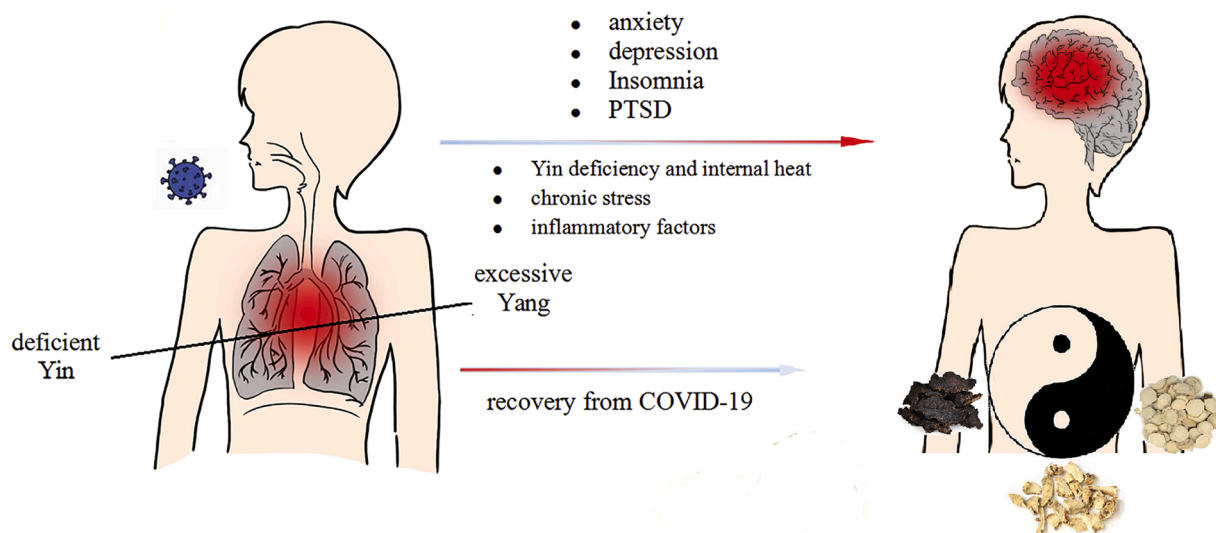


Fig. 1. COVID-19 leads to excessive Yang, internal heat and deficient Yin, which result in the imbalance of Yin and Yang. Then, COVID-19 survivors may suffer from depression, anxiety, insomnia and PTSD. Traditional Chinese medicine can restore the balance of Yin and Yang in human body to treat the mental and psychological symptoms.

investigation suggested that the medical workers infected with COVID-19 had varying extent of depression, anxiety and sleep disorders [21]. A recent study on 714 COVID-19 patients confirmed that the prevalence of significant post-traumatic stress symptoms among the recovered patients was 96.2% [22]. Furthermore, studies demonstrated that patients with COVID-19 showed higher level of depression, anxiety, and PTSD than people without COVID-19 [23]. Therefore, the mental health of COVID-19 survivors needed to be noticed.

2.2. The close relationship between inflammatory cytokines and mental disease

Wang et al. [24] analyzed 138 cases of hospitalized COVID-19 patients, and they observed that the number of neutrophils cell were increased in patients. That might be related to cytokine storm during the invasion of virus. Recent clinical studies had been done to [25,26] summarize the clinical characteristics of COVID-19 patients. It's also proposed that compared with healthy people, COVID-19 patients' lymphocyte count was significantly less. Besides this, their inflammatory factors such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10) and the tumor necrosis factor alpha (TNF- α) were markedly high. These levels of cytokines were sharper in critically ill patients with pneumonia [26]. Therefore, patients with COVID-19 showed signs of immune dysfunction and elevated levels of inflammatory cytokines.

Meanwhile, several researches had provided obvious evidences which indicates that immune system activation, pro-inflammatory cytokines were concern with psychiatric symptoms [27]. Consequently, patients with COVID-19 could have a higher propensity to be attacked by mental disorders than normal people. There was evidence to support the cross-correlation between cytokine levels and depression risk in many diseases [28]. Along with this, depression may be related to infectious diseases which had been supported by the conclusion of relevant studies [29]. In addition, a meta-analysis which brought into 54 studies demonstrated that levels of pro-inflammatory cytokines, especially IL-1 β , IL-6, and TNF- α , were associated with depressive symptoms [30]. An excessive dose of interleukin-1beta had been affirmed to be associated with neuro-inflammatory degenerative diseases and mental disorders [31]. Shim et al. stated that lateral ventricular IL-1 β could induce anxiety-like behavior in rats [32]. Moreover, systematic reviews had also found that higher levels of interleukin 6, interleukin 1beta, and TNF- α were interrelated with PTSD [33]. As a result, it is necessary to pay close attention to their mental health during and after the treatment.

3. The pathogenesis explained by traditional Chinese Medicine theory

Traditional Chinese medicine doctors named highly infectious and easily prevalent disease as "Yi disease", which meant epidemic, and considered its etiology as "Yi Qi" [34]. Thus, in accordance with TCM theory, COVID-19 pertained to the category of "Yi disease" [35]. Referring to the theory of TCM, "Yi Qi" entered the human body from the mouth and nose, while the mouth connected the spleen as well as the whole digestive system, and the nose linked the lung as well as the total respiratory system [36]. While, COVID-19 in the infected patients would first affect the lung and spleen, leading to abnormal function of lung and spleen, and triggering a series of digestive and respiratory symptoms [36]. The above statements were consistent with the clinical reports that patients with COVID-19 had not only respiratory symptoms, but also metabolic disorder symptoms such as diarrhea and vomiting [37].

The harmonious and consistent unity of body and emotion was the stand point of TCM. Therefore, the emotions of patient were concerned with the function of Five Organs (heart, liver, spleen, lungs and kidneys) [38]. Seven main emotions in TCM (anger, joy, worry, thinking, sadness, fear, shock) were regulated by the state of function of the Five Organs, meaning that the Five Organs control the generation and change of

Seven emotions. When the status of Five Organs changed, the moods changed accordingly [38]. The lung controlled worry and sadness, while the spleen controlled thinking [39]. As a result, once lung and spleen was invaded by "Yi Qi", the moods controlled by them would also be abnormal. Then, the patients would be bothered with sadness, or they could be tired of over thinking. Consequently, there was a tendency that the COVID-19 survivors suffered from psychological disorders.

Additionally, there was a view in the TCM theory that the diseases with sign of fever could cause the loss of Yin fluid in human body [34]. Yin fluid referred to body fluid and blood [40]. During the development of COVID-19, "Yi Qi" could cause internal heat in body resulting in the symptom of fever that consumed yin fluid. As a result, the balance of Yin and Yang was broken and the deficiency of Yin led to the relative excess of Yang. Yin was supposed to be cold while Yang was considered hot. Then the relative excess of Yang could make the internal body hotter than normal, which contributed to the internal heat and Yin deficiency syndrome.

Recently evidences demonstrated that 81.8% of the COVID-19 survivors had been identified by TCM as deficiency of QI and YIN, the main symptoms of them were dry mouth, thirsty, palpitation, dry cough without phlegm, and the symptoms were caused by the internal heat and Yin deficiency [41]. As long as the internal heat and Yin deficiency syndrome occurred, the heart would be influenced. In the TCM theory, the emotions were controlled by the Five Organs and their generations and changes were decided by heart [38,42]. Internal heat could disrupt the heart's dispensing and commanding, Therefore, the patients would feel more sadness, and over thinking as well as abnormal anxious and grim [42].

Synopsis of Prescriptions of the Golden Chamber is a classic book of TCM, which provided a record of "Lily disease" caused by internal heat and Yin deficiency in heart and lung. The main symptoms were willingness to eat, loss of appetite, daily in a bad mental, less words, fatigue but unable to sleep, unable to walk. They concluded that a series of symptoms could appears including psychological abnormalities; paresthesia and eating behavior abnormalities [43]. These symptoms were very similar to those of depression [44].

Another classic book of TCM *Typhoid fever theory* recorded an opinion that after fever, internal heat had not been cleaned, which contributed to "deficient dysphoria disease", an internal heat disease due to deficiency of Yin. The symptoms of "deficient dysphoria" such as insomnia, restlessness were consistent with the clinical manifestations of anxiety [45].

"Lily disease" can be characterized by wandering mind and confusing the illusion and reality, which was similar to PTSD patients' traumatic memory forced into mind to reproduce the event scene in the form of flashbacks or nightmares, compelling them repeatedly to experience the emotion and feeling of that time. On the basis of concept and clinical manifestations of PTSD, Guo also considered PTSD as a kind of "Lily disease", and proposed PTSD of heart-lung Yin deficiency syndrome type [46]. Therefore, as explained in TCM, the abnormal functions of the Five Organs and seven emotions caused by "Yi Qi" and internal heat and Yin deficiency syndrome were the main etiological factors of mental disorders in patients recovering from COVID-19.

4. Therapeutic methods proposed by traditional Chinese Medicine theory

4.1. Depression

Classic decoctions of TCM such as Lily Bulb and Rehmannia Decoction, Lily Bulb and Anemarrhenae Decoction and Ganmai Dazao Decoction were used to treat the depression (Table 1). Lily Bulb and Rehmannia Decoction were composed of lily bulb and raw Rehmannia root juice. It had the functions of nourishing Yin and clearing heat, tonifying and normalizing heart and lung, and was the first decoction for Lily disease. Lily Bulb and Rehmannia Decoction could be applied to the treatment of depression induced by various etiologies [47]. Change the

Table 1
Ingredients of commonly used TCM decoctions for the treatment of depression.

Decoctions	Components	TCM efficacy
Lily Bulb and Rehmannia Decoction	<i>Lilii Bulbus (lily bulb) and Rehmannia glutinosa Linosch (raw Rehmannia root juice)</i>	nourishing Yin and clearing heat
Lily Bulb and Anemarrhenae Decoction	<i>Lilii Bulbus (lily bulb) and Rehmannia glutinosa Linosch (raw Rehmannia root juice), Anemarrhena asphodeloides Bge (Rhizoma Anemarrhena)</i>	nourishing Yin and powerful clearing heat
Ganmai Dazao Decoction	<i>Liquorice Root Radix Glycyrrhizae (licorice), Triticum aestivum L. (Float wheat fruit), Jujubae Fructus (jujube)</i>	nourishing Yin of heart and calming mind

composition of Lily Bulb and Rehmannia Decoction and add Anemarrhena asphodeloides Bge, then Lily Bulb and Rehmannia Decoction became Lily Bulb and Rhizoma Anemarrhena Decoction. Anemarrhenae was cold in TCM theory, and it would turn the efficacy of decoction colder [48]. By adding Anemarrhena asphodeloides Bge., the heat-clearing function of the decoction could be strengthened, making it more suitable for those who were already diagnosed as internal heat and Yin deficiency syndrome with more heat.

Ganmai Dazao Decoction was indicated for “Hysteria disease”, whose symptoms were sadness, crying, mood disorders, and abnormal behavior, which were very similar to the symptoms of depression. Ganmai Dazao Decoction was composed of Liquorice Root Radix Glycyrrhizae (licorice), Triticum aestivum L. (Float wheat fruit) and Jujubae Fructus (jujube), which was a decoction aiming at nourishing Yin of heart and calming mind [49]. Lily Bulb and Rehmannia Decoction, commonly used in modern clinical practice for a long time in combination with modern medical drugs, had achieved considerable results in the treatment of depression caused by multiple causes [50]. Guo et al. had observed the curative effect of Lily Bulb and Rehmannia Decoction combined with Flupentixol and Melitracen Tablets in the treatment of menopausal depression and found that the total clinical effective rate of the combined group was significantly higher than that of the single group [51].

Furthermore, Lily Bulb and Rehmannia Decoction was able to alleviate the symptoms of depression patients with Yin deficiency and internal heat syndrome remarkably and long-term administration was not harmful [52]. In addition, the investigation used Lily Bulb and Rehmannia Decoction combined with fluoxetine for 6 weeks, confirmed that it was able to reduce the anxiety somatization factor and sleep factor, and the efficacy was more obvious than single modern depression intervention medicine [53]. Yan et al. adopted Ganmai Dazao Decoction combined with Lily Bulb and Rhizoma Anemarrhena Decoction to treat depression. Compared with conventional modern medicine, the decoctions were safer and the incidence of adverse reactions was less [54]. Liu et al. took use of Ganmai Dazao Decoction combined with Lily Bulb and Rhizoma Anemarrhena Decoction in the treatment of depression, which effectively alleviated the depression symptoms of patients and improve the sleep status [55]. The research indicated that modified Ganmai Dazao Decoction had clinical efficacy and safety in the treatment of perimenopausal patients with initial severe depression, which mechanism may be related to the regulation of monoamines and amino acid neurotransmitters, the regulation of immune inflammation, and the reduction of the level of inflammatory factors [56].

In addition to this, some animal experiments had been carried out to explore the antidepressant pharmacological mechanism of above decoctions. After Lily Bulb and Rehmannia Decoction intervention, the content of monoamine such as neurotransmitters norepinephrine (NE), 5-hydroxytryptamine (5-HT) and dopamine (DA) were greatly increased in the hippocampus of CUMS rats, and the activity of monoamine oxidase was significantly reduced [57]. Bi et al. treated depressed rats with Ganmai Dazao Decoction, and the results showed that it could

significantly improve the depressed behavioral characteristics of rats, and significantly increase the activity and content of neurotransmitters 5-HT and NE in the brain of rats [58]. Study confirmed that Ganmai Dazao Decoction could significantly improve the depression-like behavior of CUMS rats by regulating HPA axis elevation and protecting hippocampus injury [59]. The intervention of Lily Bulb and Rehmannia Decoction combined with Ganmai Dazao Decoction could also increase the content of monoamine neurotransmitters in the brain of depression animal model [60]. Besides this, research proposed that Lily Bulb and Rhizoma Anemarrhena Decoction could alleviate the loss of pleasure and despair in depressed rats, and promote the remodeling of neurons. The mechanism behind this was related to inhibiting the hyperfunction of HPA axis and up-regulating the expression of BDNF mRNA in hippocampus of depressed rats [61]. Previous evidence showed that antidepressant mechanism of Lily Bulb and Rhizoma Anemarrhena Decoction was also related to up-regulation of monoamine transmitters in serum and cerebral cortex [62].

Furthermore, there are some experiments about active compounds of these decoctions. Evidence from Guo et al. confirmed that lily saponins, as the main component of *Lilii Bulbus*, could relieve depression symptoms, whose effect might be related to the increased level of monoamine neurotransmitters in brain and the hyperfunction inhibition of HPA axis [63]. Research suggested that lily saponins treated depression with irritable bowel syndrome by synergistically regulating the content of brain-gut peptide and the function of 5-HT nervous system in blood, stomach and intestine [47]. Further, in the alcohol extract of *Rehmannia glutinosa Linosch* is one of the main effective components with higher content of it. Study proved that catalpol had more remarkable antidepressant effect by involving monoamine nervous system than other ingredients in *Rehmannia glutinosa Linosch* [64]. Besides, research that Licorice flavonoids could shorten the immobility time of forced swimming test (FST) and tail suspension test (TST) in mice, antagonize the blepharoptosis induced by reserpine in mice and increase the number of autonomous activities in mice. By decreasing the expression of Caspase-3 protein in hippocampus of depressed rats to reduce the apoptosis of nerve cells in depressed mice, it could play an antidepressant role [65]. Moreover, Gong et al. suggested that Timosaponin in *Anemarrhena asphodeloides Bge.* reduced the contents of TNF- α , IL-1 β and IL-6 in mouse brain tissue for anti-inflammatory treatment of depression [66].

Therefore, these three TCM decoctions can be applied to the treatment of depression.

4.2. Anxiety

Suanzaoren Decoction, Huang lian E jiao Decoction, Zhizi Chi Decoction, were used for anxiety of internal heat and Yin deficiency

Table 2
Ingredients of commonly used TCM decoctions for the treatment of anxiety.

Decoctions	Components	TCM efficacy
Suanzaoren Decoction	<i>Ziziphus spinosa Hu (Ziziphi Spinosa Semen), Liquorice Root Radix Glycyrrhizae (licorice), Anemarrhena asphodeloides Bge (Rhizoma Anemarrhena), Poria Cocos (Schw.) Wolf. (tuckahoe), Chuanxiong Rhizoma (rhizome of Chuanxiong)</i>	nourishing Yin and blood and promoting sleep
Huanglian E jiao Decoction	<i>Coptidis Rhizoma (coptis), Scutellariae Radix (scutellaria), Paeoniae Radix Alba (paeonia), Colla Corii Asini (donkey-hide gelatin), fresh egg yolk</i>	nourishing Yin and heart, reducing heat and calming the mind
Zhizi Chi Decoction	<i>Gardeniae Fructus (cape jasmine), Sojae Semen Praeparatum (fermented soya beans)</i>	nourishing Yin and reducing intrathoracic heat

syndrome (Table 2). They were recorded in Typhoid fever theory, and were classic decoctions for “deficient dysphoria” and insomnia. Suanzaoren Decoction was composed of the Ziziphus spinosa Hu (Ziziphi Spinosae Semen), Liquorice Root Radix Glycyrrhizae (licorice), Anemarrhena asphodeloides Bge. (Rhizoma Anemarrhena), Poria Cocos (Schw.) Wolf. (tuckahoe) and Chuanxiong Rhizoma (rhizome of Chuanxiong), which nourished Yin and blood, and helped to promote sleep. Coptidis Rhizoma (coptis), Scutellariae Radix (scutellaria), Paeoniae Radix Alba (paeonia), Colla Corii Asini (donkey-hide gelatin) and fresh egg yolk constituted the Huang lian E jiao Decoction, which nourished yin and heart, reduced heat and calmed the mind. Zhizi Chi Decoction nourished yin and reduced intrathoracic heat especially.

Meng et al. [67] randomly divided 90 patients with generalized anxiety disorder into the observation group and the control group with 45 cases each, the observation group was treated with modified Suanzaoren Decoction, and the positive control group was treated with estazolam, the results proved that the total effective rates of the observation group and the control group were 91.11 % and 75.56 % respectively, suggesting that modified Suanzaoren Decoction was more appropriate than modern medicine in the treatment of generalized anxiety disorder. Zhang et al. [68] analyzed the clinical effect of modified Suanzaoren Decoction on cancer patients who met the CCMD-3 anxiety diagnosis standard, the total effective rate of clinical effect was higher than that of the control group and no adverse reactions were found. It indicating that modified Suanzaoren Decoction can significantly improve the mild and moderate anxiety of cancer patients. It was proved that the anti-anxiety effect of Suanzaoren Decoction might be related to the increase of NO concentration in blood and the decrease of IL-1 β , TNF- α in serum [69]. Zhang et al. [70] selected 60 patients with generalized anxiety, and randomly divided them into treatment group (30 cases) treated with Huanglian E jiao and Decoction, and control group (30 cases) that treated with lorazepam. The total effective rate of the treatment group was 93.33 % and that of the control group was 73.33 % at the fourth week of treatment. And the treatment effect of the decoction was more lasting and the adverse reactions were less than that of lorazepam. Huanglian E jiao Decoction had a better curative effect and fewer adverse reactions than fluvoxamine in the treatment of anxiety that pertained to yin deficiency and fire hyperactivity Syndrome [71]. Liu et al. reported 50 cases of anxiety treated with Zhizi Chi Decoction, and the total effective rate was 96 % [72].

In addition, study confirmed that Suanzaoren Decoction combined with Zhizi Chi Decoction was more effective than diazepam in the treatment of anxiety disorder, and the relapse rate after cessation of the medication was lower [73]. Liu et al. applied Suanzaoren Decoction combined with Zhizi Chi Decoction to the treatment of 60 cases of anxiety insomnia, and consequently the symptoms of anxiety and insomnia were significantly improved [74].

Meanwhile, there are some reports about the therapeutic mechanism and effective compounds of the above decoction. Researches considered that the anti-anxiety effects of Suanzaoren Decoction and Huanglian E jiao Decoction were both related to the increase of γ -GABAA level [75, 76]. Besides, Suanzaoren Decoction also decreased the release of NE in hippocampus and inhibited the synthesis of 5-HT [76]. Sanjoinine A isolated from Ziziphi Spinosi Semen had been proved to be concerned the GABA ergic transmission [77]. Polysaccharides and flavonoids which had certain synergistic effect on anti-anxiety in Ziziphus spinosa Hu, Anemarrhena asphodeloides Bge. and Poria Cocos (Schw.) were also important compounds in Suanzaoren Decoction [78]. In addition, study confirmed that berberine which was the main component of Coptidis Rhizoma in Huanglian E jiao Decoction could regulate the expression of monoamine neurotransmitters and their metabolites and 5-HT receptors to resist anxiety [79]. Baicalin and wogonin isolated from Scutellariae Radix both perform anti-anxiety effects mediated by γ -GABAA [80,81]. Moreover, A research mentioned that geniposides, as the main component of Gardeniae Fructus water extract, was one of the anti-anxiety components of Gardeniae Fructus [82].

Complementarily, mixed anxiety-depression disorder (MAD) was also a common comorbid psychiatric disorder that frequently-observed with PTSD [83]. Thus, COVID-19 survivors may suffer from MAD. The above three kinds of decoctions have been proved to be effective in treating depression [84].

In conclusion COVID-19 survivors with anxiety could be treated with the above three decoctions, and patients with insomnia and MAD could also take the decoctions.

4.3. Post-traumatic stress disorder

Lily Bulb and Rehmannia Decoction and Guilu Erxian Decoction were the decoctions for PTSD of internal heat and Yin deficiency syndrome (Table 3). Most of the researches on the treatment of PTSD with Chinese herbal medicine were done on animal but the less clinical studies were reported. Research suggested that patients with PTSD of Yin deficiency of heart and lung Syndrome were suitable to be treated with Lily Bulb and Rehmannia Decoction. As they showed lung dryness symptoms such as lung heat cough, which are also a common symptom in the convalescence of COVID-19. It was suggested to add Tuber Raidix Ophiopogonis (ophiopogon japonicas), Liquorice Root Radix Glycyrrhizae (licorice) in the decoction [46]. Meanwhile, if patients had insomnia, they can add Ziziphus spinosa Hu and Radix Pseudostellariae (Heterophylly Falsesatarwort Root) [46]. Furthermore, the investigation confirmed that Lily Bulb and Rehmannia Decoction could up regulate 5-HT level in hippocampus and deal with the symptoms of PTSD [85]. The results demonstrated that Lily Bulb and Rehmannia Decoction down regulated the expression of glucocorticoid receptor (GR) in hippocampus, up regulated the expression of glucocorticoid receptor (MR), and improve the symptoms of PTSD in rats [86].

Guilu Erxian Decoction was composed of antler gum, tortoise plate gum, ginseng and wolfberry fruit which nourished Yin. Li et al. demonstrated that Guilu Erxian Decoction may play an anti-PTSD role by regulating synaptic plasticity, anti-apoptosis, anti-inflammation and promoting fear memory extinction through network pharmacology [87]. Moreover, researches had confirmed that the therapeutic mechanism of was to regulating the function of the HPA axis, the expression of GR and 5-HT receptors in the hippocampus to improve the emotional and behavioral abnormalities in PTSD rats [88,89]. Besides this, study confirmed that *Lycium barbarum* polysaccharide in Guilu Erxian Decoction can reduce the level of cortisol in serum to improve the symptoms of PTSD [90]. Previous evidence showed that ginsenoside Rg2 can regulate the function of HPA axis to treat PTSD [91]. Consequently, PTSD patients could be treated with the two decoctions.

5. Conclusion

From the perspective of modern medicine, survivors of SARS, MERS and other severe and major infectious diseases were more likely to suffer from mental illness. Clinical investigation about the mental health status of patients and survivors of COVID-19 also indicated that COVID-19 was accompanied by higher possibility of psychological disorder such as depression, anxiety and PTSD. Disturbance of immune cytokines in patients with COVID-19 was also an inducing factor of mental diseases.

Table 3
Ingredients of commonly used TCM decoctions for the treatment of PTSD.

Decoctions	Components	TCM efficacy
Lily Bulb and Rehmannia Decoction	<i>Lilii Bulbus</i> (lily bulb) and <i>Rehmannia glutinosa</i> Linosch (raw Rehmannia root juice)	nourishing Yin and clearing heat
Guilu Erxian Decoction	<i>Colla Corni Cervi</i> (antler glue), <i>Tortoise Shell Caraoax et Plastrum Testudinis</i> (Tortoise-plastron glue), <i>Root Radix Ginseng</i> (Ginseng), <i>Fructus Lycii</i> (Chinese Wolfberry fruit)	nourishing kidney Yin

In regards to TCM, COVID-19 survivors are in a state of internal heat and Yin deficiency during recovery period, which leads to the abnormality of seven emotions. Therefore, the COVID-19 survivors have the tendency to develop mental disorder. “Lily disease”, “hysteria” and “deficient dysphoria” are Yin deficiency and internal mental diseases recorded in ancient Chinese medicine books. Their symptoms are very similar to those of depression, anxiety and post-traumatic stress disorder. Western medicine has many side effects and high recurrence rate in the treatment of mental diseases.

Thus, the use of traditional Chinese medicine such as “Lily disease”, “Hysteria disease” and “Deficient dysphoria disease” could be a better treatment plan option for survivors of COVID-19 suffering from mental diseases. Lily Bulb and Rehmannia Decoction, Lily Bulb and Anemarrhenae Decoction and Ganmai Dazao Decoction were used to treat the depression after the recovery of COVID-19. Suanzaoren Decoction, Huang lian E jiao Decoction, Zhizi Chi Decoction, was suggested for anxiety. Moreover, Lily Bulb and Rehmannia Decoction and Guilu Erxian Decoction were the decoctions for PTSD.

Author's contributions

ZB and KM to the concept of this study. XX, XW, SF, HZ, YL and XL contributed to literature review and data analyses. XX, HZ, AR, YW, SWG and XZ contributed to draw diagram. KM and ZB draft and finalize the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of Competing Interest

All authors declare no competing interest. All funding source just support in conduct of experiments. We strictly disclosed that all funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

This work was supported by Shandong Provincial Natural Science Foundation (ZR2019BH027, ZR2019ZD23), the major science and technology special project of Yunnan Province No. 2019ZF004, Shandong Province Universities' Development Plan for Youth Innovation Teams (2019-9-202, 2019-9-201 and 2019KJK013), National Nature Science Foundation of China (81903948), and Shandong Province University Scientific Research Project (J18KZ014J18KZ014).

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