

Five traditional Chinese medicine formulations for addressing COVID-19

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Abstract. Covid-19 has spread worldwide, with its initial outbreak occurring in China. The Chinese government employed not only Western medicine but also traditional Chinese medicine (TCM) in their response. TCM, due to its potential to enhance human immunity, was considered a valuable tool in prevention. Furthermore, the analysis of TCM recipes has shed light on their efficacy. Some of the five recipes, including LHQW, XFBD and LCDD, have been found to have the capacity to enhance the patients' immunity responses. Furthermore, specific formulations like LHQW, XFBD, and HSBD have the capability to disrupt the attachment of COVID-19 to host cells by impeding its interaction with the ACE2 receptor. It is worth noting that Western medicine (WM) has limitations, thus, leading to the exploration of a combined approach involving both TCM and WM. Clinical observations have demonstrated that the treatment combining TCM and WM is more effective compared to treatments with either approach isolation. However, further research is needed to identify more favorable treatment strategies.

Keywords: Traditional Chinese Medicine; COVID-19; LHQW; XFBD; LCDD.

1. Introduction

COVID-19, a global pandemic, is caused by an RNA virus. It emerged in 2019 and rapidly spread worldwide, originating from Wuhan, China. The widespread transmission triggered panic on a large scale because of thousands of individuals falling ill. Initially, there didn't exist any treatment for this disease, resulting in a high mortality rate around the world. COVID-19 has displayed the capacity for genetic variation across multiple generations, posing substantial challenges for prevention and treatment. Immunity alone is insufficient to fight against the virus, making it a formidable adversary for the humans. At the beginning, controlling and treating the disease proved to be an unaccomplishable task. However, contemporary medicine has developed several ways for its treatment. COVID-19 infection relies on host cell factors TMPRSS2 and ACE2. Besides, protease inhibitors are able to block it [1]. Therefore, the evaluation of herbal remedies in terms of their ability to inhibit these two proteins assumes paramount importance in assessing the potential utility of Traditional Chinese Medicine (TCM) with respect to COVID-19 therapy.

Fever, chills, and a sore throat are among the most frequently observed symptoms linked to COVID-19. Additionally, there are a spectrum of less common manifestations, such as muscle aches, a sensation of heaviness in the limbs, severe fatigue, runny or blocked nose, sneezing, among others. It is important to acknowledge that COVID-19 is an indiscriminate pathogen, capable of infecting anyone, potentially leading to severe illness or fatality. However, a majority of people will recover without the need of medical intervention. But if the patients have the symptoms like breathing difficult especially when they are at rest, an inability of speaking complete sentences, states of confusion, drowsiness or loss of consciousness, persistent chest pain or pressure, skin exhibiting cold or clammy characteristics, pallor or a bluish discoloration, as well as a loss of speech or mobility, they need to seek immediate medical attention. Despite over 13 billion doses of vaccination administered until June 2023, COVID-19 is still a large challenge owing to its capacity to infect individuals regardless of vaccination status. The people who get COVID-19 after vaccination may experience mild or no presentations [2].

Traditional Chinese Medicine (TCM) boasts a rich historical legacy and holds considerable promise for contemporary medical research. As an illustration in the field of Rheumatology, emodin, a derivative, has demonstrated its ability to prevent the binding between ACE and the S protein. Furthermore, chemical components such as glycyrrhizin, Sinigrin, and Baicalein [3-5] exhibit therapeutic promise in the context of influenza. Notably, the Chinese government has advocated for the integration of TCM with Western Medicine (WM) when treating COVID-19. During the period of epidemic, TCM has played a pivotal part in fighting in opposition to COVID-19 [2], with great achievements resulting from such strategies. However, Traditional Chinese Medicine has existed for a long time. In order to adapt it to modern technology, the analysis of drugs, compounds and targets of traditional Chinese medicine is needed. This essay will thus undertake a comprehensive review of select drugs, elucidating their constituent compounds and their respective effects for managing COVID-19.

Table 1. The effect of five recipes

Recipes	Effects
LHQW	adjust inflammatory factors block the binding between COVID-19 and ACE2
XFBD	anti-inflammatory adjust inflammatory factors
HSBD	inhibit the binding between COVID-19 and ACE2 adjust inflammatory factors antiviral activity improve oxygen saturation status
XBJ	anti-inflammatory and immune-boosting effects interfering with ACE receptors
LCDD	regulate inflammatory responses

2. LianHuaQingWen (LHQW)

2.1. Components of LHQW recipes

The LHQW capsule consists of a combination of medicinal components, including Licorice, Rhodiola, Menthol, Rhubarb, Ephedra, Wild honeysuckle flower, Patchouli, Forsythiae Fructus, Gypsum, Bitter Almond, Houttuyniae Herba, Indigowoad Root, Dryopteris Crassirhizoma [6].

2.2. The effect of LHQW in treating COVID-19

LHQW has shown efficacy in alleviating symptoms associated with COVID-19, including fever, cough, nasal obstruction, and headache [7-8]. And in the context of COVID-19 management, LHQW operates on three fronts: suppressing cytokine activity, obstructing viral attachment to host receptors, and improving its clinical utility.

When individuals contract influenza, their immune system begins to work, aiming to combat the virus, which can lead to the damage of both viral and host cells. Although the immune function helps patients defend against the disease, if it persists excessively, it can result in deleterious effects on one's health. When LHQW is used as a treatment against the virus, it has been shown to effectively inhibit the activity of four cytokines, including IL-6, TNF α , CXCL-10/IP-10 and CCL-2/MCP-1[9]. These cytokines are related to pulmonary inflammation and extensive lung damage [10]. Accumulated evidence underscores the important role of a cytokine storm in the development of life-threatening pneumonia. The positive influence of LHQW for mitigating Inflammatory factors in the treatment COVID-19 shows its effectiveness in managing the disease.

According to the *vitro* research findings, LHQW can decline the viability of COVID-19 virus. Furthermore, LHQW has been observed to induce alterations in the virus's morphology. Typically, common viruses exhibit spherical particle shapes, whereas the COVID-19 virus, when subjected to LHQW treatment, assumes a spindle-shaped configuration [9]. This process contributes to the eradication of the COVID-19 virus by LHQW. The mechanism of COVID-19 infection involves entering target cells through endocytosis, following binding to the ACE2 receptor. As a result, the virus can replicate, undergo reverse transcription and then infect other healthy cells. Certain constituents found in LHQW, such as *Lonicera japonica* and *Forsythia*, have the ability to hinder the binding interaction between COVID-19 and ACE2 receptors on the surface of cells [9]. Besides, another herb, *Rheum palmatum*, possess the capacity to antagonize the binding of β coronavirus and ACE2 [8]. Consequently, LHQW demonstrates significant promise in treating COVID-19 by efficiently managing the quantity of the virus within host cells and thereby contributing to the elimination of the COVID-19 virus.

3. XuanFeiBaiDu (XFBD)

3.1. Components of XFBD recipes

The XFBD granules are formulated using components sourced from four classic traditional recipes. These constituents include Blackberrylily Rhizome, Tomentose Pummelo Peel, European Verbena Herb, Ephedra, Licorice, Bitter Almond, Gypsum, Sweet Wormwood Herb, Giant Knotweed Rhizome, Pepperweed Seed, Coix Seed, Patchouli, Swordlike *Atractylodes* Rhizome, and Lalang Grass Rhizome [6].

3.2. The impact of XFBD on COVID-19 treatment

XFBD is the first TCM recipe employed for managing COVID-19. The primary treatment approach of XFBD focuses on preventing the virus from entering and replicating within host cells by targeting the interaction between ACE2 and 3CLP-ro. What's more, XFBD modulates critical targets, like MAPK3, IL6, MAPK1, NOS2, CCL2, IL1 β , and EGFR [12]. The multifaceted action of XFBD includes the inhibition of viral infections, facilitation of lung inflammation absorption, and reduction of inflammatory factors, collectively contributing to its therapeutic efficacy for managing COVID-19.

The immune system is essential for patients' fight against viruses, and while treatment is sometimes necessary, bolstering the immune system remains one of the most crucial strategies for recovery from diseases. Enhancing the immune system is thus a viable approach to combat the COVID-19 virus. Treatment with XFBD leads to a notable increase in white blood cells and lymphocytes, thereby enhancing individuals' immunity [13]. Furthermore, XFBD exhibits anti-inflammatory effects by decreasing C-reactive protein levels and the sedimentation rate of erythrocyte [13]. Consequently, XFBD serves as a valuable means to empower patients in their defense against the COVID-19 virus.

However, the excessive immune response can potentially inflict harm upon bodily functions. When individuals contract COVID-19, they often experience discomfort characterized by fever and the secretion of a plethora of inflammatory factors. Paradoxically, this heightened immune response can exacerbate the severity of symptoms in patients. Inflammatory cytokines can result in the emergence of conditions like acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). In XFBD, there are two important chemical components - Pachypodoland I-SPD. They possess the capacity to suppress the activation of the NLRP3 gene, with the goal of decreasing both the inflammatory reaction and apoptosis, thereby reducing the production of inflammatory response. Another significant component, Vestitol, plays a crucial part in blocking the activation and movement of inflammatory cells by Colony-stimulating factor 2 [14]. Thus, the XFBD serves as a valuable therapeutic agent to prevent excessive immune response, safeguarding patients from the deleterious effects of an overly heightened immune reaction.

4. HuaShiBaiDu (HSBD)

4.1. Components of HSBD recipes

The components of XFBD are originated from 4 classic traditional recipes. The components of it are Caoguo, Pinellia Tuber, Rhubarb Tangute Rhubarb, Milkvetch Root, Red Paeoniae Triclocarban, Bitter Almond, Poria, Ageratum, Ephedra, Gypsum, Pepperweed See, Licorice, Officinal magnolia bark, Atractylode [6].

4.2. The effect of HSBD in treating COVID-19

In the analysis of the components of HSBD, eight primary active components have been identified, which include kaempferol, quercetin, isorhamnetin, beta-sitosterol, stigmasterol, baicalein, formononetin and naringenin. Baicalein has shown a stable appeal for SARS-CoV-2, while Quercetin has demonstrated a strong affinity for ACE2 and 3CL. The quercetin exerts its inhibitory effect on COVID-19 by competitively binding to the S-protein, thereby preventing its interaction with ACE2 [15] Furthermore, quercetin possesses the capacity to regulate the activation of MAPK, a routine responsible for the production of inflammatory factors, thus aiding in the enhancement of the immune system and viral defense [6]. Moreover, quercetin can hinder the PI3K-Akt pathway by reducing the presence of AKT1. This pathway plays a role in controlling the release of inflammatory mediators and the activation of inflammatory cells, potentially contributing to lung damage in patients. For this reason, quercetin holds promise as a treatment for treating lung fibroblast-related conditions.

The HSBD can not only enhance the immunity system, but also be an antiviral activity. Further investigation suggests that emodin, derived from Rhubarb Tangute Rhubarb, has strong antiviral activity. It can disrupt the attachment interactions between ACE-2 and the S protein of SARS-CoV, thereby preventing viral entry. The SNE-3a protein of SARS-CoV has the capability to create an ion channel that regulates the release of the virus from host cells [17]. As a result, the emodin can prevent the COVID-19 from entering host cells and subsequently inhibiting viral replication, which offers potential benefits in the treatment of the disease.

HSBD can enhance oxygen saturation status, which is particularly crucial for patients with severe COVID-19, as an important decline in lung function can lead to life-threatening issues related to gas exchange [16]. Therefore, its capacity to improve oxygen saturation status proves to be highly beneficial for patients, ultimately contributing to an enhanced quality of life.

5. XueBiJing (XBJ)

5.1. Components of XBJ recipes

The XBJ injection is composed of Angelica root, Salvia, Red Paeoniae Trichocarpa, Safflower, Szechuan Lovage Rhizome [6].

5.2. The influence of XBJ in managing COVID-19

In individuals suffering from COVID-19, the lungs exhibit extensive proteinaceous and serous exudates [17]. Furthermore, there has been a substantial rise in the levels of erythrocyte sedimentation rate (ESR) IL-6, and C-reactive protein (CRP), among COVID-19 patients [18]. Hence, the unmanageable lung inflammation emerges as a leading factor in COVID-19 fatalities. Looking at the potential active ingredients in XBJ, this concoction shows potential for anti-inflammatory and immune-enhancing effects [8]. Safflower, found in XBJ, contains three active components: hydroxysafflor yellow A (HSYA), hydroxysafflor yellow B (AHSYB) and safflor yellow A (SYA), which can mitigate lung inflammation and harm caused by lipopolysaccharide (LPS) [19]. LPS can increase the inflammatory factors. In this way, SYA, HSYA and AHSYB serve as the agent to protect patients' lungs. In light of these attributes, XBJ has the capacity to regulate uncontrollable lung inflammation and decline COVID-19 mortality. Therefore, when patients exhibit symptoms

indicative of uncontrolled lung inflammation, XBJ injection can be considered as a therapeutic intervention.

There are four primary routines in COVID-19 pathogenesis, named cytokine storm, cell death, the renin-angiotensin system (RAS), OS, and endothelial dysfunction. The virus uses the receptor called ACE in order to get into the type II pneumocytes or intestinal epithelial cells, causing ACE2 internalization and shedding, which culminates in the development of acute respiratory distress syndrome (ARDS) [20]. Several active ingredients found in XBJ play an important part in interfering with ACE receptors. The NF- κ B, a transcription factor, has been implicated in exacerbating lung inflammation [21] and inducing the expression of viral genes [22]. And XBJ can inhibit NF- κ B expression [23]. NF- κ B is additionally involved in controlling inflammatory factors like TNF- α , IL-1 β and IL-6, and the adjustment of these factors can be pivotal in the management of lung inflammation. In this manner, XBJ can help manage severe lung damage when the disease is serious.

6. Lung Cleansing and Detoxifying Decoction (LCDD)

6.1. Components of LCDD recipes

The LCDD granules consist of components derived from four classic traditional recipes, comprising a total of 21 Chinese herbs. These herbs include Manchurian Wildginger Herb, Blackberry Lily Rhizome, Common Yam Rhizome, Common Coltsfoot Flower, immature Bitter Orange, Tatarian Aster Root, Bitter Almond, Tangerine Peel, Fresh Ginger, Baikal Skullcap Root, Ramulus cinnamomi, Ephedra, Pinellia ternata processed with ginger, Poria, Ageratum, and Prepared Liquorice Root [6].

6.2. The impact of LCDD on the treatment of COVID-19

G protein-coupled receptors (GPCRs) offer advantages by having physiological roles that encompass the regulation of immunity, anti-inflammatory properties, and respiratory control [24]. The human immune cells can express the orphan receptor GPR35. The agonist of GPR35 is useful for the regulation of the immune system and for their anti-inflammatory properties [25]. The LCDD recipe comprises numerous herbs, and the formulation can yield a plethora of bioactive compounds. As shown in the experiment, there are 13 compounds, serving as potential GPR35 agonists, including kynurenic acid, luteolin, is liquiritigenin, baicalein, scutellarin, gallic acid, baicalin, and quercetin [26]. Activation of the Bradykinin receptor 2 (B2) may confer therapeutic benefits by limiting the release of inflammatory cytokines [27]. Notably, atractyline and alisol A 24-acetate have agonistic activity on CB receptor [26]. The receptors of B2 may be one of the possible targets for the regulation of inflammatory responses [28]. And compounds such as icochalcone B, alisol A, and is liquiritigenin can be used in B2 receptors [26]. Therefore, LCDD might play a role in controlling inflammatory reactions, potentially averting the harm caused by the immune system while combatting the COVID-19 virus.

7. Discussion about TCM and WM

Remdesivir is a western medicine known for its ability to inhibit viral RNA polymerases, rendering it a potential therapy choice for individuals with severe COVID-19. However, this medicine may cause serious side effects. Other WMs, such as lopinavir/ritonavir and favipiravir, also have similar concerns [13,29]. In contrast to WM, TCM has unique features, including multi-target, multi-pathway approach and multi-component, which are beneficial for anti-inflammatory, organ protection, broad-spectrum antiviral, and immune regulation [30,31]. Thus, compared with WM, TCM is associated with fewer side effects.

The symptom of patients receiving combined treatment with WM and TCM has demonstrated improvement. Notably, these patients have exhibited reduced coughing and sputum production compared to individuals treated solely with WM or TCM [32]. Compared with the treatment only with WM, treatment combined with WM and TCM can increase the rate of symptoms disappearance

[32]. Additionally, the use of TCM and WM yielded more favorable outcomes in terms of lymphocytes recovery in the blood [33]. As a consequence, patients who receive a combined treatment approach comprising both TCM and WM experience improved health states when afflicted with COVID-19 and following treatment.

8. Conclusion

TCM boasts a rich history and maintains its prevalence in modern medicine. TCM recipes often combines numerous herbs, making it complex when analyzing the compounds in herbs. Accordingly, the utilization of databases becomes essential for effective research in TCM. Five recipes have been high lightened. All of them can treat COVID-19. Certain herbs share similarities, their use in COVID-19 therapy varies, reflecting the nuanced approach required for different individuals in varying phases of the illness. The relatively mild side effects of TCM also underscores how meaningful it is to the study TCM. The treatment combined with TCM and WM achieved a good result. The success achieved through combined treatment strategies involving both TCM and Western Medicine (WM) underscores the importance of diversifying treatment approaches for COVID-19 beyond the use of WM alone. This shift in focus toward TCM has the potential to catalyze advancements in traditional medicine. Despite the progress made in TCM research, there are still some unknown effects in the herbal compounds used for managing COVID-19. Hence, additional extensive research is required to enhance our comprehension of the potential advantages and the mechanisms by which Traditional Chinese Medicine (TCM) manages COVID-19.

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