Herbal medicine in the treatment of COVID-19 based on the gut–lung axis

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Abstract
Respiratory symptoms are most commonly experienced by patients in the early stages of novel coronavirus disease 2019 (COVID-19). However, with a better understanding of COVID-19, gastrointestinal symptoms such as diarrhea, nausea, and vomiting have attracted increasing attention. The gastrointestinal tract may be a target organ of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The intestinal microecological balance is a crucial factor for homeostasis, including immunity and inflammation, which are closely related to COVID-19. Herbal medicine can restore intestinal function and regulate the gut flora structure. Herbal medicine has a long history of treating lung diseases from the perspective of the intestine, which is called the gut–lung axis. The physiological activities of guts and lungs influence each other through intestinal flora, microflora metabolites, and mucosal immunity. Microecological modulators are included in the diagnosis and treatment protocols for COVID-19. In this review, we demonstrate the relationship between COVID-19 and the gut, gut–lung axis, and the role of herbal medicine in treating respiratory diseases originating from the intestinal tract. It is expected that the significance of herbal medicine in treating respiratory diseases from the perspective of the intestinal tract could lead to new ideas and methods for treatment.

Keywords: COVID-19, Gut-lung axis, Gut microbiota, Herbal medicine, Respiratory disease, SARS-CoV-2

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Introduction
Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Owing to its continuous spread around the world, the number of infections and deaths is still increasing, posing a serious threat to public health security[1–2]. SARS-CoV-2 is an unsegmented, enveloped β-coronavirus of spherical positive single-stranded RNA virus, which is highly contagious, pathogenic, and can infect a variety of mammals and birds[3–4]. Compared with SARS, the case fatality rate of COVID-19 is low and the infectivity is high[5–9]. Its transmission routes mainly include respiratory droplets, contact, and fecal-oral transmission, which are characterized by fast transmission and strong infectivity. Although respiratory-related symptoms such as fever and cough are dominant in the clinical manifestations of COVID-19, a considerable proportion of patients show gastrointestinal symptoms, such as nausea and diarrhea[10–13]. There is a higher proportion of severe pneumonia cases among COVID-19 patients with gastrointestinal symptoms[14]. In COVID-19 patients, the composition of the gut microflora changes significantly, and SARS-CoV-2 can be directly detected in fecal samples[15]. In addition, the expression and activity of angiotensin-converting enzyme 2 (ACE2) receptors in intestinal tissue are higher than that in lung tissue[16], suggesting that the gastrointestinal tract may be a treatment target for patients with SARS-CoV-2. Thus, maintaining the intestinal microecological balance is crucial for the COVID-19 patients’ treatment and prognosis.

Current therapeutic agents mainly use antiviral drugs, including remdesivir, lopinavir/ritonavir, favipiravir, convalescent plasma, and ACE2 blockers. However, their clinical efficacy is unsatisfactory and controversial[17]. Clinically, traditional Chinese medicine [TCM, eg, Jinhua Qinggan granule, Lianhua Qingwen capsule, Xuebijing injection, Qingfei Paidu decoction, Huashi Baidu decoction, and Xuanfeng Baidu decoction (XFBD)] have been proven to be safe and effective for COVID-19 treatment. The Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Eighth Edition)[18] in China highlights the criticality of gut microecological regulators for maintaining gut flora balance and preventing secondary bacterial infections. This review summarizes the relationship between COVID-19 and the gut, gut–lung axis, and herbal medicines to restore intestinal receptors and intestinal flora, which may effectively alleviate the special complications caused by COVID-19. The search database used is Web of Science (http://www.webofknowledge.com). Moreover, the keywords used are COVID-19, herbal medicine, gut, and gut–lung axis, and the retrieval time is left at default.

In this study, we aim to explore the application and significance of herbal medicine in treating COVID-19 from the perspective of regulating intestinal microecology, which can result in new treatment ideas and methods against the disease.
**The relationship between COVID-19 and gut**

**Role of the gut in the treatment of COVID-19**

To prevent secondary bacterial infection caused by COVID-19, the National Health Commission of the People’s Republic of China uses the “intestinal microbiological regulator” method, which is different from previous epidemic diagnoses and treatment programs and lists the maintenance of intestinal microbiological balance in the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (Trial Fourth Edition). In COVID-19 patients, the numbers of *Lactobacillus, Bifidobacterium, Eubacterium rectale,* and *Faecalibacterium prausnitzii* in the intestines decrease, whereas the number of conditionally pathogenic bacteria such as *Enterococcus* increases. The degree of imbalance in intestinal flora is positively correlated with disease severity, suggesting that the gastrointestinal tract may be one of the target organs of SARS-CoV-2[21]. A study by Tang et al.[20] reported an imbalance of gut flora is observed in COVID-19 patients, and the dynamic changes in the flora are related to the disease severity and hematological parameters. This suggests that attention should be paid to the gastrointestinal microecological balance in treating respiratory diseases.

As an important immune organ of the body, the intestinal tract inhabits a large number and variety of intestinal microflora. Moreover, it participates in a variety of physiological functions, including energy intake, metabolism, and immune regulation. The proportion of intestinal microflora plays a key role in maintaining intestinal homeostasis and the pathogenesis of diseases[21]. There is a potential relationship between the impairment of intestinal microflora and the COVID-19 severity[22–23]. In light of gastrointestinal symptoms in COVID-19 patients, intestinal microecology regulation may play a therapeutic role in the pathogenesis of COVID-19, mainly including intestinal receptors and flora.

**The effect of intestinal receptor ACE2 in the treatment of COVID-19**

ACE2 is a functional host receptor of SARS-CoV-2. It is a key enzyme in the renin-angiotensin system (RAS) and plays a crucial effect in regulating gut inflammation and diarrhea[24]. Studies show that the ACE2 protein is highly expressed in gastric, duodenal, and rectal epithelial glandular cells. Researchers observe that over 20% of COVID-19 patients have viral RNA in their stool even when the respiratory virus RNA is negative, indicating that gastrointestinal infection and fecal-oral transmission of the virus may persist even after the respiratory virus is cleared[25]. In the intestinal tract, ACE2 regulates antimicrobial peptides and amino acids expression and maintains homeostasis of the intestinal flora. There is almost no expression of the neutral amino acid transporter B0AT1 in the intestines of ACE2 mutant mice, which results in severe damage to local tryptophan homeostasis, decreases the production of antimicrobial peptides, and changes in intestinal microflora, thus increasing susceptibility to intestinal inflammation[26]. As a result, we speculate that the binding of SARS-CoV-2 to ACE2 in the gastrointestinal tract reduces available receptors level, affects tryptophan absorption, and finally destroys the intestinal flora homeostasis, which is one of the causes of gastrointestinal symptoms in COVID-19 patients. Therefore, maintaining intestinal homeostasis is critical for COVID-19 treatment.

**The effect of intestinal flora in treating COVID-19**

It has been confirmed that *Coprobacillus* can upregulate ACE2 expression in the intestinal tract of mice, suggesting that changes in the intestinal flora may change the ability of SARS-CoV-2 to infect intestinal cells, further indicating the possible effect of flora regulation in treating COVID-19[27]. A study of an aseptic Sprague Dawley (SD) rat model shows that the colonization of gut flora can affect the expression of ACE2, Lcn2, and Nlrc5 genes in the intestine, and can regulate the systemic inflammatory response to affect the susceptibility of intestinal cells to SARS-CoV-2. Moreover, it is speculated that the highly variable gut microflora among individuals may be another factor that regulates ACE2 expression in the colon, thus affecting the infectivity of COVID-19[28]. Clinical studies confirm oral bacteriotherapy can significantly improve gastrointestinal symptoms of COVID-19 patients and relieve cough, dyspnea, and other clinical symptoms, and improve the patients’ survival rate[29]. Another study shows that the addition of washing microbiota transplantation (WMT) to routine treatment can not only effectively correct the imbalance of intestinal flora but also help to repair intestinal mucosal shielding function. Therefore, it is beneficial in intestinal microbiota rehabilitation of COVID-19 patients with gut microbiota dysbiosis (GMD), relieving systemic inflammation, and maintaining organ function and homeostasis[30].

The stability of lung and gut microecological balance is restricted by each other. Intestinal flora is related to the pathological immune response to SARS-CoV-2[31]. During SARS-CoV-2 infection, the respiratory and gastrointestinal tracts mucosa are affected, and local microbiota and inflammation levels also change accordingly[32]. Intestinal immune function accounts for 70% of the entire body. The consumption or loss of intestinal microbiota leads to an impaired immune response, which can indirectly regulate the immune function of the lung through the gut–lung axis[33]. In light of the common pulmonary inflammation in COVID-19 patients, the intestinal microflora may play a role in directly inhibiting or promoting viral infection. Therefore, the maintenance of intestinal function cannot be ignored in COVID-19 treatment.

The intestinal flora imbalance caused by COVID-19 aggravates the destruction of intestinal mucosal barrier function, leading to endotoxin and bacterial metabolites entering the circulatory system and causing an inflammatory storm[34]. Clinical data show that in SARS-CoV-2 infection cases, neutrophils increases from 7 to 9 d after onset in the death group, suggesting high inflammation in these patients[35]. Disturbance of microflora is an important cause of high inflammation in a short time. Changes in intestinal microflora are closely related to local and systemic inflammation[36]. Healthy eating habits and dietary quality can promote beneficial bacteria growth in the intestinal tract, thus reducing the SARS-CoV-2...
infection risk[37]. Reasonable supplementation of probiotics can not only maintain the intestinal flora homeostasis and protect the intestinal barrier but also reduce gastrointestinal symptoms such as diarrhea in COVID-19 patients by regulating immune homeostasis and the inflammatory response[38–39]. Moreover, fecal microbiota transplantation (FMT) in COVID-19 patients not only restores the damaged intestinal microflora but also alleviates the course of COVID-19[40]. As a result, intestinal flora intervention may become a new strategy for COVID-19 prevention and treatment.

The intervention mechanism of Xuanfei Baidu Decoction from the perspective of intestinal flora

In a previous study, we combined ultra-high performance liquid chromatography, quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS), and fecal metabolomics with 16S rDNA sequencing, to evaluate the effects of XFBD on the overall metabolism and intestinal microbial community composition. Then, short-chain fatty acids (SCFAs) content in feces was determined by gas chromatography-mass spectrometry (GC-MS). The immune and inflammatory indices of the plasma samples were detected using an enzyme-linked immunosorbent assay (ELISA). Finally, the results were verified in rats with intestinal disorders. The results showed that XFBD significantly increased the levels of immunoglobulin A (IgA), immunoglobulin G (IgG), and immunoglobulin M (IgM) in plasma. Furthermore, 16SrDNA sequencing showed that XFBD could significantly regulate the intestinal flora composition in rats, mainly in key metabolic pathways, including carbohydrate metabolism, cofactors and vitamins metabolism, and amino acid metabolism. Metabonomic analysis showed that there was an obvious trend of separation of fecal metabolic profiles between groups, and 271 differential metabolites were identified, which mainly involved D-glutamine and D-glutamate metabolism, arginine biosynthesis, and biotin metabolism. XFBD exerts regulatory effects on acetic acid. In addition, it could partially account for the relative abundance of intestinal microflora in rats with bacterial disorders. It is suggested that the intervention mechanism of XFBD may be related to regulating intestinal flora composition, affecting the overall metabolism, and improving immune function. The herbs used in XFBD are shown in Figure 1.

Gut–lung axis

Role of intestinal flora, microflora metabolites, and mucosal immunity in the gut–lung axis

The lungs and guts are related to disease development, which affects host health. The two-way communication hub between the gut and lung is called the gut–lung axis. The changes in intestinal flora composition can affect the development of lung diseases, while pulmonary flora disorders can also affect the intestinal tract through immune

![Figure 1. The herbs of XFBD (line A from left to right is Ephedra sinica Stapf; Prunus armeniaca L.; Gypsum Fibrosum; Coix lacryma-jobi var. L. ma-yuen (Rom.Caill.) Stapf; Atractylodes macrocephala Koidz. line B from left to right is Pogostemon cablin (Blanco) Benth.; Polygonum cuspidatum Sieb. et Zucc.; Verbena officinalis L.; Phragmites australis (Cav.) Trin. Ex Steud.; line C from left to right is Descurainia Sophia (L.) Webb ex Prantl; Citrus maxima (Burm.) Merr.; Artemisia annua L.; line D is Glycyrrhiza glabra L.). COVID-19: Coronavirus disease 2019; XFBD: Xuanfei Baidu decoction.](image-url)
The existence of gut–lung axis indicates that intestinal microflora and lungs are related and influence each other in immunity, pathology, and physiology. Maintaining homeostasis of the intestinal microflora can reduce respiratory tract inflammation and protect against the development of atopic diseases. Microbes play a vital role in the crosstalk between the guts and lungs. Intestinal microbial disorders may affect the lung's dynamic balance and vice versa. At the same time, flora metabolites also affect lung disease development through the gut–lung axis. The lungs and guts are connected by the public mucosal immune system. Therefore, the interaction of the gut–lung axis was explored from the aspects of intestinal flora, microflora metabolites, and mucosal immunity.

Role of gut flora in the gut–lung axis
Microorganisms colonizing the mucous membrane of the respiratory and digestive tracts can regulate the tissue, which is the material basis of the gut–lung connection. Studies show that there is a relationship between gut flora and lung health, lymph can act as a carrier of microflora between the intestinal and lung organs. Lung diseases change due to the influence of the intestinal microenvironment, and the microflora abundance of the two organs is highly related; the change in microflora has a similar trend. From the point of view of the change in microecological flora, it is confirmed that the lung and gut are interconnected and influence each other. SARS-CoV-2 invades the body, produces pro- and anti-inflammatory responses, and releases a large number of inflammatory mediators that lead to sepsis. In mice with impaired intestinal barrier function, intestinal flora translocation reduces the lifespan of red blood cells by affecting membrane fluidity, increasing the iron load in circulation, and promoting the growth and survival of translocation bacteria, ultimately increasing the susceptibility to sepsis in mice. Intestinal flora can induce pulmonary inflammation and promote neutrophil infiltration through Toll-like receptor 4 (TLR4) in mice. One study investigated 118 patients with advanced non-small-cell lung cancer who received immune checkpoint blocking therapy. The results reveal that the intestinal microflora characteristics of patients with lung cancer are different, and probiotic treatment can significantly prolong the survival time of patients. In addition, respiratory tract infection is associated with changes in the intestinal microflora composition, indicating that there may be crosstalk between the lung and intestinal microflora and that intestinal microorganisms can indirectly affect the development of lung diseases through the “gut–lung axis”. In severe COVID-19 patients, flora disorders can lead to abnormal intestinal inflammation, affecting the gut–lung axis, thus aggravating the systemic inflammation degree. The regulation of intestinal microflora may play a unique role in improving the preventive effect and accelerating the rehabilitation of COVID-19 patients. Adjuvant therapy based on regulating the gut–lung axis and rebuilding the ecological balance may be an effective treatment to limit the harmful consequences of COVID-19. The potential pathway for herbal medicines to treat COVID-19 via regulation of the intestinal tract is shown in Figure 3.

Role of microflora metabolites in the gut–lung axis
The systemic effects of the intestinal microflora are partly attributed to the metabolites. SCFAs, including acetate, propionate, and butyrate, are the most widely studied metabolites. They play key roles in maintaining lung homeostasis and immune regulation. It is reported that SCFAs can inhibit pulmonary inflammation by activating G protein-coupled receptors. Moreover, SCFAs can generate an extrathymic peripheral Treg cell pool and dampen allergic airway diseases through histone deacetylase (HDAC) inhibition. In addition, the microbial metabolite desaminotyrosine (DAT) protects mice from influenza virus infection by enhancing type I interferon (IFN) signal transduction. These studies demonstrate the importance of the intestinal flora and its metabolites in the regulation of the gut–lung axis.

Role of mucosal immunity in the gut–lung axis
Both the respiratory and digestive tract mucosa belong to the mucosal immune system, which acts as the first defense barrier to protect the body from external stimulation. As a part of mucosa-associated lymphoid tissue (MALT), gut-associated lymphoid tissue (GALT)
and bronchus-associated lymphoid tissue (BALT) can transfer immune cells and factors to each other through blood vessels and lymphatic vessels,[56] thus enhancing the host’s ability to resist pathogens. It is confirmed that type 2 innate lymphoid cells (ILC2) can be induced by IL-25 and migrate from the gut to the lung to participate in the immune response.[57–58] Mucosal immunity plays a role in connecting the lung and gut.

The ancient records of the gut–lung axis

“Simultaneous treatment of the lung and gut” theory has been raised since ancient times. The modern theoretical basis of the “gut–lung axis” is that “the lung stands in interior-exterior relationship with the intestine”. The theory that “the lung stands in the interior-exterior relationship with the intestine” first appeared in Inner Canon of Huangdi (Huáng Dì Nèi Jīng, 黄帝内经). In clinical practice, it can be applied to “treating lung from the intestine”, “treating intestine from lung”, and “treating lung and intestine simultaneously”. Ancient Chinese literature records that “the lung governs qi”. The lung stands in an “interior-exterior relationship” with the intestine and “qi intensive treatment” in the lungs. This reveals that the lung and gut are interconnected and influence each other from a physiological and pathological perspective.[59–60]. Furthermore, the normal conduction of the intestine contributes to lung dispersion and descent. If the lung qi is lost in dispersing and descending, the body fluid cannot be released, or the lung qi promotion is weak, and constipation can be observed. If the intestine is hot and the bowel qi is blocked, it will cause lung qi to fall unsmoothly in the dispersion and descend, resulting in cough and chest tightness.[61]. The lung and gut interact with each other through the “gut–lung axis”, and has a long history of “simultaneous treatment of lung and gut”.

The influence of herbal medicines on intestinal receptors and flora to treat respiratory diseases

Herbal medicine has been used in treating lung diseases from the intestinal perspective, including COVID-19. Lung diseases are often accompanied by intestinal lesions, such as an impaired intestinal barrier and intestinal flora imbalance. Therefore, the targeted regulation of the intestine may be a new strategy for lung disease treatment. Ethnic medicines have long been reported to alleviate intestinal microecological disorders caused by bacterial infection.[62–64]. Herbal medicines mainly treat respiratory diseases by regulating intestinal receptors, cytokines, intestinal flora, and their metabolites.[65–69]. The communication pathway of herbal medicine between the intestinal tract and the respiratory system is reviewed below to provide a reference for revealing the nature of the “gut–lung” axis. A summary of herbal medicines used for treating COVID-19 is shown in Table 1. The herbal medicines’ Latin names are based on Kew Science (http://mpns.science.kew.org/mpns-portal/) and the Chinese Pharmacopoeia 2020 Edition.
Table 1
The summary of herbal medicines for treating COVID-19

| Herbal medicine prescription | Latin name | Chinese name | Relief or treatment of symptoms | References |
|------------------------------|------------|--------------|--------------------------------|------------|
| Qingfei Paidu decoction     | Ephedra sinica Stapf | Ma Huang | Improve symptoms such as fever and cough, promote the regression of pulmonary inflammation, reduce the virus detachment period and course of disease, shorten hospital stay, and reduce mortality | Shi et al. (2021)[73] |
|                             | Glycyrrhiza glabra L. | Gan Cao |                                    |            |
|                             | Prunus armeniaca L. | Ku Xing Ren |                                    |            |
|                             | Gypsum fibrosum | Sheng Shi Gao |                                    |            |
|                             | Cinnamomi Ramulus | Gui Zhi |                                    |            |
|                             | Alisma plantago-aquatica Linn | Ze Xie |                                    |            |
|                             | Polyporus | Zhu Ling |                                    |            |
|                             | Atractylodes macrocephala Koidz. | Bai Zhu |                                    |            |
|                             | Poria | Fu Ling |                                    |            |
|                             | Bupleuri Radix | Chai Hu |                                    |            |
|                             | Scutellaria baicalensis Georgi | Huang Qin |                                    |            |
|                             | Pinelliae Rhizoma Praeparatum Cum Zingibere et Alumine | Jiang Ban Xia |                                    |            |
|                             | Zingiber officinalis Rosc. | Zi Wan |                                    |            |
|                             | Aster tataricus L.f. | Kuan Dong Hua |                                    |            |
|                             | Tussilago farfara L. | She Gan |                                    |            |
|                             | Belamcandae Rhizoma | Xi Xin |                                    |            |
|                             | Asari Radix et Rhizoma | Shan Yao |                                    |            |
|                             | Dioecreea Rhizoma | Zhi Shi |                                    |            |
|                             | Aurantii fructus immaturas | Chen Pi |                                    |            |
|                             | Citri reticulatae pericarpium | Guang Huo Xiang |                                    |            |
|                             | Pogostemon cablin (Blanco) Benth. | |                                    |            |
| Huashi Baidu decoction      | Ephedra sinica Stapf | Ma Huang | Relieve fever, cough, and other symptoms. Inhibit inflammation, reduce cytokine storm, accelerate virus clearance, promote turbid absorption of lung lesions, and reduce mortality | Liao et al. (2020)[74] |
|                             | Glycyrrhiza glabra L. | Ku Xing Ren |                                    |            |
|                             | Prunus armeniaca L. | Sheng Shi Gao |                                    |            |
|                             | Gypsum fibrosum | Huo Xiang |                                    |            |
|                             | Magnolia officinalis Rehd. et Wils | Fa Ban Xia |                                    |            |
|                             | Atractylodes lancea (Thunb.) DC. | Hou Po |                                    |            |
|                             | Tsaoko Fructus | Cang Zhu |                                    |            |
|                             | Poria | Cao Guo |                                    |            |
|                             | Atragalai Radix | Fu Ling |                                    |            |
|                             | Paonia lactiflora Pall. | Sheng Huang Qi |                                    |            |
|                             | Descurainia Sophia (L.) Webb ex Prantl | Chi Shao |                                    |            |
|                             | Rheum palmatum L. | Ting Li Zi |                                    |            |
|                             | | Da Huang |                                    |            |
| Xuanfei Baidu decoction     | Ephedra sinica Stapf | Ma Huang | Relieve clinical symptoms such as cough, fever, chest tightness, fatigue, and loss of appetite, increase white blood cell and lymphocyte count, decrease erythrocyte sedimentation rate and C-reactive protein, significantly shorten the virus clearance time, promote the absorption of pulmonary inflammation, reduce the density of pulmonary lesions, significantly reduce the scope, and delay the development of the disease | Xiong et al. (2020)[75] |
|                             | Glycyrrhiza glabra L. | Ku Xing Ren |                                    |            |
|                             | Coix lacryma-jobi L. var. ma-yuen (Rom.Caill.) Stapf | Sheng Shi Gao |                                    |            |
|                             | Atractylodes lancea (Thunb.) DC. | Yi Ren |                                    |            |
|                             | Pogostemon cablin (Blanco) Benth. | Cang Zhu |                                    |            |
|                             | Polygonum cuspidatum Sieb. et Zucc. | Guang Huo Xiang |                                    |            |
|                             | Verbena officinalis L. | Hu Zhang |                                    |            |
|                             | Phragmites communis Trin. | Ma Bian Cao |                                    |            |
|                             | Descurainia Sophia (L.) Webb ex Prantl | Gan Lu Gen |                                    |            |
|                             | Citri Grandis Exocarium | Ting Li Zi |                                    |            |
|                             | Artemisia annua L. | Hua Ju Hong |                                    |            |
|                             | Glycyrrhiza glabra L. | Qing Hao Cao |                                    |            |
|                             | | Gan Cao |                                    |            |

(Continued)
Blocking the binding of viruses to ACE2 receptors in the intestinal tract to treat respiratory diseases

The S protein of SARS-CoV-2 can decrease the expression of ACE2 by binding to the ACE2 receptor on the surface of intestinal epithelial cells. The decreased expression of ACE2 inhibits the ACE2-Ang (1-7)-Mas axis, regulates the expression of the antimicrobial peptides, and downregulates the expression of SARS-CoV-2 in the intestinal flora, homeostasis and damage, and its barrier function, leading to digestive system lesions, diarrhea, etc.[96–97]. The Sini decoction (Aconitum carmichaeli Debeaux, Zingiber officinale Rosc., Glycyrrhiza uralensis Fisch.) can improve sepsis-induced acute lung injury by regulating the ACE2-Ang (1-7)-Mas axis and inhibiting the MAPK signaling pathway.[65]. In addition, acute lung injury induced by Escherichia coli in mice is alleviated by balancing the ACE-AngII-AT1R and ACE2-Ang-(1-7)-Mas axes.[98]. Some studies show that emodin, an anthraquinone compound in rhubarb and Polygonum multiflorum, can improve the clinical symptoms of SARS virus infection and block the interaction between the S protein and ACE2 receptor in a dose-dependent manner, thus inhibiting the infectivity of the S protein pseudotype retrovirus to VeroE6 cells.[66]. In TCM, glycyrrizic acid can interfere with the binding of viruses to ACE2 receptors.[99]. In summary, intestinal microbiota plays a role in regulating the host's immune response to respiratory virus infection. The regulation of TCM on intestinal microflora may be of great value in COVID-19 prevention and treatment. Meanwhile, TCM can also block the binding of the virus to ACE2 receptors and inhibit virus replication, which can facilitate the recovery of COVID-19 patients.

Restoring intestinal flora to treat respiratory diseases

Herbal medicines improve pneumonia by restoring intestinal flora. Pneumonia is an infectious disease that affects human health worldwide. Antibiotics have become the

| Herbal medicine prescription | Latin name | Chinese name | Relief or treatment of symptoms | References |
|----------------------------|------------|--------------|---------------------------------|------------|
| Jinhua granule             | Lonicera japonica Thunb. | Ren Dong | Effectively relieve fever, headache, dyspnea, loss of appetite, and other symptoms. Shorten the length of stay and reduce the mortality | Zhang et al. (2020)[83] |
| Qinggan granule            | Gypsum fibrous | Sheng Shi Gao | | An et al. (2021)[84] |
|                       | Ephedra sinica Stapf | Me Huang | | Shah et al. (2022)[85] |
|                       | Prunus armeniaca L. | Ku Xing Ren | | Lin et al. (2022)[86] |
|                       | Scutellaria baicalensis Georgi | Huang Qin | | |
|                       | Forsythia suspensa (Thunb.) Vahl | Lian Qiao | | |
|                       | Frullalaria thunbergii Miq. | Zhe Bei Mu | | |
|                       | Anemarrhena asphodeloides Bge. | Zhi Mu | | |
|                       | Arctium lappa L. | Niu Bang | | |
|                       | Artemisia annua L. | Qing Hao Cao | | |
|                       | Mentha haplocalyx Briq. | Bo He | | |
|                       | Glycyrrhiza glabra L. | Gan Cao | | |
| Lianhua capsule          | Forsythia suspensa (Thunb.) Vahl | Lian Qiao | Improve clinical symptoms such as fever, cough, stuffy nose, and headache. Inhibit viral activity and excessive activation of cytokines. Reduce the expression level of chemokine/cytokine and enhance the function of immune system. Shorten the time of hospitalization and treatment | Xiao et al. (2020)[87] |
| Qingwen capsule          | Lonicera japonica Thunb. | Ren Dong | | Shen et al. (2021)[88] |
|                       | Prunus armeniaca L. | Ma Huang | | Zeng et al. (2020)[89] |
|                       | Gypsum fibrous | Ku Xing Ren | | Fan et al. (2022)[90] |
|                       | Isatis Radix | Sheng Shi Gao | | |
|                       | Dryopteris crassirhiza Nakai | Ban Lan Gen | | |
|                       | Houttuynia cordata Thunb. | Mian Ma Guan | | |
|                       | Rheum palatum L. | Zhong | | |
|                       | Rhodiola crenulata (Hook. f. et Thoms. ) H. Ohba | Yu Xing Cao | | |
|                       | Pogasteromon cablin (Blanco) Berth. | Guan Huo Xiang | | |
|                       | Mentha haplocalyx Briq. | Da Huang | | |
|                       | Glycyrrhiza glabra L. | Hong Jing Tian | | |
|                       | | Bo He | | |
| Xuebijing injection      | Carthamus tinctorius L. | Gan Cao | Improve fever, dyspnea, and other clinical symptoms, reduce the level of inflammatory factors, improve immunity, shorten hospital stay, improve patients’ PSI risk score and clinical prognosis | Guo et al. (2020)[91] |
|                       | Paeonia lactiflora Pall. | Hong Hua | | Luo et al. (2021)[92] |
|                       | Ligusticum chuanxiong Hort. | Chi Shao | | Chen et al. (2021)[93] |
|                       | Salvia miltiorrhiza Bge. | Chuan Xiong | | Liu et al. (2021)[94] |
|                       | Angelica sinensis (Oliv.) Diels | Dan Shen | | Fu et al. (2020)[95] |
|                       | | Gangui | | |

COVID-19: Coronavirus disease 2019; PSI: pneumonia severity index.

 Herbal medicines improve pneumonia by restoring intestinal flora. Pneumonia is an infectious disease that affects human health worldwide. Antibiotics have become the
main treatment strategy for bacterial infectious diseases\textsuperscript{[108-109]} However, their use is often accompanied by disorders of gut flora and the emergence of drug-resistant bacteria\textsuperscript{[102-103]} TCM can reverse the intestinal microecological imbalance caused by pathogen infection. This experiment confirmed that the Gegen Qianjin decoction (\textit{Pueraria lobata} (Willd.) \textit{Olive}, \textit{Scutellaria baicalensis Georgi, Coptis chinensis Franch., Glycyrrhiza glabra L.}) can alleviate gastrointestinal symptoms caused by the influenza virus, increase the abundance of beneficial bacteria such as \textit{Akkermansia muciniphila}, \textit{Desulfovibrio_C21_c20}, and \textit{Lactobacillus salivarius}, and reduce the pathogenic bacteria abundance such as \textit{E. coli}. Decoction also promotes the recovery of intestinal mucosal immune function, inhibits inflammatory factors expression in mesenteric lymph nodes (mLN)s and serum, alleviates pulmonary inflammation, and reduces mortality in mice\textsuperscript{[67]} Qingfei Yin (\textit{Scutellaria baicalensis Georgi, Forsythia suspensa} (Thunb.) Vahl, \textit{Belamcanda chinensis} (L.) DC., \textit{Fritillaria cirrhosa} D. Don) inhibits the activation of the NF-κB-NLRP3 pathway through targeted regulation of intestinal microflora and metabolites, thus alleviating the inflammatory injury caused by bacterial pneumonia\textsuperscript{[104]}. \textit{Houttuynia cordata} is a TCM used for treating respiratory diseases. Its active component, \textit{Houttuynia cordata} polysaccharides, can inhibit the pulmonary inflammatory cytokines release and TLR4-NF-κB expression, improve the damaged immune and intestinal physical barriers, reduce lung and intestinal pathological damage caused by influenza A virus (IAV), improve the survival rate, and protect multiple organs from influenza virus infection\textsuperscript{[103]}.

Herbal medicines improve acute lung injury (ALI) by restoring intestinal flora. ALI is a phenomenon of excessive inflammatory reactions and oxidative stress caused by many factors, which are characterized by respiratory sive inflammatory reactions and oxidative stress caused restoring intestinal flora. ALI is a phenomenon of excessive bacteria\textsuperscript{[102–103]}. TCM can reverse the intestinal microecological imbalance caused by gut–lung axis in critically ill patients, which affects the intestinal flora. Xuanbai Chengqi decoction (\textit{Rheum officinale Baill., gypsum fibrosum, Prunus armeniaca L., Trichosanthes kirilowii Maxim.}) has a protective effect against pulmonary inflammation caused by COPD by promoting the growth of the probiotics \textit{Gordonibacter} and \textit{Akkermansia}, inhibiting the pathogenic \textit{Streptococcus} growth, regulating microbiological disorders, and restoring the Th17/Treg cells balance\textsuperscript{[69]}. The key compounds of the Xixin-Ganjiang herb pair (XGHP) can inhibit the PTGS2 expression and promote the PPAR expression in the lung tissue of COPD rats, which may be effective targets for XGHP in the treatment of COPD\textsuperscript{[118]}. Yufeiining [\textit{Codonopsis pilosula} (Franch.) Namnfs., \textit{Astragal Radix, Atractylodes macrocephala Koidz., Saposhnikovia divaricata (Turcz.) Schischk., Polygonatum odoratum (Mill.) Druce, \textit{Cornus officinalis Sieb. et Zucc., Schisandra chinensis (Turcz.) Baill., Juglans regia L., Cuscuta chinensis Lam., Morinda officinalis How, Trichosanthes kirilowii Maxim., Pinellia ternata (Thunb.) Breit., Frutillaria thunbergii Miq., Salvia miltiorrhiza Bge., and Prunus persica (L.) Batsch.] can reduce cough, sputum, and chest tightness to improve symptoms in patients with COPD\textsuperscript{[119-120]}. Compared with the placebo group, the interleukin (IL)-8, tumor necrosis factor (TNF)-α, IL-17A, leukotriene B4 (LTB4), and C-reactive protein (CRP) levels decreased significantly in serum after Yufeiining treatment. TCM can be used as a drug and an anti-inflammatory agent for stable COPD\textsuperscript{[121]}.

Herbal medicines improve asthma by restoring intestinal flora. Asthma is a heterogeneous disease characterized by chronic airway inflammation and airway hyper responses. It is one of the most common chronic respiratory diseases in the world\textsuperscript{[122]} Intestinal homeostasis is closely associated with the development of asthma\textsuperscript{[123-124]}. \textit{Eriobotrya japonica}(Thunb.) Lindl leaves can increase intestinal flora diversity and richness, inhibit the expression of MMP9 and TIMP-1, reduce inflammatory cell infiltration in lung tissue, and improve the pathological structure of lung tissue\textsuperscript{[125]}. For decades, Guben Fangxiang decoction (\textit{Astragal Radix, Codonopsis pilosula (Franch.) Namnfs., Atractylodes macrocephala Koidz.,}}
Cinnamomum Cassia Presl, and Angelica sinensis (Oliv.) Cuscuta chinensis Lam., Dioscorea oppositifolia L., Lycium barbarum L., Lonicera japonica Thunb., and Phellodendron chinense Schneid) can significantly improve the inflammatory symptoms of ovalbumin-induced allergic asthma in mice by changing the intestinal microbial community structure and SCFAs content[126]. A pentaherb formula (Lonicera japonica Thunb., Mentha haplocalyx Briq., Paonia suffruticosa Andr, Atractylodes lancea (Thunb.) DC., Phellodendron chinense Schneid) can significantly improve the inflammatory symptoms of ovalbumin-induced allergic asthma in mice by changing the intestinal microbial structure and SCFAs content[126]. Youguiwan (Rehmannia glutinosa Libosch, Dioscorea oppositifolia L., Eucommia ulmoides Oliv., Lycium barbarum L., Cornus officinalis Sieb Zucc., Cascuta chinensis Lam., Aconitum carmichaeli Debeaux, Cinnamomum Cassia Presl, and Angelica sinensis (Oliv.) Diels, Cervi Cornus Colla.) can effectively alleviate disorders of amino acid metabolism, improve intestinal microecological disorders, and have a therapeutic effect on house dust mite-induced allergic asthma in mice[127].

Discussion and conclusions

In addition to the common clinical symptoms, such as fever, dry cough, and dyspnea, most COVID-19 patients also present with gastrointestinal symptoms including diarrhea and vomiting. Recently, many studies confirmed that SARS-CoV-2 can be detected in the feces of COVID-19 patients[128,132]. According to the classical theory of TCM, the application of “treating lung from the intestine”, “treating intestine from lung,” and “simultaneous treatment of lung and intestine” has been conducted in clinical practice. The results show that the lungs and guts influence each other from a physiological and pathological perspective. Microecological modulators are recommended to maintain the intestinal microecological balance and prevent secondary bacterial infection in the “diagnosis and treatment protocol for novel coronavirus pneumonia” in China. Therefore, restoring the intestinal microecological balance, regulating the enteric-lung axis to reduce inflammatory damage and improve immunity, not only improves gastrointestinal symptoms but also plays a positive role in promoting the prognosis of patients with coronavirus infection or pneumonia.

In our previous study, we found that XFBD improved immunity by regulating intestinal flora. Moreover, it can significantly change the intestinal microorganisms’ abundance and regulate the acetic acid content. In addition, it can partially adjust the relative abundance of the intestinal microbiota in rats with intestinal flora disturbance caused by antibiotics. Other studies[139] found that short-term intervention with Qingfei Paidu decoction can significantly regulate intestinal flora composition and increase Romboutsia, Turricibacter, and Clostridium_sensu_stricto_I abundance. Intestinal flora intervention may be one of the ways to treat COVID-19. The regulation of TCM in the disordered intestinal flora may play a crucial role in treating COVID-19.

Existing clinical literature suggests that, compared with single compound treatment, TCM is more effective in treating COVID-19[72,77–78,84]. However, whether the maintenance of host intestinal homeostasis mediates efficacy in treating COVID-19 remains to be confirmed in further clinical studies. TCM may be of great value in the prevention and treatment of respiratory symptoms caused by COVID-19 by regulating the intestinal receptors, cytokines, intestinal flora, and their metabolites to reduce intestinal barrier damage. Therefore, there is potential for further research on herbal medicines to treat COVID-19 from the intestinal tract.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Mei Wang, Qiaoyu He, and Xiaopeng Chen conceived and designed this review. Qiaoyu He, Xiaopeng Chen, Yumeng Shi, Qian Tang, and Hong Xing drafted this article. Mei Wang, Xiaopeng Chen, and Han Zhang revised the manuscript. All the authors read and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

Data availability

The data used to support the findings of this study are included in the article.

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