Acupuncture and Herbal Medicine

OPEN

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

Qiaoyu He[1], Yumeng Shi[1], Qian Tang[1], Hong Xing[1], Han Zhang[1], Mei Wang[2], Xiaopeng Chen[1,*]

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

Graphical abstract: http://links.lww.com/AHM/A33.

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 Xuanfei 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.

[1] State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China;
[2] LU-European Center for Chinese Medicine and Natural Compounds, Institute of Biology, Leiden University/SU Biomedicine, Leiden, Netherlands

*Corresponding author. Xiaopeng Chen, State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China, E-mail: xpchen@tjutcm.edu.cn.

Acupuncture and Herbal Medicine (2022) 2:3

Received 22 July 2022 / Accepted 12 September 2022

http://dx.doi.org/10.1097/HM9.0000000000000038

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 microecological regulator" method, which is different from previous epidemic diagnoses and treatment programs and lists the maintenance of intestinal microecological 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[19]. 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. An overview of XFBD for COVID-19 treatment is shown in Figure 2.

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.

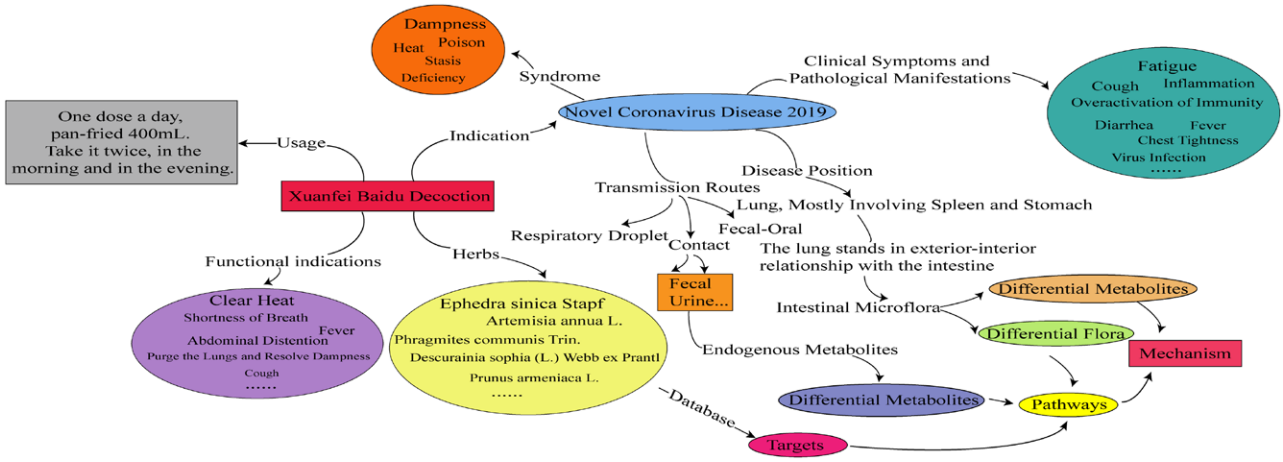

Figure 2. The overview of XFBD for COVID-19 treatment. XFBD: Xuanfei Baidu decoction.

regulation[41]. 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[42–43].

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[44]. 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[41]. 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[45]. Intestinal flora can induce pulmonary inflammation and promote neutrophil infiltration through Toll-like receptor 4 (TLR4) in mice[28]. One study investigated 118 patients with advanced non–small-cell lung cancer who received immune checkpoint blocking therapy[46]. 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[47], 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[48–49]. 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[50–51]. It is reported that SCFAs can inhibit pulmonary inflammation by activating G protein-coupled receptors[52]. Moreover, SCFAs can generate an extrathymic peripheral Treg cell pool and dampen allergic airway diseases through histone deacetylase (HDAC) inhibition[53]. In addition, the microbial metabolite desaminotyrosine (DAT) protects mice from influenza virus infection by enhancing type I interferon (IFN) signal transduction[54]. 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[55]. As a part of mucosa-associated lymphoid tissue (MALT), gut-associated lymphoid tissue (GALT)

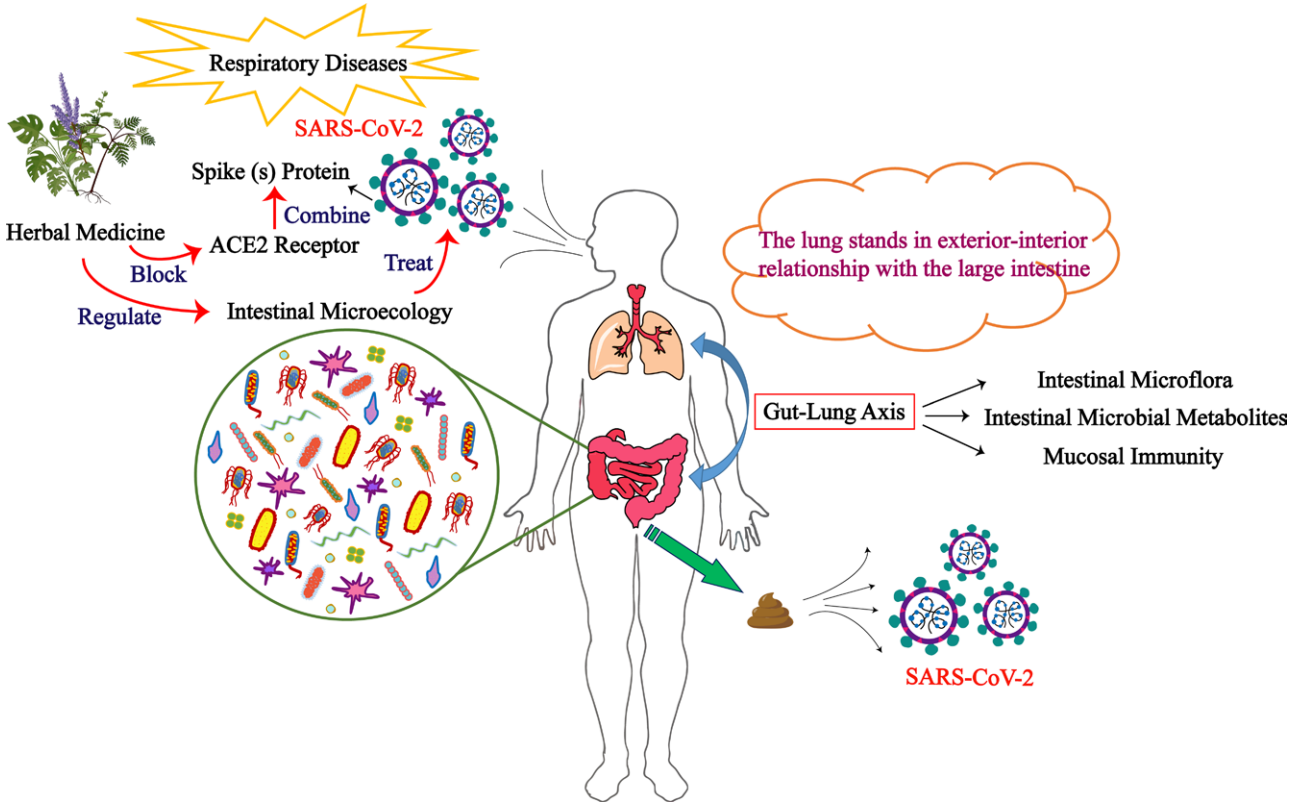

Figure 3. The potential pathway for herbal medicine to treat COVID-19 by regulating the intestinal tract. ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

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. (2020)[70]
	Glycyrrhiza glabra L.	Gan Cao		
	Prunus armeniaca L.	Ku Xing Ren		Zhang et al. (2021)[71]
	Gypsum fibrosum	Sheng Shi Gao		
	Cinnamomi Ramulus	Gui Zhi		Xin et al. (2020)[72]
	Alisma plantago-aquatica Linn	Ze Xie		
	Polyporus	Zhu Ling		Zong et al. (2022)[73]
	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		
		Sheng Jiang		
	Zingiber officinale 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		
	Dioscorea Rhizoma	Zhi Shi		
	Aurantii fructus immaturus	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]
	Prunus armeniaca L.	Ku Xing Ren		
	Gypsum fibrosum	Sheng Shi Gao		Wang et al. (2021)[75]
	Glycyrrhiza glabra L.	Gan Cao		
	Agastache rugosa (Fisch. & C.A.Mey.) Kuntze	Huo Xiang		Li et al. (2020)[76]
	Pinelliae Rhizoma Praeparatum	Fa Ban Xia		
	Magnolia officinalis Rehd. et Wils	Hou Po		Shi et al. (2019)[78]
	Atractylodes lancea (Thunb.) DC.	Cang Zhu		
	Tsaoko Fructus	Cao Guo		
	Poria	Fu Ling		
	Astragali Radix	Sheng Huang Qi		
	Paeonia lactiflora Pall.	Chi Shao		
	Descurainia Sophia (L.) Webb ex Prantl	Ting Li Zi		
	Rheum palmatum L.	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, reduce 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)[78]
	Prunus armeniaca L.	Ku Xing Ren		
	Gypsum Fibrosum	Sheng Shi Gao		Li et al. (2021)[79]
	Coix lacryma-jobi L. var. ma-yuen (Rom.Caill.) Stapf	Yi Ren		
	Atractylodes lancea (Thunb.) DC.	Cang Zhu		Zhou et al. (2021)[80]
	Pogostemon cablin (Blanco) Benth.	Guang Huo Xiang		
	Polygonum cuspidatum Sieb. et Zucc.	Hu Zhang		Pan et al. (2020)[81]
	Verbena officinalis L.	Ma Bian Cao		
	Phragmites communis Trin.	Gan Lu Gen		Li et al. (2022)[82]
	Descurainia Sophia (L.) Webb ex Prantl	Ting Li Zi		
	Citri Grandis Exocarium	Hua Ju Hong		
	Artemisia annua L.	Qing Hao Cao		
	Glycyrrhiza glabra L.	Gan Cao		

(Continued)

Table 1
(Continued)

Herbal medicine prescription	Latin name	Chinese name	Relief or treatment of symptoms	References
Jinhua Qinggan granule	*Lonicera japonica Thunb.* *Gypsum fibrosum* *Ephedra sinica Stapf* *Prunus armeniaca L.* *Scutellaria baicalensis Georgi* *Forsythia suspensa (Thunb.) Vahl* *Fritillaria thunbergii Miq.* *Anemarrhena asphodeloides Bge.* *Arctium lappa L.* *Artemisia annua L.* *Mentha haplocalyx Briq.* *Glycyrrhiza glabra L.*	Ren Dong Sheng Shi Gao Ma Huang Ku Xing Ren Huang Qin Lian Qiao Zhe Bei Mu Zhi Mu Niu Bang Qing Hao Cao Bo He Gan Cao	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] An et al. (2021)[84] Shah et al. (2022)[85] Lin et al. (2022)[86]
Lianhua Qingwen capsule	*Forsythia suspensa (Thunb.) Vahl* *Lonicera japonica Thunb.* *Ephedra sinica Stapf* *Prunus armeniaca L.* *Gypsum fibrosum* *Isatidis Radix* *Dryopteris crassirhizoma Nakai* *Houttuynia cordata Thunb.* *Pogostemon cablin (Blanco) Benth.* *Rheum palmatum L.* *Rhodiola crenulata （Hook. f. et Thoms.） H. Ohba* *Mentha haplocalyx Briq.* *Glycyrrhiza glabra L.*	Lian Qiao Ren Dong Ma Huang Ku Xing Ren Sheng Shi Gao Ban Lan Gen Mian Ma Guan Zhong Yu Xing Cao Guang Huo Xiang Da Huang Hong Jing Tian Bo He Gan Cao	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] Shen et al. (2021)[88] Zeng et al. (2020)[89] Fan et al. (2022)[90]
Xuebijing injection	*Carthamus tinctorius L.* *Paeonia lactiflora Pall.* *Ligusticum chuanxiong Hort.* *Salvia miltiorrhiza Bge.* *Angelica sinensis (Oliv.) Diels*	Hong Hua Chi Shao Chuan Xiong Dan Shen Dang Gui	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] Luo et al. (2021)[92] Chen et al. (2021)[93] Liu et al. (2021)[94] Fu et al. (2020)[95]

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

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, synthesizes and releases a large number of inflammatory factors, and downregulates the expression of the antimicrobial peptides, which destroy the intestinal flora homeostasis and damage 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, glycyrrhizic 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

main treatment strategy for bacterial infectious diseases[100–101]. However, their use is often accompanied by disorders of gut flora and the emergence of drug-resistant bacteria[102–103]. TCM can reverse the intestinal microecological imbalance caused by pathogen infection. This experiment confirmed that the Gegen Qinlian decoction (*Pueraria lobata (Willd.) Ohwi*, *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 *Akkermansia muciniphila*, *Desulfovibrio_C21_c20*, and *Lactobacillus salivarius*, and reduce the pathogenic bacteria abundance such as *E. coli*. Decoction also promotes the recovery of intestinal mucosal immune function, inhibits inflammatory factors expression in mesenteric lymph nodes (mLNs) and serum, alleviates pulmonary inflammation, and reduces mortality in mice[67]. Qingfei Yin (*Scutellaria baicalensis Georgi*, *Forsythia suspensa (Thunb.) Vahl*, *Belamcanda chinensis*（*L.*）*DC*., *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[104]. *Houttuynia cordata* is a TCM used for treating respiratory diseases. Its active component, *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[105].

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 distress and refractory hypoxemia, further developing into acute respiratory distress syndrome (ARDS)[106]. Studies confirm that intestinal and pulmonary microorganisms change significantly through the gut–lung axis in critically ill patients, which affects ALI or ARDS[107–108]. In addition, there are some indications in rats with ALI, such as damage to the intestinal mucosa, an increase in intestinal microflora, and an increase in microflora diversity[109]. Moreover, gut flora plays an important role in ALI development. TCM has a unique advantage in regulating intestinal flora. The traditional herbal medicine rhubarb alleviates the inflammatory reaction caused by ALI by reducing the imbalance of intestinal microflora, increasing the abundance of *Alistipes*, *Clostridium*, and *Lactobacillus*, improving the function of HDAC, inducing the differentiation and maturation of the Th17 cells, and repairing the intestinal mucosal barrier[110]. *Ephedra sinicaStapf* polysaccharide, a component of *Ephedra sinicaStapf*, can significantly upregulate the *Lactobacillales* and *Bifidobacteriaceae* abundance, and downregulate the *Enterococcus* abundance. Therefore, it has an obvious therapeutic effect on ALI caused by H1N1 influenza, suggesting that intestinal flora regulation may be an important mechanism of *Ephedra sinica* Stapf polysaccharide against H1N1 influenza[111]. *Houttuynia cordata* polysaccharides can also regulate the composition, diversity, and abundance of functional genes of gut microflora to restore the dynamic balance of intestinal microflora, thus reducing lung injury caused by H1N1 infection[112].

Herbal medicines improve chronic obstructive pulmonary disease (COPD) by restoring intestinal flora. COPD is a chronic progressive pulmonary pathological heterogeneous disease characterized by persistent airflow obstruction, increased airway inflammation, and lung tissue destruction[113]. Moreover, COPD is associated with high morbidity and fatality, and has become a global public health problem[114]. According to modern clinical studies, the intestinal flora is related to COPD prevention and treatment[115]. Intestinal flora composition in COPD patients changes and the abundance and diversity of pulmonary and gut flora have the same trend at different stages of the disease[116–117], suggesting that the intestinal flora may improve the pulmonary symptoms of COPD patients through the "gut–lung axis". TCM can directly contact the intestinal flora through the oral form, which affects the intestinal flora. Xuanbai Chengqi decoction (*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 *Gordonibacter* and *Akkermansia*, inhibiting the pathogenic *Streptococcus* growth, regulating microecological disorders, and restoring the Th17/Treg cells balance[68]. The key compounds of the Xixin-Ganjiang herb pair (XGHP) can inhibit the PTGS2 expression and promote the PPARG expression in the lung tissue of COPD rats, which may be effective targets for XGHP in the treatment of COPD[118]. Yufeining [*Codonopsis pilosula (Franch.) Nannf*., *Astragali Radix*, *Atractylodes macrocephala Koidz*., *Saposhnikovia divaricata (Turcz.) Schischk*., *Polygonatum odoratum*（*Mill.*）*Druce*, *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*., *Fritillaria thunbergii Miq*., *Salvia miltiorrhiza Bge*., and *Prunus persica (L.) Batsch*.] can reduce cough, sputum, and chest tightness to improve symptoms in patients with COPD[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 Yufeining treatment. TCM can be used as a drug and an anti-inflammatory agent for stable COPD[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[122]. Intestinal homeostasis is closely associated with the development of asthma[123–124]. *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[125]. For decades, Guben Fangxiao decoction (*Astragalic Radix*, *Codonopsis pilosula (Franch.) Nannf*., *Atractylodes macrocephala Koidz*.,

Poria cocos (Schw.) Wolf., *Ostrea gigas Thunberg.*, *Cryptotympana pustulata Fabricius.*, *Citrus aurantium L.*, *Saposhnikovia divaricate (Turcz.) Schischk.*, *Magnolia biondii Pamp.*, *Schisandra chinensis (Turcz.) Baill.*, and *Glycyrrhiza glabra L.*) have been used to treat lung-spleen *qi* deficiency syndrome in ARS in China. According to the experiment, it could reverse the intestinal microflora imbalance, as well as increase the abundance of bacteria producing SCFAs in asthmatic mice, and improve asthma in the remission stage symptoms through the microflora-acetate-Tregs axis[126]. A pentaherb formula (*Lonicera japonica Thunb.*, *Mentha haplocalyx Briq.*, *Paeonia 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 community structure and SCFAs content[69]. Youguiwan (*Rehmannia glutinosa Libosch*, *Dioscorea oppositifolia L.*, *Eucommia ulmoides Oliv.*, *Lycium barbarum L.*, *Cornus officinalis Sieb Zucc.*, *Cuscuta 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[133] found that short-term intervention with Qingfei Paidu decoction can significantly regulate intestinal flora composition and increase *Romboutsia*, *Turicibacter*, and *Clostridium_sensu_stricto_1* 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.

Funding

This work was supported by the Tianjin Science and Technology Program (22ZXGBSY00020).

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.

Acknowledgments

None.

References

[1] Davis EL, Lucas TCD, Borlase A, et al. Contact tracing is an imperfect tool for controlling COVID-19 transmission and relies on population adherence. *Nat Commun* 2021;12(1):5412.
[2] Li Q, Guan XH, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020;382(13):1199–1207.
[3] Munster VJ, Koopmans M, van Doremalen N, et al. A novel coronavirus emerging in China-key questions for impact assessment. *N Engl J Med* 2020;382(8):692–694.
[4] Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China. *N Engl J Med* 2020;382(8):727–733.
[5] Mittal A, Manjunath K, Ranjan RK, et al. COVID-19 pandemic: insights into structure, function, and hACE2 receptor recognition by SARS-CoV-2. *PLoS Pathog* 2020;16(8):e1008762.
[6] Andersen KG, Rambaut A, Lipkin WL, et al. The proximal origin of SARS-CoV-2. *Nat Med* 2020;26(4):450–452.
[7] Chan JF, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* 2020;9(1):221–236.

[8] World Health Organization (WHO). Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. Available from: https://www.who.int/csr/sars/country/table2004_04_21/en/. Accessed May 20, 2022.

[9] World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report-52. Available from: https://www.who.int/docs/default-source/coronaviruse/20200312-sitrep-52-covid-19.pdf?sfvrsn=e2bfc9c0_2. Accessed May 20, 2022.

[10] Lamers MM, Beumer J, Vaart JVD, et al. SARS-CoV-2 productively infects human gut enterocytes. *Science* 2020;369(6499):50–54.

[11] Cholankeril G, Podboy A, Aivaliotis VL, et al. High prevalence of concurrent gastrointestinal manifestations in patients with severe acute respiratory syndrome coronavirus 2: early experience from California. *Gastroenterology* 2020;159(2):775–777.

[12] Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020;382(18):1708–1720.

[13] Dousari AS, Moghadam MT, Satarzadeh N. COVID-19 (coronavirus disease 2019): a new coronavirus disease. *Infect Drug Resist* 2020;13:2819–2828.

[14] Zhou ZL, Zhao N, Shu Y, et al. Effect of gastrointestinal symptons in patients with COVID-19. *Gastroenterology* 2020;158(8):2294–2297.

[15] Qian Q, Fan LF, Liu WC, et al. Direct evidence of active SARS-CoV-2 replication in the intestine. *Clin Infect Dis* 2021;73(3):361–366.

[16] Du ML, Cai GS, Chen F, et al. Multiomics evaluation of gastrointestinal and other clinical characteristics of COVID-19. *Gastroenterology* 2020;158(8):2298–2301.

[17] Zhang JC, Xie B, Hashimoto K. Current status of potential therapeutic candidates for the COVID-19 crisis. *Brain Behav Immun* 2020;87:59–73.

[18] The National Health Commission of the People's Republic of China, The State Administration of TCM. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (eighthed. trial version). Available from: http://www.nhc.gov.cn/yzygj/s7653p/202008/0a7bdf12bd4b46e5bd28ca7f9a7f5e5a.shtml. Accessed January 18, 2022.

[19] Kim HS. Do an altered gut microbiota and an associated leaky gut affect COVID-19 severity? *mBio* 2021;12(1):e03022–e03020.

[20] Tang LL, Gu S, Gong YW, et al. Clinical significance of the correlation between changes in the major intestinal Bacteria Species and COVID-19 Severity. *Engineering* 2020;6(10):1178–1184.

[21] Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol* 2020;17(4):223–237.

[22] Wang JJ, Qi FH. Traditional Chinese medicine to treat COVID-19: the importance of evidence-based research. *Drug Discov Ther* 2020;14(3):149–150.

[23] Zuo T, Zhang F, Lui GCY, et al. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization. *Gastroenterology* 2020;159(3):944–955.e8.

[24] Gheblawi M, Wang KM, Viveiros A, et al. Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. *Circ Res* 2020;126(10):1456–1474.

[25] Xiao F, Tang MW, Zheng XB, et al. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology* 2020;158(6):1831–1833.

[26] Hashimoto T, Perlot T, Rehman A, et al. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. *Nature* 2012;487(7408):477–481.

[27] Geva-Zztorsky N, Sefik E, Kua L, et al. Mining the human gut microbiota for immunomodulatory organisms. *Cell* 2017;168(5):928–943.

[28] Yang T, Chakraborty S, Saha P, et al. Gnotobiotic rats reveal that gut microbiota regulates colonic mRNA of ACE2, the receptor for SARS-CoV-2 infectivity. *Hypertension* 2020;76(1):e1–e3.

[29] d'Ettorre G, Ceccarella G, Marazzato M, et al. Challenges in the management of SAR-CoV2 infection: the role of oral bacteriotherapy as complementary therapeutic strategy to avoid the progression of COVID-19. *Front Med (Lausanne)* 2020;7:389.

[30] Wu LH, Ye ZN, Ping P, et al. Efficacy and safety of washed microbiota transplantation to treat patients with mild-to-severe COVID-19 and suspected of having gut microbiota dysbiosis: study protocol for a randomized controlled trial. *Curr Med Sci* 2021;41(6):1087–1095.

[31] Oliveira GLV, Oliveira CNS, Pinzan CF, et al. Microbiota modulation of the gut-lung axis in COVID-19. *Front Immunol* 2021;12:635471.

[32] Ivashkin V, Fomin V, Moiseev S, et al. Efficacy of a probiotic consisting of Lacticaseibacillus rhamnosus PDV 1705, Bifidobacterium bifidum PDV 0903, Bifidobacterium longum subsp. infantis PDV 1911, and Bifidobacterium longum subsp. longum PDV 2301 in the treatment of hospitalized patients with COVID-19: a randomized controlled trial. *Probiotics Antimicrob Proteins* 2021;13:1–9.

[33] Fujimura KE, Sitarik AR, Havstad S, et al. Neonatal gut microbiota associates with childhood multisensitized atopy and T cell differentiation. *Nat Med* 2016;22(10):1187–1191.

[34] Hanada S, Pirzadeh M, Carver KY, et al. Respiratory viral infection-induced microbiome alterations and secondary bacterial pneumonia. *Front Immunol* 2018;9:2640.

[35] Wang DW, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323(11):1061–1069.

[36] Belkaid Y, Hang TW. Role of the microbiota in immunity and inflammation. *Cell* 2014;157(1):121–141.

[37] Kalantar-Zadeh K, Ward SA, Kalantar-Zadeh K, et al. Considering the effects of microbiome and diet on SARS-CoV-2 infection: nanotechnology roles. *ACS Nano* 2020;14(5):5179–5182.

[38] Mak JWY, Chan FKL, Ng SC. Probiotics and COVID-19: one size does not fit all. *Lancet Gastroenterol Hepatol* 2020;5(7):644–645.

[39] Hu JL, Zhang L, Lin W, et al. Review article: probiotics, prebiotics and dietary approaches during COVID-19 pandemic. *Trends Food Sci Technol* 2021;108:187–196.

[40] Biliński J, Winter K, Jasiński M, et al. Rapid resolution of COVID-19 after faecal microbiota transplantation. *Gut* 2022;71(1):230–232.

[41] Enaud R, Prevel R, Ciarlo E, et al. The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. *Front Cell Infect Microbiol* 2020;10:9.

[42] Kao HF, Wang YC, Tseng HY, et al. Goat milk consumption enhances innate and adaptive immunities and alleviates allergen-induced airway inflammation in offspring mice. *Front Immunol* 2020;11(18):184.

[43] Barcik W, Boutin RCT, Sokolowska M, et al. The role of lung and gut microbiota in the pathology of asthma. *Immunity* 2020;52(2):241–255.

[44] Chakradhar SA. Curious connection: teasing apart the link between gut microbes and lung disease. *Nat Med* 2017;23(4):402–404.

[45] Kumai M, Coria AL, Cornick S, et al. Increased intestinal permeability exacerbates sepsis through reduced hepatic SCD-1activity and dysregulated iron recycling. *Nat Commun* 2020;11(1):483.

[46] Tomita Y, Ikeda T, Sakata S, et al. Association of probiotic Clostridium butyricum therapy with survival and response to immune checkpoint blockade in patients with lung cancer. *Cancer Immunol Res* 2020;8(10):1236–1242.

[47] Groves HT, Higham SL, Moffatt MF, et al. Respiratory viral infection alters the gut microbiota by inducingInappetence. *mBio* 2020;11(1):e03236–e03219.

[48] Dhar D, Mohanty A. Gut microbiota and COVID-19-possible link and implications. *Virus Res* 2020;285:198018.

[49] Lelie Dvd TS. COVID-19 and the gut microbiome: more than a gut feeling. *mSystems* 2020;5(4):E00453–E00420.

[50] Koh A, Vadder FD, Kovatcheva-Datchary P, et al. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. *Cell* 2016;165(6):1332–1345.

[51] Theiler A, Bärnthaler T, Platzer W, et al. Butyrate ameliorates allergic airway inflammation by limiting eosinophil trafficking and survival. *J Allergy Clin Immunol* 2019;144(3):764–776.

[52] Antunes KH, Fachi JL, d PR, et al. Microbiota-derived acetate protects against respiratory syncytial virus infection through a GPR43-type 1 interferon response. *Nat Commun* 2019;10(1):3273.

[53] Arpaia N, Campbell C, Fan XY, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature* 2013;504(7480):451–455.

[54] Steed AL, Christophi GP, Kaiko GE, et al. The microbial metabolite desaminotyrosine protects from influenza through type I interferon[J]. *Science* 2017;357(6350):498–502.

[55] Tulic MK, Piche T, Verhasselt V, et al. Lung-gut cross-talk: evidence, mechanisms and implications for the mucosal inflammatory diseases. *Clin Exp Allergy* 2016;46(4):519–528.

[56] Samuelson DR, Welsh DA, Shellito JE. Regulation of lung immunity and host defense by the intestinal microbiota. *Front Microbiol* 2015;6:1085.

[57] Mjösberg J, Rao A. Lung inflammation originating in the gut. *Science* 2018;359(6371):36–37.

[58] Huang YF, Mao KR, Chen X, et al. S_1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense. *Science* 2018;359(6371):114–119.

[59] Miao J, Yang X, Yan YF, et al. Experiment and clinical research of "Exterion and Interior of the Lung and Large Intestine". *Liaoning J Tradit Chin Med* 2017;19(12):183–185.

[60] Xia XT, Wen MY, Zhan SF, et al. Treatment to COVID-19 based on theory of simultaneous treatment to lung and large intestine: a preliminary clinical trial. *Liaoning J Tradit Chin Med* 2021;48(10):35–37.

[61] Zhang WJ, Dai Y. Research advances of lung-gut axis. *J Pharm Res* 2022;41(1):53–56.

[62] Zhang Q, Yue SJ, Wang WX, et al. Potential role of gut microbiota in traditional Chinese medicine against COVID-19. *Am J Chin Med* 2021;49(4):785–803.

[63] Lu HR, Zhang LX, Xiao JF, et al. Effect of feeding Chinese herb medicine ageratum-liquid on intestinal bacterial translocations induced by H9N2 AIV in mice. *Virol J* 2019;16(1):24.

[64] Wang J, Ishfaq M, Li J. Baicalin ameliorates mycoplasma gallisepticum-induced inflammatory injury in the chicken lung through regulating the intestinal microbiota and phenylalanine metabolism. *Food Funct* 2021;12(9):4092–4104.

[65] Chen QH, Liu JJ, Wang WQ, et al. Sini decoction ameliorates sepsis-induced acute lung injury *via* regulating ACE2-Ang (1-7)-Mas axis and inhibiting the MAPK signaling pathway. *Biomed Pharmacother* 2019;115:108971.

[66] Ho TY, Wu SL, Chen JC, et al. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Res* 2007;74(2):92–101.

[67] Deng L, Shi YC, Liu P, et al. GeGen QinLian decoction alleviate influenza virus infectious pneumonia through intestinal flora. *Biomed Pharmacother* 2021;141:111896.

[68] Wang YA, Li N, Li QY, et al. Xuanbai Chengqi decoction ameliorates pulmonary inflammation *via* reshaping gut microbiota and rectifying Th17/Treg imbalance in a murine model of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2021;16:3317–3335.

[69] Tsang MSM, Cheng SW, Zhu J, et al. Anti-inflammatory activities of pentaherbs formula and its influence on gut microbiota in allergic asthma. *Molecules* 2018;23(11):2776.

[70] Shi NN, Liu B, Liang N, et al. Association between early treatment with Qingfei Paidu decoction and favorable clinical outcomes in patients with COVID-19: a retrospective multicenter cohort study. *Pharmacol Res* 2020;161:105290.

[71] Zhang LH, Zheng X, Bai XK, et al. Association between use of Qingfei Paidu Tang and mortality in hospitalized patients with COVID-19: a national retrospective registry study. *Phytomedicine* 2021;85:153531.

[72] Xin SY, Cheng XQ, Zhu B, et al. Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with Western medicine for COVID-19 treatment. *Biomed Pharmacother* 2020;129:110500.

[73] Zong XY, Liang N, Wang JY, et al. Treatment effect of Qingfei Paidu decoction combined with conventional treatment on COVID-19 patients and other respiratory diseases: a multicenter retrospective case series. *Front Pharmacol* 2022;13:849598.

[74] Liao Y, Yin B, Jin Z, et al. TCM theoretical analysis and modern pharmacological mechanism of Huashi Baidu decoction in treating severe novel coronavirus pneumonia. *J Hainan Med Coll* 2020;26:1209–1213.

[75] Wang Y, Lu C, Li H, et al. Efficacy and safety assessment of severe COVID-19 patients with Chinese medicine: a retrospective case series study at early stage of the COVID-19 epidemic in Wuhan, China. *J Ethnopharmacol* 2021;277:113888.

[76] Li Q, Wang H, Li X, et al. The role played by traditional Chinese medicine in preventing and treating COVID-19 in China. *Front Med* 2020;14(5):681–688.

[77] Shi N, Guo L, Liu B, et al. Efficacy and safety of Chinese herbal medicine versus lopinavir-ritonavir in adult patients with coronavirus disease 2019: a non-randomized controlled trial. *Phytomedicine* 2021;81:153367.

[78] Xiong WZ, Wang G, Du J, et al. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: a pilot randomizedclinical trial. *Integr Med Res* 2020;9(3):100489.

[79] Li F, Li YJ, Zhang JX, et al. The therapeutic efficacy of Xuanfei Baidu Formula combined with conventional drug in the treatment of coronavirus disease 2019: a protocol for systematic review and meta-analysis. *Medicine* 2021;100(3):e24129.

[80] Zhou L, Wang XN, Liu XK, et al. Report on the case of Xuanfei Baidu recipe for curing COVID-19's critically ill patients. *J Tianjin Univ Tradit Chin Med* 2021;38(5):556–559.

[81] Pan X, Dong L, Yang L, et al. Potential drugs for the treatment of the novel coronavirus pneumonia (COVID-19) in China. *Virus Res* 2020;286:198057.

[82] Li XC, Zhang J, Xia WG, et al. Clinical observation of Xuanfei Baidu decoction in treatment of severe coronavirus disease 2019 (COVID-19). *Zhongguo Zhong Yao Za Zhi* 2022;47(13):3667–3674.

[83] Zhang QS, Cao F, Wang YF, et al. The efficacy and safety of Jinhua Qinggan granule (JHQG) in the treatment of coronavirus disease 2019 (COVID-19): a protocol for systematic review and meta analysis. *Medicine (Baltim)* 2020;99(24):e20531.

[84] An XD, Xu X, Xiao MZ, et al. Efficacy of Jinhua Qinggan granules combined with western medicine in the treatment of confirmed and suspected COVID-19: a randomized controlled trial. *Front Med (Lausanne)* 2021;8:728055.

[85] Shah MR, Fatima S, Khan SN, et al. Jinhua Qinggan granules for non-hospitalized COVID-19 patients: a double-blind, placebo-controlled, and randomized controlled trial. *Front Med (Lausanne)* 2022;9:928468.

[86] Lin TPH, Lau EMC, Wan KH, et al. Initial observations of Jinhua Qinggan granules, a Chinese medicine, in the mitigation of hospitalization and mortality in high-risk elderly with COVID-19 infection: a retrospective study in an old age home in Hong Kong. *Front Med (Lausanne)* 2022;9:948149.

[87] Xiao MZ, Tian JX, Zhou YN, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: a randomized controlled trial. *Pharmacol Res* 2020;161:105126.

[88] Shen XH, Yin FG. The mechanisms and clinical application of traditional Chinese medicine Lianhua-Qingwen capsule. *Biomed Pharmacother* 2021;142:111998.

[89] Zeng MJ, Li LJ, Wu ZQ. Traditional Chinese medicine Lianhua Qingwen treating corona virus disease 2019 (COVID-19): meta-analysis of randomized controlled trials. *PLoS One* 2020;15(9):e0238828.

[90] Fan SJ, Liao JK, Wei L, et al. Treatment efficacy of Lianhua Qingwen capsules for eraly-stage COVID-19. *Am J Transl Res* 2022;14(2):1332–1338.

[91] Guo H, Zheng JY, Huang G, et al. Xuebijing injection in the treatment of COVID-19: a retrospective case-control study. *Ann Palliat Med* 2020;9(5):3235–3248.

[92] Luo ZJ, Chen W, Xiang MQ, et al. The preventive effect of Xuebijing injection against cytokine storm for severe patients with COVID-19: a prospective randomized controlled trial. *Eur J Integr Med* 2021;42:101305.

[93] Chen L, Zhang A, Li QT, et al. Evaluation of clinical value of Xuebijing combined with human immunoglobulin in severe and critically ill patients with coronavirus disease 2019. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2021;33(4):399–404.

[94] Liu XS, Song YL, Guan WJ, et al. A multicenter prospective cohort study of Xuebijing injection in the treatment of severe coronavirus disease 2019. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2021;33(7):774–778.

[95] Fu JM, Wu LL, Ma YY, et al. The efficacy and safety of Xuebijing injection for corona virus disease 2019: a protocol for a systematic review and meta-analysis. *Medicine (Baltim)* 2020;99(49):e23401.

[96] Viana SD, Nunes S, Reis F. ACE2 imbalance as a key player for the poor outcomes in COVID-19 patients with age-related comorbidities-role of gut microbiota dysbiosis. *Ageing Res Rev* 2020;62:101123.

[97] Perlot T, Penninger JM. ACE2-from the renin-angiotensin system to gut microbiota and malnutrition. *Microbes Infect* 2013;15(13):866–873.

[98] Liu JJ, Chen QH, Liu SZ, et al. Sini decoction alleviates E. coli induced acute lung injury in mice *via* equilibrating ACE-AngII-AT1R and ACE2-Ang-(1-7)-Mas axis. *Life Sci* 2018;208:139–148.

[99] Cinatl J, Morgenstern B, Bauer G, et al. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet* 2003;361(9374):2045–2046.

[100] Kadri SS, Boycher HW. U.S. efforts to curb antibiotic resistance-are we saving lives? *N Engl J Med* 2020;383(9):806–808.

[101] Buckel WR, Stenehjem E, Sorensen J, et al. Broad-versus narrow-spectrum oral antibiotic transition and outcomes in health care-associated pneumonia. *Ann Am Thorac Soc* 2017;14(2):200–205.

[102] Ramirez J, Guarner F, Fernandez LB, et al. Antibiotics as major disruptors of gut microbiota. *Front Cell Infect Microbiol* 2020;10:572912.

[103] Duan YJ, Chen ZY, Tan L, et al. Gut resistomes, microbiota and antibiotic residues in Chinese patients undergoing antibiotic administration and healthy individuals. *Sci Total Environ* 2020;705:135674.
[104] Sun XZ, Wang DD, Wei LN, et al. Gut microbiota and SCFAs play key roles in QingFei Yin Recipe anti-streptococcal pneumonia effects. *Front Cell Infect Microbiol* 2021;11:791466.
[105] Zhu HY, Lu XX, Ling LJ, et al. Houttuynia cordata polysaccharides ameliorate pneumonia severity and intestinal injury in mice with influenza virus infection. *J Ethnopharmacol* 2018;218:90–99.
[106] Jiang WJ, Luo F, Lu QF, et al. The protective effect of Trillin LPS-induced acute lung injury by the regulations of inflammation and oxidative state. *Chem Biol Interact* 2016;243:127–134.
[107] Mukherjee S, Hanidziar D. More of the gut in the lung: how two microbiomes meet in ARDS. *Yale J Biol Med* 2018;91(2):143–149.
[108] Dickson RP, Singer BH, Newstead MW, et al. Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome. *Nat Microbiol* 2016;1(10):16113.
[109] Li Y, Liu XY, Ma MM, et al. Changes in intestinal microflora in rats with acute respiratory distress syndrome. *World J Gastroenterol* 2014;20(19):5849–5858.
[110] Tang TY, Wang F, Liu J, et al. Rhubarb alleviates acute lung injury by modulating gut microbiota dysbiosis in mice. *Curr Microbiol* 2022;79(4):116.
[111] Lin XT, Liang SS, Wang QH, et al. Metagenomics approach the intestinal microbiome structure and function in the anti-H1N1 of a traditional Chinese medicine acid polusaccharide. *Microb Pathog* 2020;147:104351.
[112] Chen MY, Li H, Lu XX, et al. Houttuynia cordata polysaccharides alleviated intestinal injury and modulated intestinal microbiota in H1N1 virus infected mice. *Chin J Nat Med* 2019;17(3):187–197.
[113] Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet* 2017;389(10082):1931–1940.
[114] Riley CM, Sciurba FC. Diagnosis and outpatient management of chronic obstructive pulmonary disease: a review. *JAMA* 2019;321(8):786–797.
[115] Huang YJ, Erb-Downward JR, Dickson RP, et al. Understanding the role of the microbiome in chronic obstructive pulmonary disease: principles, challenges, and future directions. *Transl Res* 2017;179:71–83.
[116] Bowerman KL, Rehman SF, Vaughan A, et al. Disease-associated gut microbiome and metabolome changes in patients with chronic obstructive pulmonary disease. *Nat Commun* 2020;11(1):5886.
[117] Sun Z, Shen Y ZQ, et al. Dynamic changes of gut and lung microorganisms during chronic obstructive pulmonary disease exacerbations. *Kaohsiung J Med Sci* 2020;36(2):107–113.
[118] Huang P, Huang T, Li DS, et al. Treating chronic obstructive pulmonary disease-integrated network pharmacology and molecular docking. *Evid Based Complement Alternat Med* 2021;2021:5532009.
[119] Hong ML, Chen WX, Cai SH, et al. Study on the intervention effect of Yufeining on pulmonary function in patients with chronic obstructive pulmonary disease. *Chin J Trad Chin Med* 2005;20:92–95.
[120] Hong ML, Yang GZ, Chen WX, et al. Effect of Yufeining on induced sputum interleukin-8 in patients with chronic obstructive pulmonary disease at the stable phase. *Chin J Integr Med* 2005;11:179–182.
[121] Hong ML, Hong CL, Chen HN, et al. Effects of the Chinese herb formula Yufeining on stable chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled trial. *Medicine (Baltim)* 2018;97(39):e12461.
[122] Campo P, Rodríguez F, Sánchez-García S, et al. Phenotypes and endotypes of uncontrolled severe asthma: new treatments. *J Investig Allergol Clin Immunol* 2013;23(2):76–88.
[123] Frati F, Salvatori C, Incorvaia C, et al. The role of the microbiome in asthma: the gut-lung axis. *Int J Mol Sci* 2018;20(1):123.
[124] Gangi AD, Cicco MED, Comberiati P, et al. Go with your gut: the shaping of T-cell response by gut microbiota in allergic asthma. *Front Immunol* 2020;11:1485.
[125] He Q, Liu C, Shen L, et al. Theory of the exterior-interior relationship between the lungs and the large intestine to explore the mechanism of Eriobotrya japonica leaf water extract in the treatment of cough variant asthma. *J Ethnopharmacol* 2021;281:114482.
[126] Dong YM, Yan H, Zhao X, et al. Gu-Ben-Fang-Xiao decoction ameliorated murine asthma in remission stage by modulating microbiota-acetate-tregs axis. *Front Pharmacol* 2020;11:549.
[127] Hsu WH, Lin LJ, Lu CK, et al. Effect of You-Gui-Wan on house dust mite-induced mouse allergic asthma *via* regulating amino acid metabolic disorder and gut dysbiosis. *Biomolecules* 2021;11(6):812.
[128] Holshue ML, Debolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the united states. *N Engl J Med* 2020;382(10):929–936.
[129] Papoutsis A, Borody T, Dolai S, et al. Detection of SARS-CoV-2 from patient fecal samples by whole genome sequencing. *Gut Pathog* 2021;13(1):7.
[130] Chen S, Si JF, Tang WQ, et al. An asymptomatic SARS-CoV-2-infected infant with persistent fecal viral RNA shedding in a family cluster: a rare case report. *Front Med (Lausanne)* 2020;7:562875.
[131] Wong MC, Huang JJ, Lai C, et al. Detection of SARS-CoV-2 RNA in fecal specimens of patients with confirmed COVID-19: a meta-analysis. *J Infect* 2020;81(2):e31–e38.
[132] Adhikari UD, Eng G, Farcasanu M, et al. Fecal severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA is associated with decreased coronavirus disease 2019 (COVID-19) survival. *Clin Infect Dis* 2022;74(6):1081–1084.
[133] Wu GS, Zhong J, Zheng NN, et al. Investigation of modulating effect of Qingfei Paidu Decoction on host metabolism and gut microbiome in rats. *Chin J Chin Mater Med* 2020;45:3726–3739.

How to cite this article: He QY, Shi YM, Tang Q, Xing H, Zhang H, Wang M, Chen XP. Herbal medicine in the treatment of COVID-19 based on the gut–lung axis. Acupunct Herb Med 2022;2(3):172–183. doi: 10.1097/HM9.0000000000000038