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13.1 INTRODUCTION

Traditional Chinese medicine (TCM) is a brilliant component of Chinese culture with more than 3000 years of history. The ancient medicine books *Huangdi Neijing* (黄帝内经, Huangdi's internal classic), *Shennong Ben Cao Jing* (神农本草经, Shennong's herbal classic), and *Shanghan Lun* (伤寒论, Treatise on febrile disease) have clearly described the symptoms of various respiratory diseases, as well as approaches for prevention and treatment. TCM has a unique theoretical system based on the dialectical viewpoint of ancient Chinese philosophical thought, that is the guiding principles of holism and syndrome differentiation and treatment.

The traditional Chinese herbs are an especially important component of whole TCM. The specific parts of plants (roots, rhizomes, stems, flowers, fruits, seeds, plant products, extracts, and metabolites) are widely applied in treating respiratory disorders and alleviating symptoms such as cough, cold, flu, bronchitis, asthma, respiratory tract infections, as well as weakness, gastrointestinal disorders, and even alleviating anxiety. The plant-based components account for one-quarter of the most commonly used medicinal compounds (1).

The Chinese patent medicines, formulas, or prescriptions are all mixtures of various kinds of materials and have the function of treating both symptoms and root causes. The herbs in each prescription have their specific pharmacological roles in treating patients. According to the theory of TCM, the roles of these herbs in each formula, for example, can be divided into Jun (君, monarch), Chen (臣, minister), Zuo (佐, assistant), and Shi (使, guide) (2). The monarch herbs are the principal herbs with the main therapeutic activity. The minister herbs are the secondary principal components of the formula for enhancing or assisting the effect of the monarch herb. The assistant and guide herbs in the formula are for treating accompanying symptoms, enhancing the delivery of herbal ingredients, and/or controlling the toxicity of the primary components. Therefore, TCM also possess the characteristics of multiple components, multiple targets, and multiple pathways for treating patients against diseases.

With the modernization of TCM research, hundreds of Chinese herbal medicines for treating respiratory diseases have revealed the molecular mechanisms of action. Various bioactive compounds or metabolites of these herbs include flavonoids, saponins, alkaloids, phenols, terpenes, and others. Therefore, ancient Chinese medicine has been further developed, and it shows more powerful vitality when combined with Western medicine in an organic manner. In this chapter, we will introduce some common Chinese herbal remedies for treating respiratory diseases, their effective chemical compositions, and possible mechanisms of action according to modern biological theories.

13.2 INFECTION OF VIRUSES

The epidemic diseases caused by respiratory viruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV)-1 and SARS-CoV-2, influenza A viruses, and respiratory syncytial virus, often pose a great harm to society. In China, there are enriched experiences and effective prescriptions that have existed for more than 2000 years for controlling and treating epidemic infectious diseases. The theory of prevention and treatment of "pestilence" (fatal epidemic diseases) has not

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only recommended many prescriptions but also provided principles of epidemic disease prevention, which have been followed by TCM practitioners until now.

According to TCM theory, there are two main strategies in antiviral treatment: dispelling the pathogenic factors and strengthening the body. That means on one hand to directly eliminate or inhibit virus, and on the other hand to regulate immunity, control inflammation, as well as repair tissues and protect the host. In this section, we will only discuss the coronavirus infection.

13.2.1 Treatment of SARS-CoV-2 Infection with TCM in China

Since the end of 2019, the outbreak of SARS-CoV-2 infection (named COVID-19) had become a global health emergency on a pandemic scale for more than 3 years. In order to defeat the COVID-19 disease, the Chinese National Health Commission & National Administration of Traditional Chinese Medicine officially issued ten versions of *Diagnosis and Treatment Protocol for COVID-19 Patients (Trial)*. The ninth version (3), released on March 15, 2022, includes a combination strategy of TCM and Western medicine in preventing and treating COVID-19. In the TCM section, there are 27 Chinese patent medicines, formulas, and recommended prescriptions with more than 100 herbs involved. In the protocol, several acupuncture points are also recommended, including Hegu (合谷), Houxi (后溪), Yinlingquan (阴陵泉), Taixi (太溪), Feishu (肺俞), and Pishu (脾俞), Neiguan (内关), Kongzui (孔最), Quchi (曲池), Qihai (气海), Zhongwan (中脘), Dazhui (大椎), Lieque (列缺), Taichong (太冲), Guanyuan (关元), and Baihui (百会), Zusanli (足三里). In addition, separated moxibustion is also recommended to select Dazhui (大椎), Feishu (肺俞), Pishu (脾俞), and Kongzui (孔最). The therapeutic strategies of the protocol cover the entire processes of the disease with different degrees of severity.

The protocol recommended many formulas for different degrees of cases, such as Huoxiang Zhengqi (藿香正气) capsule and Shufeng Jiedu (疏风解毒) capsules for medical observation cases; Jinhua Qinggan (金花清感) granules and Lianhua Qingwen (连花清瘟) capsules for both medical observation and mild cases; Qingfei Paidu (清肺排毒) decoction for mild, moderate, and severe cases; lung-diffusing and toxin-resolving (散肺解毒) formula, lung-diffusing, dryness moistening, and toxin-resolving (散肺润燥解毒) formula for moderate cases; dampness-removing and toxin-resolving (祛湿解毒) formula, Huashi Baidu (化湿败毒) granule, and Xiyanping (喜炎平) injection for severe cases; Xuebijing (血必净) injection, Reduning (热毒宁) injection, Tanreqing (痰热清) injection and Xingnaojing (醒脑静) injection for both severe cases and critically ill cases; Suhexiang (苏合香) pill or Angong Niuhuang (安宫牛黄) pill, Shenfu (参附) injection, Shengmai (生脉) injection, Shenmai (参麦) injection for critically ill cases and the cases on mechanical ventilation with abdominal distention or constipation; as well as some recommended prescriptions for cases in convalescent period.

Through the screening in clinical practice, “three medicines and three formulas” is considered to have the most obvious curative effects. The “three medicines” include Jinhua Qinggan granules, Lianhua Qingwen capsules, and Xuebijing injection. The “three formulas” are Qingfei Paidu decoction, Huashi Baidu formula, and Xuanfei Baidu formula. All the medicines, except Xuebijing injection, are modified on the basis of a famous TCM named Ma Xing Shi Gan (麻杏石甘, ephedrae herba, armeniacae semen, gypsum fibrosum, glycyrrhizae radix) decoction from Zhang Zongjing’s *Treatise on Cold Damage Diseases* published in the late Eastern Han Dynasty (4, 5).

A plethora of clinical evidence indicates that TCM is beneficial for treating COVID-19 in (1) relieving the typical symptoms of fever, cough, fatigue, dry throat, sore throat, sputum production, shortness of breath, myalgia, and diarrhea, reducing the time to symptom recovery; (2) improving the lung features including lung inflammatory absorption, CT imaging, lung function, and related laboratory index; (3) shortening the duration of positive viral nucleic acid, and the progression to severe cases; and (4) protecting against multiorgan injury. Clinical practice has demonstrated that the strategy of combining TCM and Western medicine in the treatment of COVID-19 can achieve satisfactory results compared with the treatment of TCM or Western medicine alone (4).

13.2.2 The Active Ingredients of TCM in the Treatment of COVID-19

13.2.2.1 The Herbs and Their Active Ingredients of TCM

In addition to constantly adjusting and developing recipes for effectively treating COVID-19 patients, many scientists have also focused on discovering the effective herbs and their active ingredients. According to the analytic results of numerous prescriptions in treating COVID-19, the following herbs are most frequently used to suppress the virus: glycyrrhizae radix, armeniacae semen, ephedrae herba, poria, forsythiae fructus, scutellariae radix, pinellinae rhizoma praeparatum, pogostemonis herba, lonicerae japonicae, bupleuri radix, citri reticulatae pericarpium, atractylodis macrocephalae, rheum palmatum, magnoliae officinalis, isatidis radix, tsaoko fructus, mint, zingiberis rhizoma recens, dryopteridis crassirhizomatis rhizoma, coptidis rhizoma, rosae laevigatae fructus, propolis, linderae radix, green aucklandiae radix, polygoni cuspidati rhizoma et radix, sargassum, luffae fructus retinervus, and granati pericarpium, as well as mineral-based gypsum fibrosum (6, 7).

The active ingredients of hundreds of herbs have been identified. The ingredients that are most effective in treatment of COVID-19 include aescin, andrographolide, apigenin, astragaloside IV, baicalin, bavachinin, betulinic acid, blancoxanthone, celastrol, corylifol A, curcumin, emodin, ginkgetin, glycyrrhizin, α-hederin, hesperidin, iguesterin, isobavachalcone, jubanine G, kaempferol, lignan, luteolin, lycorine, matrine, myricetin, naringenin, neobavaisoflavone, nigellidine, patchouli alcohol, psoralidin, quercetin, resveratrol, saikosaponins, shikonin, silvestrol, tanshinone, and tingenone (8, 9).

There is a wide variety of sources of these ingredients, but primarily they can be any parts of a plant. Each plant always contains several active ingredients. A single ingredient may have several pharmacological functions and can be found in several plants.

13.2.2.2 The Mechanisms of TCM Ingredients Acting on COVID-19

The treatment of COVID-19 is largely inspired by the successful experience of SARS treatment in 2002–2003. This is because (1) SARS-CoV-2 and SARS-CoV-1 have more than 80% genetic homology, and (2) the critical targets of a spike, 3-chymotripsin-like protease (3CLpro), papain-like protease (PLpro), and RNA dependent RNA polymerase (RdRp) have 76%, 96%, 83%, and 96% sequence similarity, respectively (10). Similarly, SARS-CoV-2 virus invades into respiratory epithelial cells of host by identifying the angiotensin-converting enzyme 2 (ACE2) as the main entry point.

The key step for SARS-CoV-2 host invasion is the interaction between the virus spike glycoprotein (SGp) and host ACE2, medicated by serine protease transmembrane protease serine 2 (TMPRSS2) (10). Once the virus enters into host cells, RdRp plays a pivotal role in the replication and transcription of SARS-CoV-2. SARS-CoV-2 also encodes two proteases: 3CLpro, the viral main protease (M^{pro}), and PLpro for proteolytic processing during viral maturation. 3CLpro cleaves polyprotein pp1a and pp1ab for releasing several functional polypeptides, which establish a favorable environment for viral RNA synthesis. PLpro is required for SARS-CoV-2 replication and promotes the dysregulation of signaling cascades in the infected host cells. Nsp14, a nonstructural protein, is a functional enzyme involved in replication, fidelity, and mRNA capping (6, 11). Accordingly, the functional importance of the proteins RdRp, ACE2, SGp, 3CLpro and PLpro in the viral life cycle makes them potential targets for drug development against SARS-CoV-2 infection. On the other hand, after endocytosis, SARS-CoV-2 infection causes PAK1 (serine/threonine p21 protein–activated kinase-1) upregulation, inducing lung inflammation, pulmonary fibrosis, and other critical mortality factors. Increases in PAK1 levels also suppress the adaptive immune response, facilitating viral replication. Chemokines and activated pro-inflammatory cytokines, such as IL-6, IL-1, and TNF-α, can lead to the development of the disease with rapid respiratory impairment and pulmonary failure (12).

In short, the targets of TCM and its ingredients are focused on ACE2/TMPRSS2, 3CLpro, PLpro, SGp, RdRp, and N-terminal 3′-5′ exonuclease (Nsp14) for antivirus in addition to some key points for anti-inflammatory and immune regulation. Interestingly, each herb ingredient always has several target points that it attacks; conversely, each target can also be acted on by several different herbal ingredients. For example, rheum palmatum, glycyrrhizae radix, pogostemonis herba, and armeniacae

semen are the most often used herbs in the "three medicines and three formulas." Their active ingredients, including emodin, glycyrrhizin, quercetin, patchoulic alcohol, and kaempferol, have high affinity for binding their target PLpro, 3CL pro, ACE2, RdRp, and SGp (4, 7) (Figure 13.1).

Naringenin, a possible candidate against SARS-CoV-2 infection and the pathogenesis of COVID-19, is present in a wide variety of fruits and vegetables, especially grapefruits, tangerines, oranges, and tomatoes. Naringenin is of great interest because of its numerous beneficial activities, such as analgesic, antioxidant, hypolipidemic, hepatoprotective, elastase inhibiting, anti-inflammatory, anti-mutagenic, anti-tumor, and antimicrobial effects. Importantly, naringenin, as a natural flavonoid, is a potential inhibitor of SARS-CoV-2 infection-related proteins, such as SGp, TMPRSS2, ACE2, M^{pro}, PLpro, RdRp, and endo-lysosomal two-pore channels (TPCs), as well as anti-inflammatory and antioxidant effects (13) (Figure 13.2).

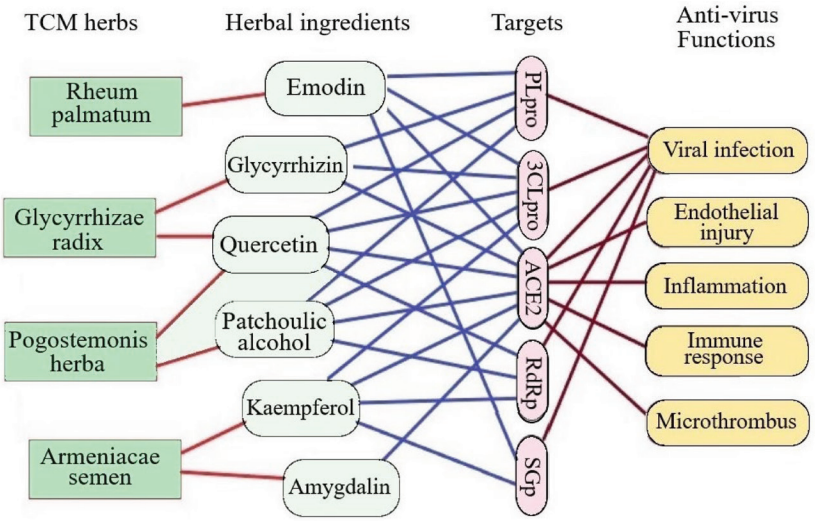

FIGURE 13.1 Network of some representative herbs and their major bioactive ingredients and functions in treating COVID-19.

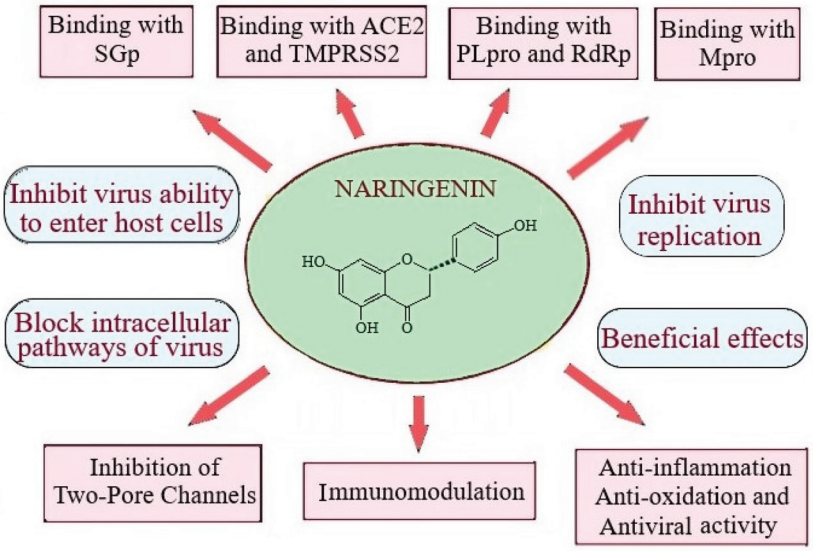

FIGURE 13.2 The possible targets and beneficial effects of naringenin against COVID-19.

Nevertheless, there is still a long way to go in the development of effective and precise drugs for the prevention and treatment of virus infections. The mechanisms of action, the characteristics of mutations of viruses, and the routes of transmission of virus infection also need to be clarified.

13.3 ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome (ARDS) is a kind of acute lung injury (ALI) with diffuse inflammation and acute respiratory failure with a series pathophysiological changes. The treatment of ALI/ARDS is still a worldwide problem. Western medicine is mostly focused on supportive treatment, which emphasizes lung-protective ventilation and fluid management. There is a lack of effective and specific pharmacotherapy being identified. Although Western medicine could improve the treatment of ALI/ARDS, there has been no substantial decrease in the fatality rate of ALI/ARDS patients. TCM, as an adjuvant therapy, is widely used in clinical practice.

13.3.1 TCM Prescriptions in Treating ALI/ARDS

In the disease list of TCM, there is no appellation of ARDS. According to TCM theory, based on the clinical characteristics of ARDS patients, such as dyspnea, shallow and rapid breathing, severe suffocation, and chest constriction, ARDS belongs to "asthma," caused by lung failure, lung Qi (气, vital energy) inversion, or Qi exchange disorder in lung and kidney (14). TCM has good potential not only in preventing and treating ARDS, but also in reducing the dosages of Western medicines and subsequently limiting adverse drug reactions.

A review article (14) analyzed 16 studies and found eight formulas were often used. They are Da Chengqi decoction (大承气汤), modified Xuanbai Chengqi decoction (宣白承气汤), Ephedra aconite asarum decoction (麻黄附子细辛汤), Qingfei decoction (清肺汤), Baihu Chengqi decoction (白虎承气汤), Tingli Dazao Xiefei decoction (葶苈大枣泻肺汤), Xiao Qinglong decoction (小青龙汤), and Fusu mixture (复苏合剂). These formulas could reduce the mortality rate of patients, improve the effective rate of clinical treatment, reduce the average mechanical ventilation time, increase the levels of PaO_2, PaO_2/FiO_2, and reduce the level of inflammatory factors. Besides the conventional therapy, Chinese medicine injection (CMI) is also wildly used in ALI/ARDS treatment, such as Tanreqing (痰热清) injection, Shengmai (生脉) injection, Shenfu (参附) injection, Danshen (Salviae miltiorrhizae radix) injection, Reduning (热毒宁) injection, and Xuebijing (血必净) injection. However, the curative effect is controversial, and current evidence cannot be determined (15).

13.3.2 The Pharmacological Functions of TCM in Treating ALI/ARDS

Dysregulated inflammation, coagulation, and oxidative stress all play central roles in ARDS pathology. Many researchers have focused their attention on the role of TCM in modulating inflammatory imbalances, abnormal coagulation, antioxidation processes, and immunomodulation in ALI/ARDS, as well as the molecular mechanisms behind its effects.

13.3.2.1 Signaling Pathways and Receptors Related to ALI/ARDS

Accumulating evidence indicated that many signaling pathways are related to alveolar injury and repair of ALI/ARDS, including NF-κB, JAK/STAT, MAPK, mTOR, Notch, TLR4, HMGB1/RAGE, and macrophage activation (16–18). Under the condition of ALI/ARDS, the injured alveolar epithelial cells, injured pulmonary capillary endothelial cells, and activated and infiltrated immune cells all release various cytokines. The constantly activated inflammatory cells can form a vicious cycle, ultimately resulting in a cytokine storm. These activated intracellular signaling pathways play vital roles in this process. Among these, NF-κB signaling, as a prototypical proinflammatory signaling pathway, plays an important role in promoting inflammatory and oxidative storms as marked by promoting the expression of cytokines IL-1, IL-2, IL-6, and TNF-α, chemokines IL-8 and MIP-1α, adhesion molecules, and COX-2. Moreover, NF-κB, as a redox-sensitive transcription

factor, is an important rendezvous with a broad spectrum of inflammatory signaling pathways to weave a complicated network.

Macrophages in lung tissue play a critical role in the inflammatory response to ALI/ARDS. In response to stimulation by foreign pathogens, the alveolar macrophages can be activated to form M1 macrophages by polarization, which subsequently release various inflammatory cytokines and chemokines to initiate a cascade of amplified inflammatory responses and mediate lung tissue injury. STAT3, NF-κB, MAPK, mTOR, and Notch can enhance the action of M1 macrophages (19, 20). The imbalance of Treg/Th17 in ALI/ARDS can increase the production of IL-2, IL-6, IL-10, IL-17, and TGF-β1. Inhibition of STAT3 activation can restore the balance (19, 21). In addition, alveolar macrophage pyroptosis may be involved in NLRP3 inflammasome participation and the development of ALI; p38-MAPK and TLR4/MyD88 may promote lung inflammation through formation of NLRP3 inflammasome and alveolar macrophage pyroptosis. Moreover, during the pyroptosis process, high-mobility group box 1 (HMGB1) is released into extracellular matrix to aggravate the inflammation of ALI (22). Nrf2/HO-1 pathway can activate the expression of HO-1, which in turn both inhibits proinflammatory cytokines activity and activates the activity of IL-10. PI3K/Akt signaling can inhibit NF-κB related inflammatory signals and exert anti-inflammatory and antioxidative stress properties. The Notch signaling pathway can also promote dendritic cells to produce IL-10 for inhibition of ALI/ARDS (17). In addition, upregulation of HO-1 by activation of PPARγ could inhibit the HMGB1-receptor of the advanced glycation end product (RAGE) signaling pathway and ameliorate the development of ALI/ARDS (23). The signaling pathways involved in ALI/ARDS are briefly illustrated in Figure 13.3.

13.3.2.2 The Molecular Mechanisms of Some Representative Formulas and Ingredients

Xuanbai Chengqi decoction (XBCQ), as a representative TCM prescription in "Systematized Identification of 'Warm Diseases,'" written by Wu Jutong in the Qing Dynasty, has been widely used to treat a variety of common respiratory diseases in China. XBCQ contains only four constituents, mineral-based gypsum fibrosum and the herbs rheum palmatum, armeniacae semen, and pericarpium trichosanthis. In the LPS-induced ALI of rats, XBCQ inhibits the PI3K/AKT/mTOR/HIF-1α/VEGF signaling pathway to decrease TNF-α, IL-6, and IL-1β production, resulting in reducing the injuries of ALI, such as exaggerated inflammatory response and pulmonary edema (24).

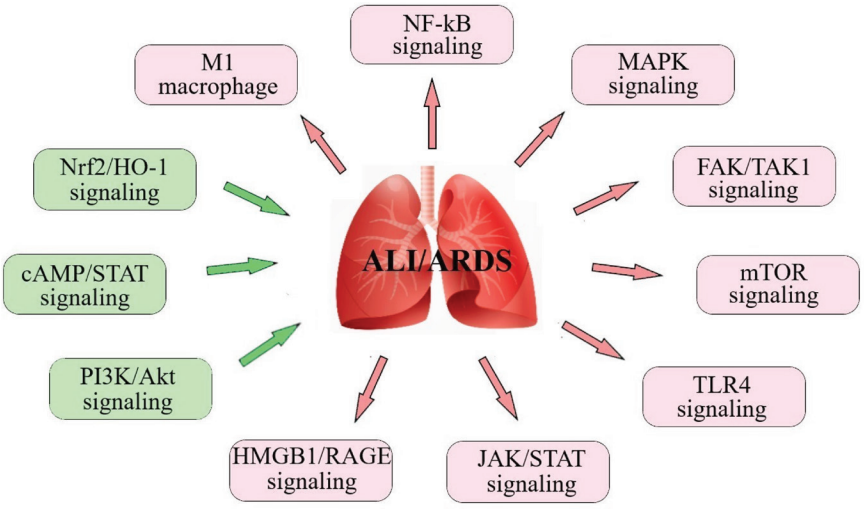

FIGURE 13.3 ALI/ARDS-related signaling pathways.

Qingfei Litan decoction (QFLT, 清肺理痰汤), included in the *Wind-Heat in Lung Syndrome TCM Diagnosis and Treatment Plan* by the TCM State Administration, has been effectively used to clinically treat ALI/ARDS for years. The combination of QFLT and Western medicine is more effective in the treatment of pneumonia cough than Western medicine alone (25). QFLT consists of gypsum fibrosum and nine herbs: herba nervilia plicatae, pericarpium trichosanthis, scutellariae baicalensis, fritillaria thunbergii, houttuynia cordata, phragmites rhizoma, armeniacae semen, platycodonis radix, and glycyrrhizae radix. Acacetin, baicalein, luteolin, liquiritigenin, wogonin, and isorhamnetin may be the important anti-inflammatory and antioxidative ingredients of QFLT against ALI/ARDS. Acacetin (25, 26), from platycodonis radix, decreases iNOS and COX-2 expression and increases HO-1 expression and SODs activity. Luteolin (27, 28), also from platycodonis radix, inhibits NF-κB activity and production of ROS, elevates the cellular GSH level, and activates the Akt/Nrf2 pathway. Baicalein (25, 27, 29), from scutellariae baicalensis, inhibits the NF-κB, MAPK, and JAK/STAT3 signaling pathways. Liquiritigenin (25, 30) from glycyrrhizae radix inhibits NF-κB activity in macrophages and decreases the production of iNOS and proinflammatory cytokines. Wogonin (5, 25, 27), from scutellariae baicalensis, armeniacae semen, platycodonis radix, and glycyrrhizae radix, can suppress IL-10 production in B cells via inhibiting the STAT3 and ERK signaling pathway. Isorhamnetin (25), from glycyrrhizae radix, blocks the MAPK and NF-κB signaling pathway, inhibiting the release of inflammatory mediators (TNF-α, IL-1β, IL-6, iNOS, and COX2) and MDA, as well as increasing SOD levels in LPS-induced ALI mice. Thus QLFT implements its therapeutic effects on ALI/ARDS mainly by anti-inflammation and antioxidation via downregulation of TLR4/NF-κB signaling pathway and upregulation of Nrf2 signaling pathway (Figure 13.4).

13.4 ASTHMA

Asthma is an allergic heterogeneous disease with a chronic airway inflammatory response in which eosinophils, mast cells, T cells, and an array of cytokines are involved. Controlling airway inflammation has become the consensus of scientists for asthma treatment. The recent treatment of asthma in clinic is mainly based on asthma calming, anti-inflammation, and bronchodilatation by using glucocorticoids, leukotriene receptor antagonists, and β2-agonists, which can only temporarily control symptoms but cannot effectively control disease recurrence. In addition, long-term use of these drugs may have certain side effects. It is estimated that up to 30% of adults and 60% of children in the United States are using complementary and alternative medicine (CAM) for asthma management (31). Due to the special theory of TCM and thousands of years of clinical practice history, the main pathogenesis of asthma is an accumulation of phlegm in lungs, classified as Tan Re Yong Fei

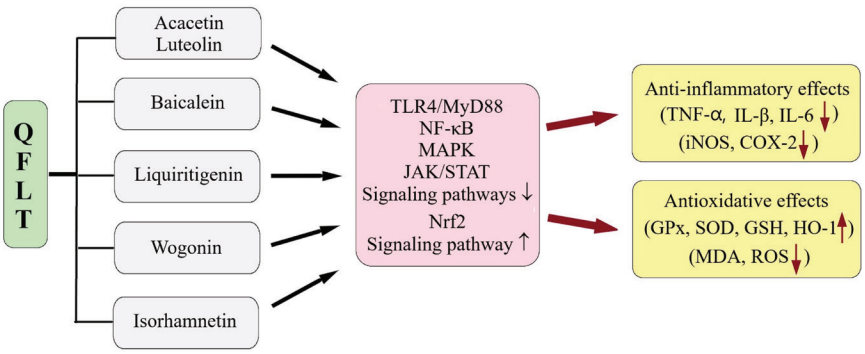

FIGURE 13.4 The proposal signaling pathways of anti-inflammatory and antioxidative mechanisms of treatment with QFLT against ALI/ARDS.

(痰热壅肺, phlegm-heat blocking the lungs) syndrome, combined with external influences, diet, emotions, and fatigue (32). TCM offers the principle of Yin (阴) rehydration and Gu Yang Qu Feng (固阳祛风, strengthening the lungs and dispelling wind), which can strengthen immune function and assist asthma patients in their recovery from the condition (33). In addition, the TCM prescriptions can also be flexibly formulated according to the patients' physical condition to achieve personalized drug use with little toxicity and side effects. Therefore, Chinese herbal medicine becomes widely used as CAM for add-on treatment of bronchial asthma.

13.4.1 The Commonly Used TCM Formulas and Active Ingredients Involved

There are variety of commonly used TCM formulas for effectively treatment of bronchial asthma including Ma Xing Shi Gan decoction, Xiaoqinglong decoction, Shegan Mahuang (射干麻黄, belamcandae rhizoma-ephedrae herba) decoction, Xiao Chaihu decoction (小柴胡汤), Suzi Jiangqi decoction (苏子降气汤), Zhichuan (治喘) formula, Liujunzi (六君子) decoction, San Ao (三拗) decoction, Fuling Xingren Gancao (茯苓杏仁甘草, poria-armeniacae semen-glycyrrhizae radix) decoction, Shaoyao Gancao (芍药甘草, paeonia lactiflora-glycyrrhizae radix) decoction, San Zi Yang Qin (三子养亲) decoction, Ban Xia Hou Po (半夏厚朴, pinellia ternata-magnoliae officinalis) decoction, Gui Zhi Jia Hou Po Xing Ren (桂枝加厚朴杏仁, cinnamomi ramulus plus magnoliae officinalis-armeniacae semen) decoction, Ling Gui Shu Gan (苓桂术甘, poria-cinnamomi ramulus-atractylodis macrocephalae-glycyrrhizae radix) decoction, Bu-Shen-Yi-Qi (补肾益气) formula, fructus schisandrae (五味子) syrup, Fang-xiao (防哮) formula, Jin Gui Shen Qi (金匮肾气) pill, Mahuang (麻黄, ephedrae herba) decoction, Pheretimaas pergillum (地龙) decoction, Soufeng Yuchuan (搜风愈喘) decoction, Wu-Hu (五虎) decoction, and Yu-Ping-Feng (玉屏风) powder (32–34).

A review article (34) rigorously screened 128 studies and identified the 26 most commonly used herbs in TCM prescriptions primarily for asthma treatment. They are glycyrrhiza uralensis, armeniacae semen, pinellia ternata, asarum sieboldii, pheretima aspergillum, aster tataricus, fritillaria cirrhosa, lepidii semen, pericarpium citri reticulatae, cortex mori, ephedrae herba, zingiberis rhizoma recens, tussilago farfara, platycodonis radix, fritillaria thunbergii, paeonia lactiflflora, magnolia officinalis, bupleurum chinense scutellaria baicalensis, anemarrhena rhizoma, gypsum fibrosum, eriobotryae folium, cinnamomi ramulus, zingiberis rhizoma, schisandra fructus, and perillae fructus. Another review article added atractylodes macrocephala, astragalus membranaceus, and codonopsis pilosula in Yi Fei Ping Chuan (益肺平喘) decoction (33).

13.4.2 The Mechanisms of Action of Active Ingredients in Asthma Treatment

Based on the known main mechanisms of action of β2 adrenoceptor agonists and corticosteroids in Western medicine for the treatment of asthma, the associated Chinese medical herbs were simply divided into β-adrenergic agonist, steroid-like, anticholinergics, phosphodiesterase (PDE) antagonist, leukotriene antagonist, and herbs with monoclonal effects or those affecting signaling pathways (34). For example, pericarpium citri reticulatae, ephedrae herba, tussilago farfara, and scutellaria baicalensis have β-adrenergic agonist effect; magnolia officinalis has steroidal effects; glycyrrhiza uralensis has both β-adrenergic and steroidal effects; fritillaria thunbergii has PDE inhibitor effect; cortex mori has anticholinergic effects; pheretima aspergillum has leukotriene antagonist like effect; lepidii semen, perillae fructus, and eriobotryae folium can regulate T helper cells; anemarrhena rhizoma, platycodonis radix, and paeonia lactiflora have multiple monoclonal effects for asthma.

The pathophysiology of asthma is extremely complicated, and the mechanisms of action of herbs may go far beyond the above-mentioned mechanisms. In general, TCM mainly covers four aspects of pathophysiological changes in asthma, including abnormal immune regulation and autoimmunity, abnormal effect of airway smooth muscle, abnormal effect of mucus, and airway remodeling. As we know, when the respiratory tract is exposed to allergens, the inhaled allergens are endocytosed

and then presented to CD4+ T cells by dendritic cells. The allergens can also attack epithelial cells to produce cytokines (IL-33, TSLP), which facilitate dendritic cells to promote the polarization of CD4+ T cell to Th2 cells, making the Th1/Th2 balance shift to Th2 phenotype for triggering lots of harmful responses. Th2 releases many inflammatory cytokines and adhesion molecules, such as IL-4, IL-5, IL-13, GM-CSF, as well as TNF-α, TGF-β1, and VCAM-1 or ICAM-1 (35). Relying on these cytokines, Th2 attacks mast cells, eosinophils, plasma cells, B cells, epithelial cells, epithelial goblet cells, and smooth muscle cells, causing airway eosinophilia, goblet cell and epithelial cell hyperplasia, and airway hyperresponsiveness (AHR). The activated plasma cells can produce IgE that acts on basophils and mast cells to further increase the production of cytokines from the two types of cells. The stimulated basophils attack smooth muscle cells making them hypertrophy/hyperplasia. The basophils also stimulate B cells. The activated B cells can also produce IgE and are required for eosinophilic access to the lung tissue to increase vascular permeability and chemotaxis. The activated mast cells then activate innate lymphoid cells (ILC2s) and eosinophils by releasing PDG2 and IL-5, respectively. The activated ILC2s, in turn, express GATA3, ROR-α, and epithelial cytokine receptors, releasing cytokines to act on eosinophils, epithelial cells, goblet cells, mast cells, and airway smooth muscle. The ILC2s also increase the production of IgE by activating the plasma cells. The activated and recruited eosinophils can further stimulate plasma cells and dendritic cells. The epithelial cells that endocytosed the allergens also produce numerous cytokines to attack several inflammation related cells, such as Th2, eosinophils, mast cells, and ILC2s, as well as dendritic cells (31, 36).

Another lymphocyte is Th17, which can result in inflammation and autoimmune tissue damage by production of the cytokines TNF-α, IL-6, and IL-17. IL-17 can induce the recruitment of polymorphonuclear neutrophils. Although regulatory T (Treg) cell is an inflammatory suppressor, it can downregulate the production of proinflammatory cytokines and chemokines in many proinflammatory cells by secreting IL-10, an immunosuppressive factor. In addition, Treg also expresses FOXP3, a significant transcription factor playing an important role in differentiation and development. The imbalance of Treg/Th17 cells is connected to the severity of asthma (31, 35). Besides the inflammatory cells, some structural cells such as airway smooth muscle cells, epithelial cells, and fibroblasts may be involved in exacerbating asthmatic progression via increasing inflammation and airway remodeling. The release of cytokines, chemokines, and extracellular matrix (ECM) proteins, including TGF-β, IL-13, and VEGF have important roles (31). The MMP-9, MMP-12, or Rho-kinase (ROCK) proteins also contribute to the remodeling process by degrading the components of ECM (37). The intricate network of relationships between the inflammatory cells and related cytokines associated with asthma is shown in Figure 13.5.

The activation of inflammatory cells and the production of cytokines and chemokines rely on the related signaling pathways. Therefore, the active ingredients of herbs exert their anti-inflammatory, antioxidant, and other biological effects by modulating these molecular targets and related signaling pathways, which include activation of allergen-inhibited CD4+Th1 cell differentiation, inhibition of Th2 cell–related signaling pathways such as PI3K, reduction of IgE levels, improvement of the balance of IL4/INFγ, and action on the signaling pathway toll-like receptors (TLRs) of dendritic cells and the Rho-ROCK, JAK-STAT, MAPK, Wnt, VEGF, TGF-β, and Nrf-2 pathways (33, 34, 36). In addition, as multiple signal pathways in inflammation converge on the NF-κB pathway, various strategies that target NF-κB signaling have been considered for asthma treatment (33, 38). Indeed, the therapeutic efficacy of glucocorticoids is largely contributed by inhibiting NF-κB (39). The effects and possible molecular mechanisms of some TCM ingredients for treating asthma have been studied in depth; these will certainly provide more scientific basis for development of new drugs and effective treatment of asthma.

Currently, many ingredients from Chinese herbal medicines have been confirmed to be effective against asthma, including icarlin, apigenin, baicalein, vitexin, catechin, gallocatechin, hesperidin, naringin, naringenin, kaempferol, quercetin, rutin, apigenidin, cyanidin, schizandrin, glycyrrhizin, emodin, mangiferin, curcumin, cordycepin, erysotrine, matrine, mitraphylline, piperlongumine

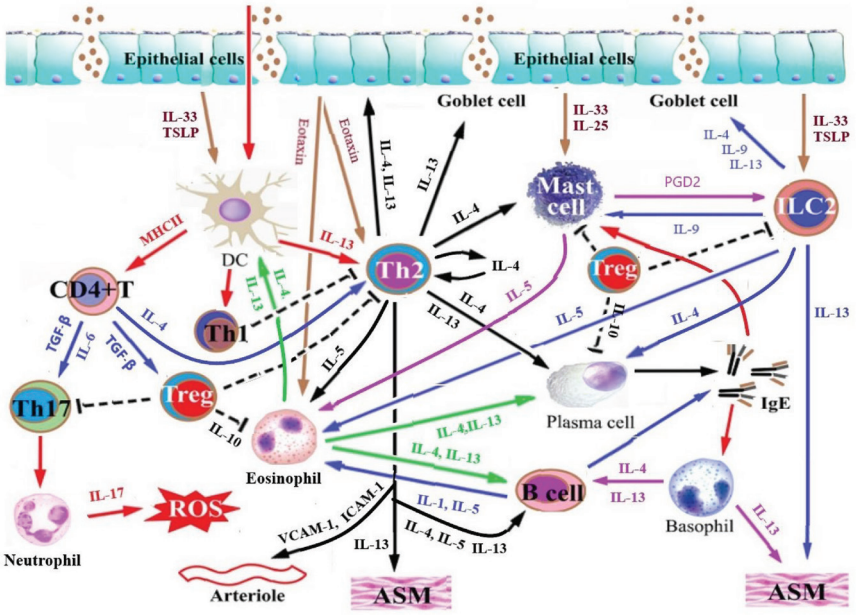

FIGURE 13.5 The role of different cells and produced cytokines, and the effect of herbal ingredients in asthma.

resveratrol, saikosaponin A and B, ginsenoside Rg, baicalin, chitin, chrysin, scholaricine, camphor, gallic acid, wedelolactone, ephedrine, ellagic acid, coumarin, luteolin, oroxylin A, galangin, frankincense, boswellic acids and so on. Most of them are categorized as flavonoids (31, 40, 41).

13.4.3 Examples of the Mechanisms of Action of Herbal Ingredients against Asthma

Quercetin, widely distributed in fruits and vegetables, is one of the main flavonoids in the human diet, and the daily requirement is 5–40 mg. Quercetin has multiple functions in treating asthma. In vitro studies with human airway epithelial cells, quercetin could inhibit neutrophil elastase induced mucin 5AC (MUC5AC) expression to decrease the hypersecretion of mucus. In studies using animal models, the anti-asthma activity of quercetin was similar to that of cromolyn sodium and dexamethasone, as it suppresses GATA-3 gene expression and increases T-box protein expression in T cells (T-bet), altering Th1/Th2 differentiation and decreasing allergic airway inflammation and AHR. Quercetin decreases IL-4, IL-5, IL-25, IL-33, IgE, thymic stromal lymphopoietin (TSLP), caspase-3, and terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL). Conversely, quercetin increases IFN-γ. The signaling pathways of quercetin action include attenuating the PI3K/Akt/NF-κB and the PKC/EGFR/ERK signaling pathways. Quercetin also lowers epithelial and subepithelial smooth muscle thickness, inhibits eosinophil growth, and decreases goblet and mast cell numbers and activation (36). The target points of quercetin action are summarized in Figure 13.6.

Curcumin is a core ingredient of rhizoma curcumae longae, often used to treat a variety of diseases, especially chronic inflammation, such as asthma. Curcumin can block NF-κB, p38 MAPK, ERK 42/44, and JNK54/56 related signaling pathways, and the PPARγ-dependent NF-κB signaling pathway, thereby reducing AHR, airway infiltration of inflammatory cells, and production of inflammatory cytokines, as well as phospholipase A2 (PLA2), PGD2, and COX2 levels. Moreover, curcumin inhibits upregulation of MCP-1 and MUC5AC, and mucus hypersecretion. Curcumin can also activate Nrf2/HO-1 signaling, reduces TNF-α, IL-1β, IL-6, eosinophils, and exerts antioxidative effects (42).

Curcumin improves the imbalance of Treg/Th17 for activating Treg cells (43). The inhibitory effect of curcumin on iNOS and NO can suppress IL-2, IL-5, GM-CSF, and IL-4 production,

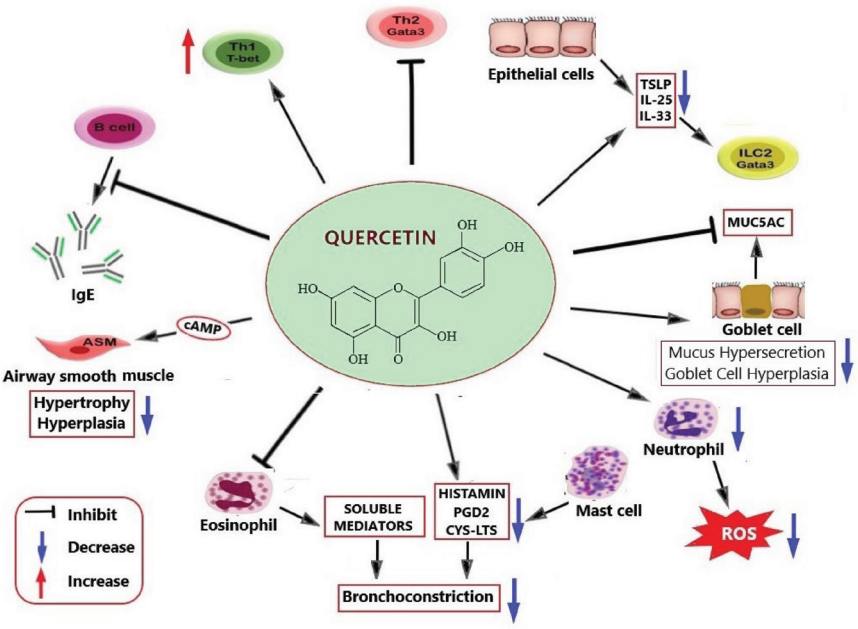

FIGURE 13.6 The possible mechanisms of quercetin in asthma.

lymphocyte proliferation, eosinophil recruitment and Th2 cell differentiation. Curcumin can also downregulate the Notch signaling pathway-associated T cell activation and proliferation. Curcumin suppresses proliferation of airway smooth muscular cells by inhibiting ERK signaling. Curcumin also reduces the activity of MMP-9 and expression of α-SMA and eotaxin for alleviating pulmonary fibrosis. Curcumin activates Wnt/β-catenin signaling pathway (possibly in dendritic cells) to reduce lung inflammation, and increase IFNγ (44, 45).

Curcumin prevents and protects from structural alterations and airway remodeling by modulating TLR-4/MAPK signaling pathway (46, 47). Curcumin also ameliorates TLR4/NF-κB/NLRP3 inflammasome signaling and pyroptosis (48). Curcumin is a histone deacetylase 1(HDAC1) inhibitor for inhibiting NF-κB expression (49).

In conclusion, the pharmacological effect of curcumin in preventing and treating asthma is achieved through its anti-inflammatory, antioxidation, and relief of trachea remodeling functions. The possible mechanisms of curcumin action is summarized in Figure 13.7.

Resveratrol possesses many means to inhibit asthma, including inhibition of inflammatory cells and production of inflammatory cytokines, AHR, oxidative stress, mucus hypersecretion, and airway remodeling. Resveratrol inhibits the proliferation and activation of Th2, Th17, mast cells and eosinophils, and inhibits DNA damage and apoptosis of bronchial epithelial cells. Resveratrol alleviates oxidative stress and repairs the mitochondrial function of lung tissue by modulating several signaling pathways, including activation of AMPK expression and inhibition of expression of iNOS, TNF-α and p47phox; reduction of ROS production; and promotion of the Nrf2 pathway to increase the production of catalase, GSH, GPx, and SOD (31, 49). Resveratrol has potential anti-inflammatory and anti-airway remodeling effects by downregulating AMPK, PI3K/Akt, TGF-β1/Smad, and HMGB1/TLR4/NF-κB signaling pathways. Resveratrol also activates SIRT1 for upregulating PTEN to inhibit PIP3 pathways. Resveratrol upregulates the expression of FOXP3a through downregulating miR34a expression. The enhanced FOXP3a subsequently upregulates ROS scavenging enzyme SOD2 and catalase expressions, and as a master regulator promotes Treg development and functions (31, 35, 50). Resveratrol inhibits proliferation of eosinophils, arrest cell cycle progression in G1/S phase by increasing p53 and p21, and concurrently reducing the expression of cyclin-dependent kinase 2 (CDK2), cyclin A and

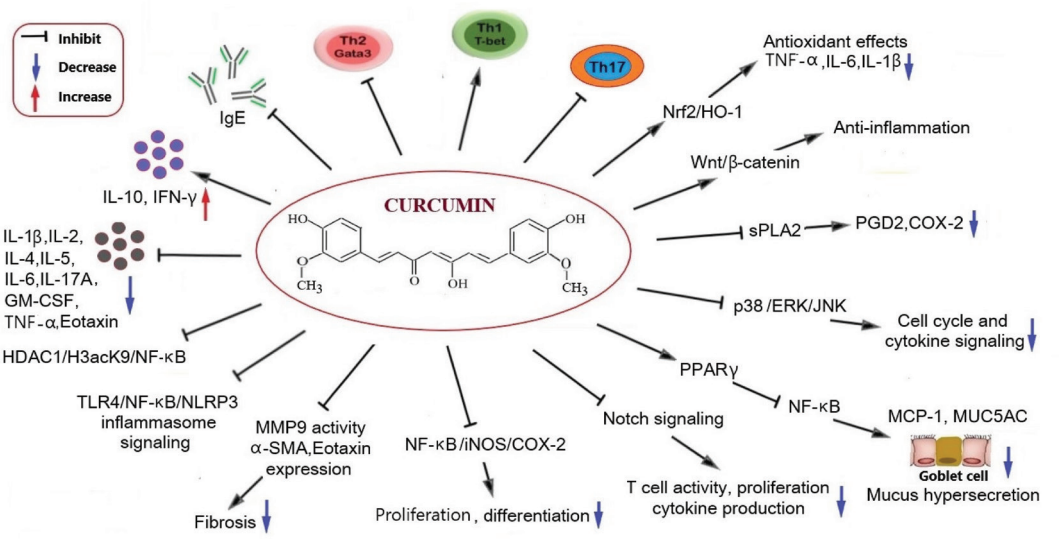

FIGURE 13.7 The possible mechanism of action of curcumin for treating asthma.

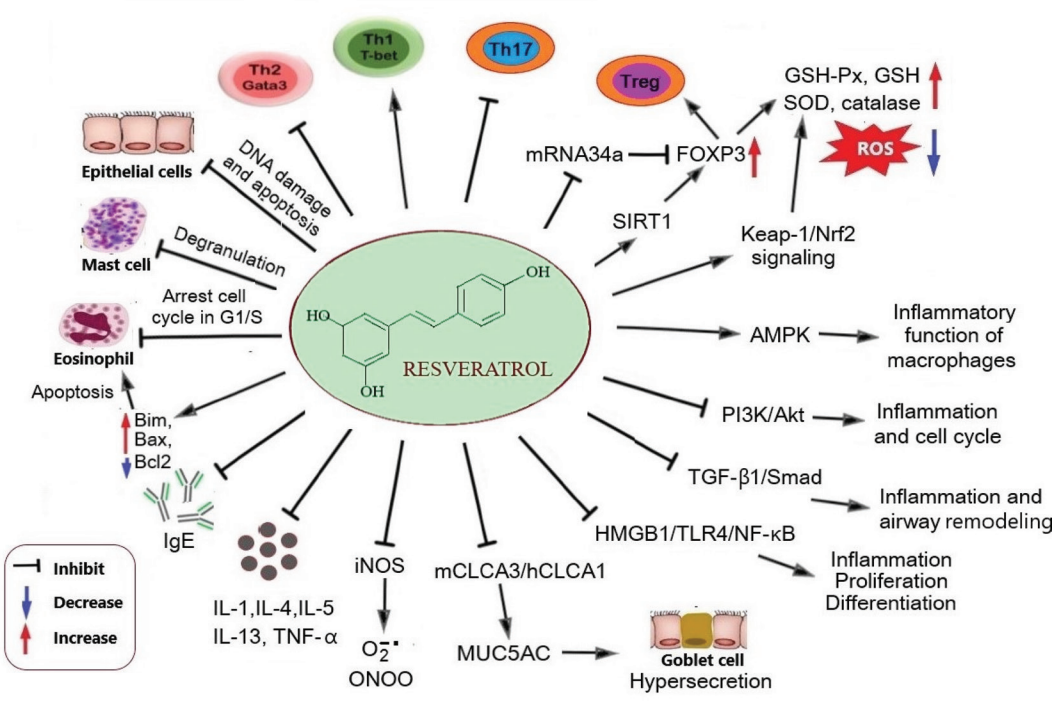

FIGURE 13.8 The possible mechanism of action of resveratrol in asthma.

cyclin E. In addition, resveratrol induces eosinophil apoptosis via upregulating Bim and Bax expressions, and downregulating Bcl-2 expression (31, 51). Resveratrol suppresses calcium-activated chloride channel (CLCA)1 signaling pathway to prevent mucus overproduction by inhibiting overexpression of MUC5AC (31, 52). Resveratrol can also reduce the expression of TGF-β1/Smad2/3 pathway in airway epithelial cells to inhibit pulmonary fibrosis (31, 53). The possible mechanisms of action of resveratrol in asthma are illustrated in Figure 13.8.

13.5 CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is a progressive airflow restrictive and not completely reversible disease that is a leading global cause of morbidity and mortality. Exposure to gases from cigarette smoking and inhaled particles such as $PM_{2.5}$ are two archetypical inducing factors for causing COPD. The pathogenesis of COPD is characterized by inexorable deterioration of small airways obstruction with chronic inflammation, oxidative stress, cellular senescence, corticosteroid resistance, cell apoptosis, and airway remodeling. The changes in pulmonary histology and functions include inflammatory cell infiltration, epithelial-mesenchymal transition (EMT), ECM deposition, and smooth muscle cell (SMC) proliferation. The COPD may be the underlying cause of emphysema and fibrosis (54). These pathological changes make the airway wall thick with fixed obstruction, persistent airflow limitation, irreversible loss of lung function, and thus poor disease prognosis. The acute exacerbation caused by COPD is often associated with respiratory failure and a high mortality rate.

In Western medicine, the treatments for COPD include infection control, airway relief, and water, electrolyte, and acid-base imbalance corrections, as well as oxygenation improvement and respiratory failure combat. Although long-term oxygen supply, corticosteroid inhalation, and bronchial pipette can effectively reduce hypoxemia and airway obstruction to some extent, respiratory muscle fatigue, poor nighttime respiratory center response, and carbon dioxide retention may contribute to further disease progression for patients with respiratory failure.

According to TCM theory, the vital Qi refers to the body's ability to self-regulate, its resistance to pathogens, and self-recovery. Lungs are in charge of the vital Qi and respiratory function, whereas the kidney governs reception of Qi. COPD belongs to the category of "syndrome characterized by dyspnea" and "lung distention," and is characterized by the deficiency of vital Qi in lung, spleen, and kidney. The Chinese herbal medicines in treating COPD have the Qi-tonifying character involved in improving the defense capacity of immune system and enhancement of ATP generation capacity. Many studies have confirmed that the nourishment of the lung and kidney has dramatic and long-term effects on boosting the weak immune system, decreasing inflammatory responses, reducing pulmonary pathological impairment and airway remodeling (55).

13.5.1 The Recommended TCM Prescriptions and Frequently Used Herbs Involved

The *International Clinical Practice Guideline of Chinese Medicine Chronic Obstructive Pulmonary Disease* compiled by the World Federation of Chinese Medicine Societies recommends corresponding TCM according to the different types of COPD and the different development periods of the disease (56). In the cases with acute exacerbation of COPD, modified San ao decoction plus Shike (止嗽, relieve a cough) powder, Tongxuan Lifei (通宣理肺) pill and Xing Su Zhike (杏苏止咳, armeniacae semen-perilla frutescens in relieving cough) granule, modified Qingqi Huatan (清气化痰) pill plus Beimu Gualou (贝母瓜蒌, fritillaria thunbergii-fructus trichosanthis) powder, Xiaoqinglong decoction or granule, Tanreqing (痰热清) injection, Ting Bei (葶贝, lepidium apetalum-fritillaria cirrhosa) capsule, Xuebijing (血必净) injection, modified Banxia Houpu (半夏厚朴, pinellia ternata-magnoliae officinalis) decoction plus Sanzi Yangqin (三子养亲) decoction, Suzi Jiangqi (苏子降气) pill, Ling Gui Kechuanning (苓桂咳喘宁) capsule, modified Ditan (涤痰) decoction, Xinnaojing (醒脑静) injection, and Qingkailing (清开灵) injection are recommended for selecting use based on the specific symptoms. In the stable COPD cases, modified Renshen Hutao (人参胡桃, panax ginseng-semen juglandis) decoction plus Renshen Yangfei (人参养肺) pill, Yupingfeng (玉屏风) granule, modified Liujunzi (六君子) decoction plus Huangqi Buzhong (黄芪补中) decoction, modified Bufei Yishen (补肺益肾) formula, Bufei Huoxue (补肺活血) capsules, modified Baoyuan (保元) decoction plus Renshen Bufei (人参补肺) decoction, or Yiqi Zishen (益气滋肾) formula, and Bufei (补肺) Granules, Shengmaiyin (生脉饮) oral liquid, Yangyin Qingfei (养阴清肺) pill, Baihe Gujin (百合固金) pill, and GeJie Dingchuan (蛤蚧定喘) pill are recommended to be selected based on the individual symptoms. In addition, other techniques of treatment for COPD, such as Taiji box, acupuncture, breathing guidance,

acupoint application (such as Shufei [舒肺] plaster, Xiaochuan [消喘] plaster, etc.), and Yifei (益肺) moxibustion are also effective in relieving clinical symptoms, improving exercise tolerance, delaying the decline of lung function, and improving the quality of life of COPD patients.

The 33 Chinese patented medicines and formulas contain a total of 150 herbs. Among those, the frequency of application of eight herbs is more than ten times, including pericarpium citri reticulatae, glycyrrhizae radix, armeniacae semen, poria, perilla frutescens, pinellia ternata, scutellaria baicalensis, and atractylodis macrocephalae. Fifteen herbs and gypsum fibrosum are used five to nine times: magnoliae officinalis, ophiopogon japonicus, ephedrae herba, platycodonis radix, pheretima aspergillum, astragari radix, fritillaria cirrhosa, fritillaria thunbergii, paeoniae radix rubra, panax ginseng C.A.Mey., schisandra fructus, gardenia jasminoides, coconopsis radix, aster tataricus, and angelica sinensis.

13.5.2 The Bioactive Ingredients of TCM and Their Mechanisms of Action

Based on the theories of TCM related to lung diseases, several review articles searched electronic databases and tried to determine the active ingredients of these commonly used herbs in clinical application for treating COPD. They found the following compounds to have high-frequency in application: are andrographolide, artemisinin, cimigenoside, astragaloside, astragaloside, crocin, celastrol. apigenin, hesperidin, kaempferol, naringenin, quercetin, naringenin, baicalin, curcumin, resveratrol, epigallocatechin, gallatic acid, procyanidins, acetylshikonin chrysophanol, tanshinone IIA sulfonate, salidroside, stemonine, matrine, tussilagone, epigallocatechin-3-gallate (EGCG), amygdalin, ursolic acid, liquiritin, and resveratrol (38, 57).

Because chronic inflammation and oxidative stress are the two crucial controlling mechanisms of COPD pathogenesis and disease progression, many studies have focused on the role of TCM in the two aspects of mechanisms. The mechanisms of action of some major herbal ingredients for treatment of COPD are illustrated in Figure 13.9. The involved signaling pathways include NF-κB

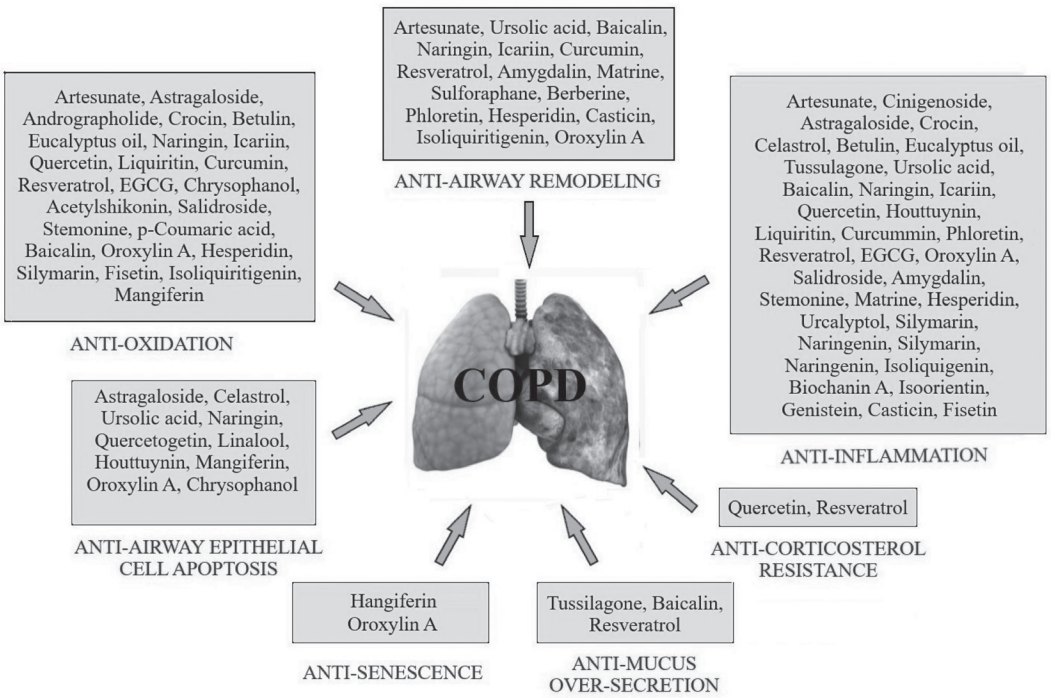

FIGURE 13.9 The diverse mechanisms of herbal ingredients targeting COPD.

(58), TLR4/MyD88/NF-κB, MAPKs (ERK, p38) (17, 46, 58, 59, 60), JNK/p38 (61), JAK3/STAT3/NF-κB (59), TGF-β1/Smad2/3 (62), AMPK/Nrf2 (58, 63), Nrf2/HO-1 (17, 58, 64), AMPK/PGC-1α (60, 65), PI3K/Akt (66), PPARγ/NF-κB (67), glucocorticoid receptor (60), and several miRs (61).

Baicalin (Figure 13.10) is an important active ingredient in dried roots of scutellaria baicalensis. In the cigarette smoke (CS)-induced COPD rat model, the baicalin can significantly improve lung function by anti-inflammatory, antioxidant, anti–airway remodeling as evidenced by reduction of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, and inflammatory cell infiltration, as well as an increase in IL-10 level, reduction of MDA, and increase in SOD and HO-1 levels. Baicalin improves the lung function also by reducing MUC5AC expression. In addition, baicalin also reduces MMP-2, MMP-9, and VEGF levels, suggesting the function of inhibiting airway remodeling. Baicalin can upregulate the expression of HSP72, resulting in inhibition of JNK signaling activation. Baicalin possesses the function of elevating cell viability by inhibiting apoptosis (57, 68). A literature reported that baicalin could improve hypothalamic-pituitary-adrenal axis (HPA axis) by increasing ACTH, cortisol, and leptin levels (69). Another research group indicated that the amelioration of baicalin on CS-induced airway inflammation in rats was partially attributed to the modulation of histone deacetylase 2 (HDAC2)/NF-κB/plasminogen activator inhibitor type-1 (PAI-1) signaling pathway though enhanced HDAC2 protein expression and inhibited the expression of NF-κB and its downstream target PAI-1 (70).

Liquiritin (Figure 13.11), mainly from glycyrrhizae radix, alleviates pulmonary inflammation by targeting TGF-β signaling pathway (38). Liquiritin also possesses antioxidant effect, increases SOD level, and decreases the MDA level and goblet cell hyperplasia to protect from the CS-induced lung injury (60, 71). Liquiritin activates the β2-adrenoceptor and effectively relaxes tracheal smooth

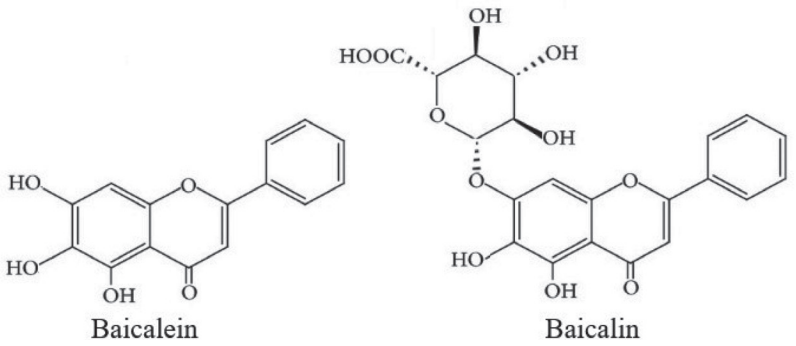

FIGURE 13.10 The structure of baicalein and baicalin.

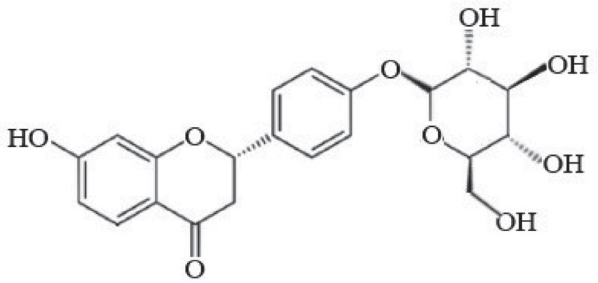

FIGURE 13.11 The structure of liquiritin.

muscle (72). Liquiritin can inhibit the abnormal upregulation of phosphorylation of nuclear receptor 4A1(Nur77), as well as the increased levels of inflammatory factors TNF-α and IL-6. Liquiritin also alleviates the secretion of eosinophil chemokine-1. As we know, the transient receptor potential cation channel subfamily V member 1 (TRPV1) and TRPA1 are expressed in subpopulations of sensory neurons and in non-nerve tissues throughout the bronchioles and alveoli. Activation of TRPV1 and TRPA1 can cause cough, bronchoconstriction, microvascular leakage, hyperresponsiveness, and excessive secretion, as well as epithelial cell death in the respiratory tract. Liquiritin inhibits TRPV1 and TRPA1 to reduce inflammatory response including decrease in expression of TGF-β, TNF-α, IL-6 IL-1β, IgE, and the counts of inflammatory cells (72, 73).

In addition, amygdalin, from armeniacae semen, ameliorates EMT via the TGF-β/Smad pathway (74). Tussilagone and EGCG from *Tussilago farfara* L., *Eriobotrya japonica* Lindl., and *Morus alba* L. can enhance anti-proliferation activity by inhibiting the NF-κB signaling pathway (38).

13.5.3 Examples of TCM Prescriptions for Treatment of COPD Studied in Depth

13.5.3.1 Bufei Yishen Formula

Bufei Yishen formula (BYF, 补肺益肾方, invigorating the lung and the kidney) is a traditional Chinese herbal formula widely used in COPD treatment. It has been confirmed that BYF can improve lung function, alleviate airway inflammation, oxidative stress, and airway remodeling. BYF is efficacious in the treatment of COPD by relieving symptoms, reducing the risk of exacerbation, and enhancing exercise endurance and life quality. BYF is constituted by 12 Chinese herbal medicines, including panax ginseng, red ginseng, astragali radix, epimedii herba, corni fructus, lycii fructus, schisandrae chinensis, fritillariae thunbergii bulbus, perillae fructus, pericarpium citri reticulatae, paeniae rubra radix, pheretima, and ardisiae japonicae herba (75).

A research group systematically studied the mechanism of action of BYF in treating COPD (76). They found 182 candidate ingredients had interactions with 195 potential targets. Most of the targets of BYF are related to activation of AP-1 family of transcription factors and MAPK. They suggested that IL-1β, IL-6, and TNF-α expressed in lung tissue of COPD patients are regulated by the MAPK/AP-1 pathway.

Indeed, BYF exerts its effects on COPD possibly by modulating lipid metabolism; reducing inflammation, mucus secretion, and oxidative stress; improving MMPs/anti-MMPs balance and collagen deposition; downregulating the EGFR/PI3K/mTOR, TLR-4/NF-κB and JNK, p38, and NF-κB pathways; and modulating cellular connectivity pathways at the systemic level (57, 77). BYF III combines with electroacupuncture can effectively suppress inflammatory response in COPD rats via regulating SIRT1/NF-κB signaling (78).

Moreover, BYF significantly inhibits Th17 cell differentiation as marked by suppressing the expressions of RORγt and IL-17. Concurrently, BYF activates Treg cell differentiation as verified by markedly increasing the expression of Foxp3 and IL-10. Finally, BYF can restore the Treg/Th17 balance via reduction of STAT3 phosphorylation in Th17 cells, and enhancement of STAT5 phosphorylation in Treg cells, and activation of adenosine receptor 2a for attenuating COPD (75).

The $PM_{2.5}$ and CS-induced COPD animals exhibit high levels of miR155 and lower levels of FOXO3a in bronchial epithelial cells. FOXO3a has a critical role in controlling the expression of genes involved in oxidative stress response, DNA damage repair, inflammation, and cellular metabolism. BYF upregulates FOXO3a expression via modulating the miR155/FOXO3a axis, thereby suppressing miR155 expression (79).

It is known that there is an accumulation of senescence cells in CS-induced COPD lung tissue, including aging alveolar epithelial cells and aging endothelial cells. The COPD cellular senescence is a state of irreversible permanent cell cycle arrest. Cyclin-dependent kinases inhibitory factors (p16, p21 and p27) accumulate in senescent cells. The senescent cells can increase secretion of senescence-related secretory phenotype (SASP) factors (IL-6, IL-8, and CCL3). BYF treatment

can inhibit CS extract (CSE)-induced cellular senescence and reduce CSE-suppressed expression and secretion of klotho in lung epithelial cells, thereby reducing inflammation, oxidative stress, and cellular senescence. In addition, BYF also reverses CSE-downregulated expression of ZNH263 in BEAS-2B cells that in turn upregulate the expression and secretion of klotho (80).

13.5.3.2 Guben Zhike Decoction

Another most commonly used TCM formula is Guben Zhike decoction (固本止咳汤, GBZKD, firm the root and relieve a cough), which is composed of seven herbs: astragari radix, epimedii herba, radix stemonae, scutellaria baicalensis, atractylodis macrocephalae, paeoniae radix rubra, and saposhnikoviae divaricata. GBZKD can improve lung function and associated pathology in COPD patients. The lung bullae and infiltration of inflammatory cells can be relatively averted, and the airway cilia can be rearranged regularly in COPD animals. A research group (81) identified 287 and 184 proteins with marked regulatory roles in lung tissue of mice belonging to COPD and GBZKD experimental group, respectively, by label-free proteomic analysis. GBZKD may improve lung injury by downregulating the complement and coagulation cascades, metabolic pathways, nitrogen metabolism, tight junction, gene and protein expression, and downregulating the multiple inflammatory pathways, including JAK/STAT signal transducer and activator of transcription signaling pathway. In addition, GBZKD also improves oxidative stress by regulatory factors, such as carbonic anhydrase 1 and 2.

GBZKD can reduce IL-6 and IL-13 levels, increase the proportion of γδT cells in lung tissue, promote the secretion of keratinocyte growth factor (KGF) and KGFR. Therefore, GBZKD can effectively reduce airway inflammation and improve the structure of the airway from damage and airway epithelial integrity, and enhance the respiratory mucosal immune function (82).

13.6 PULMONARY FIBROSIS

Pulmonary fibrosis (PF) is a serious lung disorder caused by viral infections, radiation exposure, and airborne toxins. Idiopathic PF (IPF) is related to pneumonia, and it often affects the elderly and is characterized by recurring scar formation in the lung including the irregular aggregation of ECM constituents (e.g., mesenchymal cells, fibroblasts and myofibroblasts, interstitial collagens, hyaluronic acid, proteoglycans, fibronectin, laminin, tenascin-C). The pathogenesis of PF is associated with adaptive and innate immune activation, inflammation, oxidative stress, epithelial/endothelial damage, EMT, and cell apoptosis. Numerous studies have clarified the activation of TGF-β or NF-κB pathways involved in the expression of ECM genes. Oxidant stress caused by the imbalance between oxidant/antioxidant in lung of sufferers is one of the major mechanisms presents in the pathogenesis of PF (2, 38).

13.6.1 A Brief Introduction of the Pathology of Pulmonary Fibrosis

The pathogenesis of PF is briefly illustrated in Figure 13.12. The inflammatory mediators unleashed by the injured lung epithelial cells stimulate platelets for blood clot formation and stimulate neutrophils and macrophages to secrete profibrotic cytokines such as TNF-α, IL-1β, IL-13, and TGF-β1. Subsequently, bone marrow fibrocytes and resident fibroblasts propagate and develop into myofibroblasts. Besides producing IL-13, IL-25, and TSLP to stimulate profibrotic Th2 responses, the injured epithelial cells also undergo EMT to produce fibroblasts and myofibroblasts, which secrete ECM elements for fibrosis formation. TGF-β1 can also promote EMT and induce Th17 cell differentiation. T cells facilitate Th2 differentiation by producing IL-25 and IL-21. The Th2 cells produce IL-13, enabling profibrotic macrophages to release TGF-β1 and other mediators. The Th2 cells also activate the activity of collagen-secreting fibrocytes from bone marrow. As a result, myofibroblasts form to unlock ECM elements and, therefore, lead to PF development (83–85).

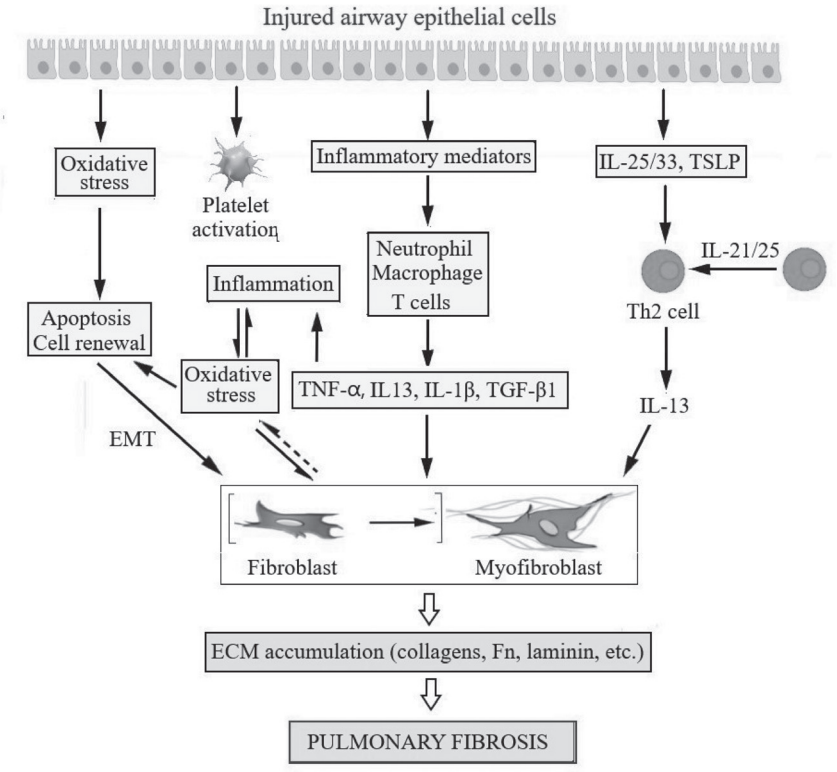

FIGURE 13.12 The pathogenesis of PF.

13.6.2 The Mechanism of Action of Some Ingredients of TCM in Treating PF

According to the pathology of PF, the therapeutic strategy includes antioxidative stress and anti-inflammation, inhibiting macrophages activation, inhibiting EMT, modulating MMP/inhibitor of TIMP balance, improving the ECM deposition, stimulating autophagy, modulating immune balance, inhibiting angiogenesis, and regulating related signaling pathways. These therapeutic functions are achieved through various active herbal ingredients in TCM. Several ingredients have been confirmed to have efficacy in treating PF in animal models in preclinical or clinical practice (83, 84). Some commonly encountered compounds in literature include terpenoids (triptolide, celastrol, tanshinone IIA, glycyrrhizic acid, andrographolide, glaucocalyxin A, and saikosaponin), flavonoids (baicalein and baicalin, quercetin, hydroxysafflor yellow A, puerarin, icariin, isoliquiritigenin, scutellarin, hesperidin, Kaempferol, and calycosin), phenolics (resveratrol, curcumin, EGCG, gallic acid, salvianolic acid B, juglanin, ellagic acid, and zingerone), glycosides (salidroside and astragalin), alkaloids (neferine, tetrahydropalmatine, oxymatrine, matrine, berberine, stemona alkaloid, and ligustrazine), saponins (astragaloside IV, dioscin, and ginsenside), quinonoids (emodin and polydatin), and others (osthole and schisandrin B).

For example, baicalein can attenuate TGF-β1/Smad signaling to improve antioxidant activity and alleviate inflammation by repressing miR-21 expression (86). Baicalein represses TGF-β1-induced fibroblast differentiation through inhibition of miR21 expression, thereby inhibiting α-SMA filament formation in fibroblasts (87). Baicalein also alleviates TGF-β1-induced Col-I production in fibroblasts via downregulation of CTGF (88). Baicalin can diminish the levels of IL-1β, IL-6, TNF-α, and TGF-β1 in lung tissues, inhibit the expression of α-SMA and vimentin, and increase the expression of E-cadherin. These results could be attributed to inhibition of the TLR4/NF-κB

signaling pathway (89). Evidence proved that the effective inhibition of PF by baicalin is partially attributed to enhancing adenosine A2a receptor and then downregulating the TGF-β1-induced ERK1/2 signaling pathway (90). The major functions of the natural ingredients in anti–pulmonary fibrosis and the related targets involved are illustrated in Figure 13.13 (83, 85).

The potential therapeutic targets of PF may include antioxidative pathways to alleviate oxidative stress (e.g., inhibition of ROS, NOX, iNOS and NO); cell signaling pathways (e.g., the PI3K/Akt/mTOR pathway, G-protein coupled receptors, Rho-associated coiled-coil-forming protein kinase [RhoA/ROCK] pathway, and MAPK/JNK pathway); cytokines and chemokines (e.g., CCL2, TGF-β, and IL-13); EMT pathways (Wnt signaling pathway); growth factors (e.g., CTGF, PDGF, VEGF, and FGF, and TGF-β1); transcription factors (e.g., FoxOs, HSP 90); and others (e.g., Pentraxin 2 (PTX-2), galectin-3, and β-galactoside-binding lectin, integrin αvβ6) (84).

13.6.3 Examples of Commonly Used TCM Formulas in the Treatment of PF

According to the dialectical treatment theory of TCM, the physicians always select different formulas and add or subtract parts of components of the formula for specific individual treatment. For example, modified Maimendong (ophiopogon japonicus) decoction for patients with deficiency of both Qi and Yin (气阴两虚), Qingzao Jiufei (清燥救肺) decoction for patients with lung injury caused by pathogenic dryness (燥邪伤肺), modified Bufei (补肺) decoction for patients with deficiency of lung Qi (肺气亏虚), modified Buyang Huanwu (补阳还五) decoction for patients with Qi deficiency and blood stasis (气虚血瘀), and so on.

Here we introduce Buyang Huanwu decoction as an example to explain the principle of treatment of PF. Buyang Huanwu decoction, as a classic prescription in the *Correction on the Errors of Medical Works* (医林改错) by Wang Qingren, a doctor in the Qing Dynasty, is widely used in the treatment of IPF based on its unique curative effect of invigorating Qi and promoting blood circulation to remove meridian obstruction. Buyang Huanwu decoction is composed of astragari radix, ligusticum wallichii, pheretima aspergillum, persicae semen, angelica sinensis, paeoniae radix rubra, and safflower (91).

There is increasing literature reporting that both Buyang Huanwu decoction and its components have certain anti-fibrotic activities, and its mechanism of action is involved in improvement of lung pathology, anti-inflammation, antioxidant, regulation of ECM metabolism, anti-thrombotic effect,

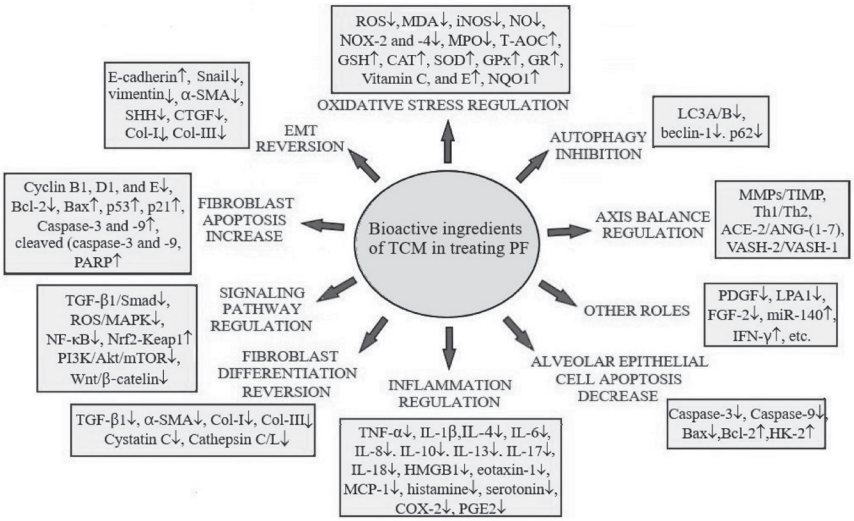

FIGURE 13.13 Emerging studies have shown the anti-fibrotic effects of the active ingredients from TCM.

regulation of angiogenesis, intervention of autophagy and apoptosis via regulation of many signaling pathways (91, 92).

Astragari radix as a monarch drug in Buyang Huanwu decoction, contains many groups of active ingredients, such as flavonoid, saponin, flavonoid polysaccharides and alkaloids. Astragari radix can regulate the metabolism of ECM, inhibiting the expression of α-SMA, Col-I and Col III. Astragaloside IV (Figure 13.14) can inhibit Smad signaling by activating miR-21 to decrease the production of EMT. Astragaloside IV also inhibit PI3K/Akt/mTOR signaling to increase autophagy via decreasing caspase-1, IL-1β, and IL-18 (92, 93). Astragalin (Figure 13.14) is effective in ameliorating oxidative stress-associated PF through disturbing airway EMT and epithelial autophagic stress (94).

Angelica sinensis, as a ministerial drug in the decoction, can protect pulmonary vascular endothelial cells from the synthesis and release of vasoconstrictor and pro-inflammatory factors, and hypercoagulable state of blood. Angelica sinensis exerts its function by decreasing the expression of CTGF and the downregulation of TGF-β1/NF-κB (86, 88). Ligustrazine (Figure 13.14), one of the major active ingredients in ligusticum wallichii, has the function of blocking PI3K/Akt/mTOR and hedgehog signaling pathways to reduce oxidative stress via increasing miR-193 expression and autophagy. Ligustrazine also activates Nrf2/HO-1 signaling. Paeoniae radix rubra contains total glycosides of peony, as well as tannin, flavonoid and volatile oils. The major content paeoniflorin (Figure 13.14) attenuates the infiltration of inflammatory cells and the deposition of ECM, and decreases the contents of hydroxyproline, Col-I, and α-SMA in myofibroblasts and ECM. Paeoniflorin could contribute to the downregulation of TGF-β1/Smad pathway and increase in the expression of IFN-γ (95).

Safflower (Figure 13.14) contains components such as safflower yellow pigment, hydroxysafflor yellow A, and total flavonoid of safflower. The target of safflower may be TGF-β1 signaling. It is proved that safflower yellow pigment can alleviate the increase of hydroxyproline content in the lung tissue of PF, inhibit the expression of TGF-β1, and increase α-SMA in stimulated fibroblasts (96). Amygdalin (Figure 13.14) is the main active ingredient of persicae semen. Pheretima aspergillum upregulates Nrf2 signaling pathway and inhibits TGF-β1 and the overexpression of HMGB1.

In the final analysis, Buyang Huanwu decoction effectively attenuates PF via processes such as regulating several signaling pathways (e.g., ERK, TGF-β1/Smad, HMGF/RAGE, PI3K/Akt,

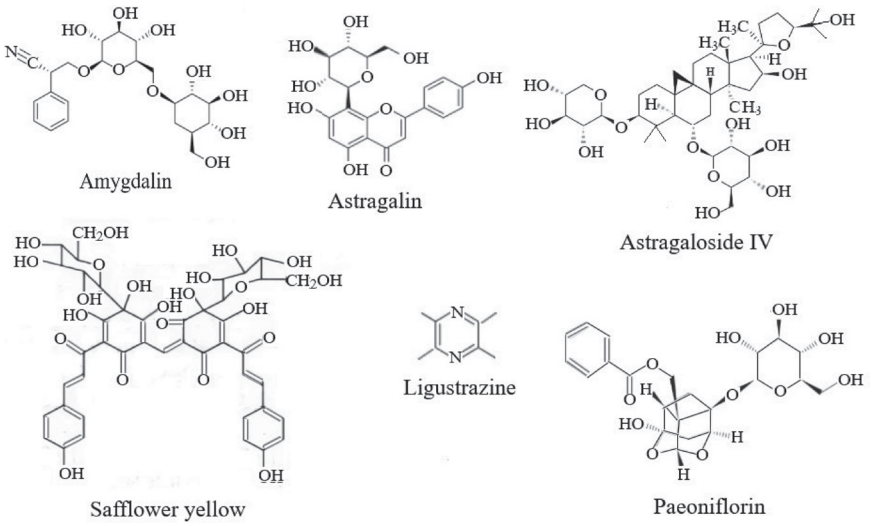

FIGURE 13.14 Some active ingredients in the Buyang Huanwu decoction

mTOR, DLL4/Notch4, and Nrf2/HO-2 signaling pathways); regulating ECM metabolism; inhibiting expression of α-SMA; differentiation of fibroblasts; and inflammation and oxidation (92, 97).

13.7 CONCLUSIONS

In conclusion, almost all TCM formulas are composed of multiple herbs, each with multiple chemical ingredients. One herb can appear in multiple formulas, and one chemical ingredient can also appear in multiple herbs. One compound can have multiple targets of action, and multiple compounds can also act on the same target concurrently. Therefore, TCM prescriptions have the characteristics of multiple composition, targets, pathways, and functions. In the prescriptions, herbs have both their own role and synergistic and mutually restrictive effects between each other for the maximum therapeutic effect and minimum toxicity. Moreover, physicians can select specific prescriptions based on the patient's specific symptoms and adjust the composition of the prescriptions to achieve personalized treatment for the goal of treating both symptoms and root causes.

The active chemical ingredients in herbs cover many classes of compounds, mainly flavonoids, terpenes, saponins, alkaloids, and phenols. Modern scientific research has found that these compounds act on various inflammatory cells, immune cells, and even structural cells. They can directly or indirectly act on biomolecules in the body, such as enzymes and mediators of signal pathways, playing roles of anti-inflammation, antioxidation, immunomodulation, anti-airway remodeling, anti–pulmonary fibrosis, regulation of water, electrolytes, acid-base balance, affecting proliferation and differentiation, and so on. They can simulate antagonists and agonists of some hormones. As part of the treatment strategy, combining with Western medicine may achieve more perfect results. Therefore, using modern scientific theories and methods to deeply explore, explain, and develop traditional Chinese medicine, and integrating TCM and Western medicine will bring greater benefits to humanity.

ABBREVIATIONS

ACE-2	angiotensin-converting enzyme 2
ACTH	adrenocorticotropic hormone
AHR	airway hyperresponsiveness
ALI	acute lung injury
AMPK	5′-AMP activated protein kinase
AP-1	activator protein-1
ARDS	acute respiratory distress syndrome
Arg-1	arginase-1
BALF	bronchoalveolar lavage fluid
3CLpro	3-chymotripsin-like protease
CDK2	cyclin-dependent kinase 2
CHOP	enhancer binding protein (c/ebp) homologous protein
CLCA1	calcium-activated chloride channel
CMI	Chinese medicine injection
COL1A1	collagen type I alpha 1 chain
Col-I	collagen-I
Col-III	collagen-III
COPD	chronic obstructive pulmonary disease
COVID-19	disease caused by SARS-CoV-2 infection
COX-2	cyclooxygenase-2
CS	cigarette smoke
CSE	cigarette smoke extract
CTGF	connective tissue growth factor
DLL4	delta-like 4

ECM	extracellular matrix
EGCG	epigallocatechin-3-gallate
EGFR	epithelial growth factor receptor
EMT	epithelial-mesenchymal transition
ERK	extracellular signal-regulated kinase
FAK	focal adhesion kinase
FDP	fibrinogen degradation product
FGF	fibroblast growth factor
FiO_2	fraction inspiration oxygen
Fn	fibronectin
FOXO3a	forkhead box O3a
FOXP3	forkhead box protein 3
GBZKD	Guben Zhike decoction
GM-CSF	granulocyte-macrophage colony–stimulating factor
GPx	glutathione peroxidase
GSH	reduced glutathione
HDAC1	histone deacetylase 1
HIF-1α	hypoxia inducible factor
HMGB	high-mobility group box 1
HO-1	heme oxygenase 1
HPA	axis hypothalamic-pituitary-adrenal axis
HSP72	heat shock protein 72
Hyp	hydroxyproline
ICAM-1	intercellular adhesion molecule-1
IgE	immunoglobulin E
IL-6	interleukin-6
ILC2s	innate lymphoid cells 2
INFγ	interferon-γ
iNOS	inducible nitric oxide synthase
IPF	idiopathic pulmonary fibrosis
JAK	Janus kinase
JNK	c-Jun *N*-terminal kinase
KGF	keratinocyte growth factor
KGFR	keratinocyte growth factor receptor
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemokine protein–1
MDA	malondialdehyde
MIP-1α	macrophage inflammatory protein–1α
miR34a	micro-RNA34a
MMP	matrix metalloproteinase
M^{pro}	Main protease
mTOR	mammalian target of rapamycin
MUC5AC	mucin 5AC
MyD88	myeloid differentiation factor 88
NF-κB	nuclear factor kappa B
NLRP	nucleotide binding oligomerization domain-like receptor
NO	nitric oxide
NOX	NADPH oxidase
NQO1	NAD(P)H:quinone oxidoreductase 1
Nrf2	nuclear factor erythroid-2-related factor 2

Nsp14	nonstructural protein 14, N-terminal 3′-5′ exonuclease
Nur77	phosphorylation of nuclear receptor 4A1
PAI-1	plasminogen activator inhibitor type-1
PAK1	serine/threonine p21 protein activated kinase-1
PaO_2	partial pressure of oxygen
PDE	phosphodiesterase
PDGF	platelet-derived growth factor
PF	pulmonary fibrosis
PGC-1α	peroxisome proliferators-activated receptor γ coactivator 1α
PGD2	prostaglandin D2
PI3K	phosphatidylinositol 3-kinase
PLA2	phospholipase A2
PLpro	papain-like protease
$PM_{2.5}$	particulate matter with a diameter of 2.5 μm or less
PPARγ	peroxisome proliferative activated receptor γ
PTEN	phosphatase and tensin homolog
QFLT	Qingfei Litan decoction
RAGE	receptor of advanced glycation end-product
RdRp	RNA-dependent RNA polymerase
ROCK	rho-associated coiled-coil-forming protein kinase
ROR-alpha	retinoic acid receptor-related orphan receptor-alpha
ROS	reactive oxygen species
SARS-CoV	severe acute respiratory syndrome coronavirus
SASP	senescence-related secretory phenotype
SGp	spike glycoprotein
SHH	sonic hedgehog
SIRT1	sirtuin 1
α-SMA	α-smooth muscle actin
SMC	smooth muscle cell
SOD	superoxide dismutase
STAT	signal transducer and activator transcription
TAK1	transforming growth factor–β activated kinase–1
TCM	traditional Chinese medicine
TGF-β1	transforming growth factor–β1
Th17	T helper 17 cell
TIMP	tissue inhibitor of metalloproteinase
TLR4	toll-like receptor–4
TMPRSS2	serine protease transmembrane protease serine 2
TNF-α	tumor necrosis factor–α
TPCs	two-pore channels
Treg cell	regulatory T cell
TRPA1	transient receptor potential cation channel subfamily A member 1
TRPV1	transient receptor potential cation channel subfamily V member 1
TSLP	thymic stromal lymphopoietin
TUNEL	terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
Wnt	wingless-type MMTV integration site family
XBCQ	Xuanbai Chengqi decoction
ZEB2	zinc finger E-box-binding homeobox 2
ZNH263	zinc finger protein 263

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