Bulbus Fritillariae Cirrhosae as a Respiratory Medicine: Is There a Potential Drug in the Treatment of COVID-19?

Yunyun Quan1,2, Li Li1, Zhujun Yin1, Shilong Chen1, Jing Yi1, Jirui Lang1, Lu Zhang1, Qianhua Yue1 and Junning Zhao1,2*

1Translational Chinese Medicine Key Laboratory of Sichuan Province, Sichuan Academy of Chinese Medicine Sciences, Schuan Institute for Translational Chinese Medicine, Chengdu, China, 2Department of Pharmacognosy, West China School of Pharmacy Schuan University, Chengdu, China

Bulbus fritillariae cirrhosae (BFC) is one of the most used Chinese medicines for lung disease, and exerts antitussive, expectorant, anti-inflammatory, anti-asthmatic, and antioxidant effects, which is an ideal therapeutic drug for respiratory diseases such as ARDS, COPD, asthma, lung cancer, and pulmonary tuberculosis. Through this review, it is found that the therapeutic mechanism of BFC on respiratory diseases exhibits the characteristics of multi-components, multi-targets, and multi-signaling pathways. In particular, the therapeutic potential of BFC in terms of intervention of “cytokine storm”, STAT, NF-κB, and MAPK signaling pathways, as well as the renin-angiotensin system (RAS) that ACE is involved in. In the “cytokine storm” of SARS-CoV-2 infection there is an intense inflammatory response. ACE2 regulates the RAS by degradation of Ang II produced by ACE, which is associated with SARS-CoV-2. For COVID-19, may it be a potential drug? This review summarized the research progress of BFC in the respiratory diseases, discussed the development potentiality of BFC for the treatment of COVID-19, explained the chemical diversity and biological significance of the alkaloids in BFC, and clarified the material basis, molecular targets, and signaling pathways of BFC for the respiratory diseases. We hope this review can provide insights on the drug discovery of anti-COVID-19.

Keywords: bulbus fritillariae cirrhosae, alkaloids, respiratory diseases, signaling pathways, targets, COVID-19

INTRODUCTION

In December 2019, the infectious disease caused by the novel coronavirus (2019 Novel Coronavirus, 2019-nCoV) began to break out. The epidemic first emerged in Wuhan and quickly swept the world (Holshue et al., 2020; Li et al., 2020a; Zhu et al., 2020; Livingston and Bucher, 2020). On January 30, 2020, the World Health Organization (WHO) declared the epidemic as a “public health emergency of international concern” (Mahase, 2020; Burki, 2020). On February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) officially designated the virus as “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” (Gorbalenya, 2020). On the same day, the WHO announced that the pneumonia caused by the 2019-nCoV was named “Coronavirus disease 2019, COVID-19” (Jiang et al., 2020; Ghebreyesus, 2019). COVID-19 is an acute respiratory
infectious disease caused by SARS-CoV-2 infection, which has become a major threat to the health of people all over the world, and the world is still in the pandemic stage (Wang et al., 2020a; Chavez et al., 2021; Song et al., 2020). Up to now, the number of confirmed COVID-19 cases in the world is 225,187,374, which has exceeded 200 million, and the death toll is 4,640,097, which is nearly 5 million (COVID-19 coronavirus pandemic, 2021; WHO, 2019). SARS-CoV-2, as a single-stranded positive-stranded RNA virus of the β subclass of the coronavirus genus (Wu et al., 2020a; Li et al., 2020b) (Figure 1A), is genetically similar to the 2003 severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) and the 2012 Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) (Perlman and Dandekar, 2005; Zumla et al., 2015; Zumla et al., 2016; Dyall et al., 2017; Hui and Zumla, 2019; Patel et al., 2020; Spagnolo et al., 2020). SARS-CoV-2 has about 79% homology with SARS-CoV in sequence, and about 50% with MERS-CoV (Lu et al., 2020a; Zhou et al., 2020a; Gu et al., 2020). SARS-CoV-2 is a virus that is more contagious and can cause acute respiratory distress syndrome (ARDS) discovered after SARS-CoV and MERS-CoV. It mainly causes mild to severe lung infections, and results in acute and highly lethal pneumonia. The clinical symptoms of COVID-19 are similar to those of SARS-CoV and MERS-CoV (Graham et al., 2013; Xu et al., 2020a). The common symptoms of patients with COVID-19 are high fever, dry cough, fatigue, myalgia, sputum production, shortness of breath, and the less common symptoms are sore throat, hemoptysis, chest pain, headache, diarrhea, and vomiting, besides, the most common complications are pneumonia, followed by ARDS, arrhythmia, shock, respiratory failure, and even death from multiple organ failure (Chen et al., 2020a; Huang et al., 2020a; Yang et al., 2020a; Wang et al., 2020b; Wu et al., 2020b; Eastin and Eastin, 2020).

Bulbus fritillariae cirrhosae (BFC), well-known as ChuanBeimu or ChuanBei in China, is derived from the dried bulbs of six different species of the genus Fritillaria that belong to the family Liliaceae, including Fritillaria cirrhosa D. Don (F. cirrhosa), Fritillaria unibracteata P.K.Hsiao and K.C.Hsia (F. unibracteata), Fritillaria przewalskii Maxim. ex Batalin (F. przewalskii), Fritillaria delavayi Franch. (F. delavayi), Fritillaria taipaiensis P.Y.Li (F. taipaiensis), Fritillaria unibracteata var. wabuensis (S.Y.Tang and S.C.Yueh) Z.D.Liu, Shu Wang, and S.C.Chen (F. wabuensis) (Chinese Pharmacopoeia Com, 2015; Chen et al., 2019; Zhang et al., 2016) (Figure 1B). BFC, as a valuable and important traditional Chinese medicine (TCM), has been used as an antitussive, expectorant, and anti-asthmatic drug, and it is considered to be the top-grade one among all Fritillaria species with positive therapeutic effects, low toxicity, and few side effects (Cai et al., 1999; Li et al., 2003a; Wang et al., 2007a; Li et al., 2009; Li et al., 2012; Xin et al., 2014; Chen et al., 2020b). BFC has the effects of eliminating phlegm and antitussive, reducing fever, and it is used for the treatment of diseases associated with

**FIGURE 1** | SARS-CoV-2 and the respiratory diseases, biological processes, and symptoms that BFC have an effect on. (A) is the 3D and 2D structure of SARS-CoV-2 with its composition. (B) is F. unibracteata, one of the plant sources of BFC with its bulb. (C) is the symptoms that BFC can relieve. (D) is the respiratory diseases and correlative biological processes that can be intervened by BFC.
| Name                          | Figure | Clinical usages                                               | References                                      |
|-------------------------------|--------|---------------------------------------------------------------|------------------------------------------------|
| Nin Jiom Pei Pa Koa           |        | Sore throat                                                  | Drugs.com, (1064a)                              |
| Chuanbei Zhike Lu             |        | Dry cough, phlegm                                            | Chinese Pharmacopoeia Com, (2015)               |
| Chuanbei Pipa Tangjiang       |        | Cough, phlegm, sore throat, chest pain, cold, bronchitis     | Chinese Pharmacopoeia Com, (2015)               |
| Chuanbei Xueli Gao            |        | Cough, dyspnea, dry throat                                   | Chinese Pharmacopoeia Com, (2015)               |
| Niuhuang Shedan               |        | Phlegm, dry cough                                            | Chinese Pharmacopoeia Com, (2015)               |
| Chuanbei Ye                   |        |                                                              |                                                 |
| Zhike Chuanbei Pipa Diwan     |        | Cold, bronchitis, phlegm, cough                              | Chinese Pharmacopoeia Com, (2015); Xiao and Li, (2013) |
| Zhike Chuanbei Pipa Lu        |        | Cold, bronchitis, phlegm, cough                              | Chinese Pharmacopoeia Com, (2015)               |
| Fufang Chuanbeijing Pian      |        | Cough, phlegm, asthma, acute and chronic bronchitis, chest distress | Chinese Pharmacopoeia Com, (2015)               |
| Shedan Chuanbei Ruanjiaonang  |        | Cough, phlegm                                                | Chinese Pharmacopoeia Com, (2015)               |
| Shedan Chuanbei Jiaonang      |        | Cough, phlegm                                                | Chinese Pharmacopoeia Com, (2015)               |
| Shedan Chuanbei San           |        | Cough, phlegm                                                | Chinese Pharmacopoeia Com, (2015)               |
| Chuanbei Pipa Capsules        |        | Cough, phlegm, chest pain, cold, sore throat, chronic bronchitis, COPD | Liu et al. (2019)                              |
| Feitai Capsule                |        | Cough, phlegm, fatigue, lung cancer, pulmonary tuberculosis  | (Deng et al., 2012; Yu et al., 2012); Liang et al., 2017 |
dry cough, chronic cough, cough with bloody sputum, consumptive cough, sores, swelling, and lung or breast abscesses (Wagner et al., 2011). In particular, BFC is effective for the treatment of the elderly and children, especially when it is difficult to recover after long-term treatment (Gao et al., 1999). Furthermore, BFC is sted with diets to nourish the lung against pulmonary diseases induced by particulate matter and smoking (Guo et al., 2017; Guo et al., 2020a). Therefore, BFC is regarded as a good medicine to promote lung health and has been utilized to treat pulmonary diseases in China and many other countries for thousands of years (Lin et al., 2015; Zhao et al., 2018a). Currently, there are more than 200 kinds of products related to BFC in the market such as Nin Jiom Pei Pa Koa, Chuanbei Zhike Lu, Chuanbei Pipa Capsules, etc., widely used to treat pulmonary diseases clinically, like dyspnea, bronchitis, chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, and lung cancer (Zhang et al., 2009; Li et al., 2013; Chinese Pharmacopoeia Com, 2015; Cunningham et al., 2018; Guo et al., 2020a) (Table 1).

So as for COVID-19, BFC can improve symptoms such as fever, dry cough, phlegm, shortness of breath, and sore throat (shown in Figure 1C). The chemical components of BFC are various and complex, including alkaloids, saponins, terpenoids, glycosides, nucleosides, nucleobases, fatty acids, and starches, among which alkaloids and saponins are considered to be the major low molecular-weight active components, especially alkaloids such as imperialine, chuanbeinone, verticine, verticinone, peimine, isoverticine, delavine, delavinone, ebeiedinone, sipenidine, puqiedinone, puqiedine, peimisine-3-O-β-D-glucopyranoside, imperialine-3-β-D-glucoside, and so on (Kaneko et al., 1986; Ding et al., 1996; Li et al., 2006; Wang et al., 2007b; Duan et al., 2011; Zhang et al., 2011; Hao et al., 2013; Li et al., 2013; Lin et al., 2013; Peng et al., 2013; Wang et al., 2014a; Wang et al., 2017a; Geng et al., 2018; Wang et al., 2019; Chang et al., 2020). It is worth noting that verticine is also known as peimine and verticinone is also known as peiminine. Modern pharmacological studies have shown that the alkaloids in BFC have significant antitussive, expectorant, anti-asthmatic, anti-inflammatory, anti-oxidant, antitumor, and angiogenesis converting enzyme (ACE) inhibition activities and exhibit good curative effect on cough, sputum, tracheobronchial contraction, acute lung injury, inflammation, and lung cancer (Luo et al., 2012; Wang et al., 2017b; Zhao et al., 2018b; Yin et al., 2019; Chen et al., 2020c). For example, imperialine is one of the essential steroidal alkaloids of BFC (Lin et al., 2013; Lin et al., 2015). Wang's research (Wang et al., 2016a) found that in the COPD-like rat model associated with abnormal inflammatory response in the lung, imperialine could reduce the damage of lung function and structure. Moreover, imperialine could inhibit inflammation by regulating the expression of related cytokines such as IL-1β, IL-6, IL-8, TNF-α, NF-kB, TGF-β1, MMP-9, and TIMP-1. What’s interesting is that the COPD has influence on the progression and outcomes of COVID-19 (Wu et al., 2020c) and recent reports demonstrate that the majority of the serum levels of the above-mentioned cytokines and growth factors in COVID-19 patients will also increase (Chen, 2020; de la Roca et al., 2020; Nile et al., 2020; Phoswa and Khaliq, 2020; Wiersinga et al., 2020; Ghazavi et al., 2021; Metzemaekers et al., 2021). Besides, BFC exerts a significant therapeutic effect on various lung diseases, such as acute lung injury and lung inflammation. While severe acute lung injury is known as ARDS (Force et al., 2012) and lung inflammation is one of the characteristics of COVID-19.

The respiratory diseases that can be intervened by BFC are asthma, COPD, ARDS, lung cancer, and pulmonary tuberculosis. BFC is mainly playing a therapeutic role in lung diseases through the biological processes about inflammatory response, immune response, apoptosis, and oxidative stress. To date, there is no specific drugs for COVID-19, and the aim of this review is to summarize and analyze the pharmacological effects and mechanisms of BFC on respiratory pulmonary diseases, then provide insights on the drug discovery of anti-COVID-19 (Figure 1D).

THE ANTITUSSIVE, EXPECTORANT, AND ANTI-INFLAMMATORY MECHANISMS OF BFC

Cough is one of the common symptoms of various respiratory diseases, such as asthma, chronic bronchitis, pneumonia, and so on (Irwin and Madison, 2013). Although cough can be relieved by morphine containing codeine and other commonly used drugs, these drugs are highly addictive and cause side effects. BFC, as an antitussive TCM, has a positive therapeutic effect for cough due to its major bioactive alkaloids and it is non-addictive. Moreover, compared with synthetic drugs, BFC has fewer or no side effects (Zhang et al., 2009; Shang et al., 2010; Wu et al., 2018).

Xu (Xu et al., 2019) studied the antitussive, expectorant, and anti-inflammatory effect of BFC extract prepared through refluxing with 80% ethanol solvent administered orally to mice, respectively. The experiment of cough caused by ammonia was used to observe the antitussive effect of BFC. Phenol red expectoration test in mice trachea was conducted to investigate the effect of phlegm expelling. Auricular swelling model of mice was induced by xylene to research on the effect of BFC on lessening the ear swelling. The results demonstrated that BFC extract could obviously prolong the period of cough latency and inhibit the cough frequency of mice induced by ammonia. Moreover, the BFC extract could also significantly increase the output of phenol red in mice trachea and inhibit the ear swelling in anti-inflammatory experiment. After that, this research group (Wang et al., 2011) continued to study and find that the specific material basis for the antitussive effect of alkaloids was imperialine, chuanbeinone, verticine, and verticinone isolated from the BFC, which could markedly inhibit the cough frequency and prolong the latent period of cough in mice caused by ammonia. Besides, the specific material basis for the expectorant effect was imperialine, verticine, and verticinone isolated from the BFC, which could significantly increase the output of phenol red in mice trachea in the expectorant test. Then the specific material basis for the anti-inflammatory effect was imperialine and chuanbeinone, which could obviously inhibit the ear edema of mice in a dose-dependent manner. Therefore, the antitussive, expectorant, and anti-inflammatory bioactive components of BFC are the four alkaloids, imperialine, chuanbeinone,
verticinone, and verticine, among which imperaline serves as the most critical role. The bulbs of *F. wabuensis* are also one of the sources of BFC. The team of Wang (Wang et al., 2012a) continued to study the antitussive, expectorant, and anti-inflammatory activities of BFC from *F. wabuensis* with the same models, respectively. The results indicated that all four alkaloids, imperaline, imperaline-β-N-oxide, isoverticine, and isoverticine-β-N-oxide isolated from BFC had significantly antitussive, expectorant, and anti-inflammatory effects, similarly. Besides, there were studies in vivo and in vitro that identified the antitussive effect of the fritillaria alkaloid crude extracts along with imperaline and among them imperaline was proved to be the most potent alkaloid (Chan et al., 2000). Zhang (Zhang et al., 2020a) investigated the potential molecular targets and mechanisms of verticine for cough through computational target fishing. The results of the study demonstrated that MAPK1, AKT1, and PPCKB were the key targets of verticine for treating cough. It was associated with the regulation of function for immunology and neurology exerting multi-proteins and multi-pathways effect (Figure 1C).

Inflammation is an automatic defense response of an organism to injury factors such as infection, noxious stimuli (chemicals), tissue injury, and so on. The typical inflammatory triggers are infection and tissue injury, which elicit the recruitment of leukocytes and plasma proteins to affected tissue sites (Galli et al., 2008; Medzhitov, 2008). Wang (Wang et al., 2016a) used different inflammatory animal models in vivo to evaluate the anti-inflammatory activity of purified total alkaloid fraction (TAF) from BFC, prepared by using H-103 resin column. Models of acetic acid-induced capillary permeability accentuation, and cotton pellet-induced granuloma formation were performed, respectively. His research demonstrated that TAF could inhibit acetic acid-induced capillary permeability accentuation, and cotton pellet-induced granuloma formation. It demonstrated that TAF had a strong anti-inflammatory effect. What is more, Wu (Wu et al., 2015) studied the anti-inflammatory activity and relative mechanisms of verticinone and imperaline, steroidal alkaloids from bulbs of *F. wabuensis* on LPS-stimulated RAW 264.7 macrophages. The research found that verticinone or imperaline could inhibit the production of NO, TNF-α, IL-1β, and the expressions of iNOS and COX-2. Meanwhile, they could decrease the phosphorylation of NF-κB in a dose dependent manner. The results of this study clearly demonstrated that the anti-inflammatory activity and mechanisms of verticinone and imperaline in BFC were associated with the inhibition of the activation of NF-κB signaling pathway. In addition, the research of Liu (Liu et al., 2020a) investigated the anti-inflammatory activity and its mechanisms of alkaloids from BFC in
LPS-induced RAW264.7 macrophage cells. The results indicated that five of the alkaloids including imperaline, verticinone, verticine, peimisine, and delavine, could lower the production of NO, TNF-α, and IL-6, and inhibit the mRNA expressions of TNF-α and IL-6. The anti-inflammatory mechanisms of alkaloids from BFC were related to the inhibition of the phosphorylated activation of MAPK signaling pathways, and ERK1/2, p38 MAPK, and JNK/SAPK were included.

In the study of Park (Park et al., 2017), it was proved that verticine was able to attenuate the production of pro-inflammatory cytokines IL-6, IL-8, and TNF-α and reduce the phosphorylation of MAPKs and the expression of NF-κB in PMACI-induced human mast cell (HMC-1). Verticine could also decrease the passive cutaneous anaphylaxis (PCA) reactions in rats. It suggested that verticine could be used to treat mast cell-derived allergic inflammatory reactions. The patch-clamp technique with HEK 293 cell lines was used to study the anti-inflammatory and pain-relieving mechanisms of verticine against selected ion channels by Xu (Xu et al., 2016). The results of this research informed that the potential mechanisms of verticine for pain relieving and anti-inflammation were to inhibit Kv1.3 ion channel in a concentration dependent manner and block the Nav1.7 ion channel. The antinociceptive effect on inflammatory pain and paclitaxel induced cancer-related neuropathic pain of verticinone were also explored to be generally through both peripheral and central mechanisms in the rat models in Xu’s study (Xu et al., 2011). Luo (Luo et al., 2019a) evaluated the anti-inflammatory effect of verticine on IL-1β induced inflammatory response in mouse articular chondrocytes and ameliorates murine osteoarthritis model. The results showed that verticine could dramatically inhibit the expression of NO, PGE2, COX-2, TNF-α, iNOS, and IL-6 through pretreatment in vitro. Verticine was able to evidently increase the expression of aggrecan and collagen-II, alleviate the degradation of extracellular matrix (ECM) and reduce the production of thrombospondin motifs 5 (ADAMTS-5) and MMP-13 in a dose-dependent manner. The anti-inflammatory mechanisms of verticine were related to the inhibition of AKT phosphorylation and NF-κB activation with the activation of Nrf2/HO-1 signaling pathways. The anti-pulmonary inflammation and anti-pulmonary fibrosis activities of verticine in rat models of bleomycin-induced lung injury were investigated by Guo (Guo et al., 2013). The data of the study informed that verticine obviously ameliorated inflammation of alveolar and lung interstitial. Verticine dramatically suppressed pulmonary fibrosis of bleomycin-induced rat model through down-regulating IFN-γ levels in serum and TGF-β, NF-κB, CTGF, ERK1/2, and FasL in pulmonary tissue markedly, which were comparable to dexamethasone. Gong (Gong et al., 2018) researched the anti-inflammatory properties of verticine on LPS-induced mastitis model in mice and the mouse mammary epithelial cells (mMECs) model stimulated with LPS in vitro via being pretreated with verticine. The data identified that verticine exhibited potent anti-inflammatory effects on LPS-induced mastitis in mice, which could distinctly alleviate the histopathological injury of the breast in vivo and noticeably lower the MPO activity. Meanwhile, it was able to decrease the production of pro-inflammatory mediator TNF-α, IL-6, IL-1β, COX-2, and iNOS in vivo and in vitro. The anti-inflammatory mechanism of verticine on mastitis was associated with the suppression for phosphorylation of AKT/ NF-κB, ERK1/2, and p38 signaling pathways. These studies indicate that alkaloids from BFC have anti-inflammatory property, and BFC may be a great potential candidate to be developed for the prevention and treatment of inflammatory diseases. The anti-inflammatory mechanisms of BFC are shown in Figure 2.

**THE MECHANISMS OF BFC IN THE TREATMENT OF ASTHMA, COPD, AND ARDS**

Asthma is a long-term inflammatory disease of the airways, which is featured by overproduction of Th2 cytokines such as IL-4, IL-5, and IL-13 as well as accumulation of pulmonary eosinophils (Bousquet et al., 2000; Douwes et al., 2002; Factor, 2003; Yeum et al., 2007). BFC is a well-known TCM for the treatment of asthma and bronchial inflammation, and pharmacological studies have demonstrated that BFC has significant anti-asthmatic effect.

Yeum (Yeum et al., 2007) investigated the eosinophilic accumulation in the lungs, regulation of Th2 cytokine, and production of histamine and immunoglobulin E (IgE) in a murine model of asthma to research the anti-asthmatic effects of BFC. Eosinophilic proliferation was carried out by the uptake of [3H] thymidine, and accumulation of eosinophils. The study found that BFC significantly down-regulated the levels of IL-5, IL-13, and IL-4 in the bronchoalveolar lavage fluid and there was also a reduction of the level of ovalbumin-specific IgE in serum. BFC could lower the number of eosinophils by inhibiting the recruitment of eosinophil and airway inflammation. Therefore, it implies that BFC possesses a strong inhibitory effect on bronchial inflammation by reducing the production of Th2 cytokines such as IL-4, IL-5, and IL-13, IgE, histamine, and decreasing the accumulation of eosinophils and increasing the production of interferon-γ. The cholinergic nervous system is of significance in asthma and COPD. When the organism is infected by virus, or the antigen is inhaled, vagally mediated reflex bronchoconstriction occurs and the increase of reflex bronchoconstriction leads to asthma attacks. The dysfunction of suppressive muscarinic M2 receptors on the vagal nerve endings can enhance the release of acetylcholine. Therefore, the anticholinergic drugs may be of great benefit to treating acute asthma and these reflections can be interrupted effectively by the modified anticholinergics, such as selective M3 antagonists (Jacoby and Fryer, 2001; Lin et al., 2006; Gosens and Gross, 2018). Studies showed that the alkaloids in BFC had potential anti-asthmatic activities. Imperaline and sinpeinine A are the two alkaloids of BFC, and 3β-acetylimperaline is a derivative of imperaline. The research of Lin (Lin et al., 2006) found that imperaline and sinpeinine A were the antagonists of selective muscarinic M2 receptor subtype, and 3β-acetylimperaline was a selective muscarinic M3 receptor subtype antagonist at the cell
level. Moreover, in tracheal smooth muscle the spasmyloytic effects of imperialine and sinpeinine A were weaker than 3β-acetylimperialine. It suggested that the effective compounds of BFC for the treatment of asthma were 3β-acetylimperialine, imperialine, and sinpeinine A. The mechanism of anti-asthmatic effect of BFC may be related to the selective...
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showed a better therapeutic effect on pulmonary inflammatory diseases such as asthma, COPD, and ARDS.

THE MECHANISMS OF BFC IN THE TREATMENT OF LUNG CANCER

Lung cancer is one of the most frequent cancers, remaining the leading cause of cancer death among males globally (Bray et al., 2018) and the pathogenesis of cancer is bound up with proliferation, apoptosis, inflammation, etc. (Xiu et al., 2015). Lung cancer comprises small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), among which SCLC accounts for approximately 15% of all lung cancers and NSCLC accounts for approximately 85% including adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma (Oser et al., 2015; Remark et al., 2015; Reck et al., 2017; Herbst et al., 2018; Osmanli et al., 2018; Yang et al., 2019). BFC displays significant anti-tumor activity, and its extract as well as alkaloids exhibit anti-proliferative effects on the growth of glioblastoma, colorectal, oral, human promyelocytic leukemia, immortalized keratinocyte, hepatoma, Ehrlich ascites carcinoma, ovarian, and endometrial cancer cells (Ping et al., 1995; Pae et al., 2002; Yun et al., 2008; Bokhari and Syed, 2015; Kavandi et al., 2015; Zheng et al., 2017; Zhao et al., 2018b). Bokhari (Bokhari and Syed, 2015) found that BFC could significantly suppress TGF-β1/SMAD signaling pathway to inhibit cancer cell proliferation, invasion, and metastasis. What’s more, studies showed that BFC exerted a potent therapeutic effect on lung cancer (Wang et al., 2014b; Chen et al., 2020d). Li suggested that BFC was the most commonly used single herb for the treatment of lung cancer (Li et al., 2018). BFC is contributing to the treatment and survival of lung cancer patients in clinical practice, and it is widely used as an adjuvant treatment of lung cancer chemotherapy in TCM (Kavandi et al., 2015), even to the extent that BFC can further enhance the treatment efficiency of lung cancer from 70 to 95% (Lin et al., 2020).

In the study of Li (Li et al., 2020c), the effects of aqueous extract of BFC (AE) along with its mechanism in NSCLC A549 cells in vitro and xenograft model of nude mice in vivo were assessed. The results in vitro revealed that AE displayed inhibition of A549 cells proliferation and colony formation and promotion of apoptosis. RNA-seq was performed using GO and KEGG pathway enrichment analysis and it was found that the dominant differentially expressed genes (DEGs) were associated with apoptosis, immune response, and cell cycle process. While AE increased the expressions of STAT 1 and STAT4 as well as their target genes IFN-γ and IL-12, triggered Bcl-2/Bax proteins attributing to cellular apoptosis in A549 cells. The results in vivo showed that AE lessened the size of tumor and induced cytokines IL-12 and IFN-γ secretion. BFC showed notably antitumor activity through a co-regulatory network mediated bySTAT1 and STAT4 for activation of immunomodulation to induce apoptosis. Wang (Wang et al., 2014b) used the human lung carcinoma cell line (A549) to investigate the antitumor activity of BFC in vitro, in which the antiproliferative activities of the different fractions from BFC including MeOH extracts (ME), petroleum ether extracts (PE), chloroform extracts (CE), n-hexane extracts (HE), water extracts (WE), and the purified total alkaloids of BFC (TAF) were to be examined. The results of the study demonstrated that CE, primarily containing total alkaloids and the TAF displayed higher antiproliferative effect than the others. The major alkaloids monomers in CE and TAF were peimisine, imperialine, and chuanbeinone and TAF displayed obviously antineoplastic activity and low toxicity in vivo. The antitumor mechanism of TAF was to suppress tumor angiogenesis and promote apoptosis through increasing the level of caspase-3 expression.

Wang (Wang et al., 2014c) similarly made an investigation of antitumor activities of BFC extracts against Lewis lung carcinoma cells (LLC). The different fractions from BFC were ME, PE, CE, HE, TAF, and WE. It was indicated that CE and TAF displayed stronger suppression of proliferation on LLC cells than others. The three dominant alkaloid compounds (peimisine, imperialine, and chuanbeinone) in CE and TAF could significantly inhibit the proliferation of LLC cells. The inhibitory effect against LLC cells growth of imperialine was weaker than chuanbeinone and peimisine in vitro. The cell cycle and sub-G1 group of LLC cells were assessed to find that the TAF could induce apoptosis and the cell cycle arrest. Moreover, the mice models were constructed by inoculating LLC cells suspension into the left armpit of C57BL/6 J mice subcutaneously with LLC cells maintaining in solid form for serial transplantation. The results in vivo indicated that TAF exerted antitumor effect obviously with low toxicity and could dose-dependently suppress the growth of transplantable LLC tumor. The antitumor mechanism of TAF was associated with the inhibition of tumor angiogenesis and promotion of apoptosis by activating caspase-3. Chuanbeinone showed obvious antitumor activity against LLC in vitro and induced S phase arrest and apoptosis of LLC in Wang’s other study (Wang et al., 2015a). Chuanbeinone decreased the antiapoptotic Bcl-2 expression and increased the proapoptotic protein Bax and caspase-3 expression. Moreover, chuanbeinone could suppress tumor angiogenesis and increase apoptosis by up-regulating caspase-3 expression in vivo, in which the LLC cells were subcutaneously inoculated into the left armpit of the mice. Verticine was also reported to suppress human lung adenocarcinoma A549/DDP cell proliferation dose-dependently and reverse multidrug resistance (MDR). The anti-lung cancer mechanisms of verticine were associated with apoptosis induction along with decreasing of lung resistance protein (LRP) and excision repair cross-complement 1 (ERCC1) mRNA expression (Yin et al., 2019). Imperialine, as quality control component (Ye and Wang, 2014), is one of the active compounds in alkaloids from BFC and is also the anti-inflammatory agent. The research of Lin (Lin et al., 2020) investigated the anti-cancer effects against NSCLC and its related molecular mechanism of imperialine in vitro and in vivo. A549 cell lines were used for NSCLC cells model in vitro and A549 tumor-bearing mouse model was built for in vivo research. It was found that the imperialine could significantly suppress the activity of NF-κB to inhibit not only NSCLC tumor but also inflammation both in vitro and in vivo through the
inflammation-cancer feedback loop with extremely low toxicity and side effects on blood cell and the main organs. The NSCLC-targeting liposomal system was effectively developed for targeted drug delivery, which could promote the cellular uptake of imperialine at tumor sites and the accumulation in vivo to enhance the overall therapeutic effect of anti-tumor. Hence, these studies indicate that the alkaloids of BFC exert anti-cancer activity against lung cancer while exhibiting systemic safety, and BFC is expected to become a promising novel anti-tumor agent for lung cancer.

The STAT family of proteins is the central in modulating immune responses in the carcinoma microenvironment to accelerate or suppress malignant tumors by regulating cytokine-dependent inflammation and immunity, which are closely relevant to human cancer (Yu et al., 2009; Gutiérrez-Hoya and Soto-Cruz, 2020; Verhoeven et al., 2020). Apoptosis is a form of programmed cell death, which is a natural manner to efficiently eliminate the aged cells or damaged cells from the body. Hence, currently most anti-cancer drugs are inducing apoptosis and triggering correlative cell death signaling pathways to get rid of carcinoma cells (Mohammad et al., 2015; Pistritto et al., 2016; Mortezaee et al., 2019). The caspase family is recognized as a key participant in the execution of apoptosis, especially caspase-3 (Cohen, 1997; Anjum et al., 1998; Green and Llambi, 2015; Nagata, 2018; Ramirez and Salvesen, 2018). Transcription factor family NF-kB has been considered the central mediator in inflammation processes and an essential role in innate and adaptive immunity responses. The activation of NF-kB is also prevalent in cancer, in which NF-kB activation is primarily triggered by inflammatory cytokines within the carcinoma microenvironment. Furthermore, the survival genes in malignant tumor cells and the proinflammatory genes in carcinoma microenvironment are activated by NF-kB conversely (DiDonato et al., 2012; Fan et al., 2013; Hoesel and Schmid, 2013; Shostak and Chariot, 2015). Therefore, NF-κB plays a crucial role in inflammation and cancer.

In this study, it is found that BFC has strong anti-tumor activity, exhibiting anti-proliferative effect on the growth of lung cancer cells, and BFC displays therapeutic effect on lung cancer in vitro and in vivo. The anti-lung cancer mechanisms of BFC include inducing apoptosis, anti-proliferation, preventing tumor invasion and metastasis, activating STATs-mediated immunomodulation to trigger apoptosis, inhibiting NF-kB-mediated inflammation-cancer feedback loop, up-regulating proapoptotic protein Bax and caspase-3, down-regulating antiapoptotic Bcl-2, reversing MDR, and decreasing LRP and ERCC1. It is of great significance to study the anti-lung cancer mechanism of BFC for its rational application and development. These results indicate that BFC may be a promising medication for lung cancer, which can be used as a new source of NF-κB.
inhibitor in the treatment of lung cancer. It also can be applied in modulating immune response to improve anti-lung cancer therapies and even to become an effective caspase-3 promoter in apoptosis signaling pathways. Besides, BFC can also be widely used in the adjuvant treatment of lung cancer owing to its extremely low adverse reactions and side effects, in order to ultimately improve the quality of life and prognosis for the lung cancer patients. The mechanisms of BFC in the treatment of lung cancer are shown in Figure 6.

THE MECHANISMS OF BFC IN THE TREATMENT OF PULMONARY TUBERCULOSIS

Tuberculosis (TB) is an infectious disease caused by bacteria *Mycobacterium tuberculosis* spread by coughing, speaking, or singing, which is still one of the top 10 causes of death (ranking above HIV/AIDS) and the leading cause of death from a communicable disease among adults in the world, with more than 10 million people getting ill due to tuberculosis every year (WHO, 2020). The pathological features of tuberculosis are typically pulmonary necrotizing granulomatous inflammation, namely the lungs are affected, which is called pulmonary tuberculosis (Wang et al., 2014d; Furin et al., 2019). The *Mycobacterium tuberculosis* in the lungs can also infect other parts of the body, such as the kidney, spine, and brain through the blood and approximately all external parts of the lung may be affected, which is called extrapulmonary tuberculosis (Dheda et al., 2016). Tuberculosis can affect anyone anywhere; therefore, it remains one of the greatest health issues worldwide.

TCM plays a crucial role in the treatment of tuberculosis and promotes the discovery and development of new anti-tuberculosis drugs (Wang et al., 2015b) and BFC has the action of anti-tuberculosis (Khare and Khare, 2007). Studies found that BFC in modern and ancient prescriptions could help improve the treatment of tuberculosis (Xu et al., 2020b). Feitai Capsule is made up of several Chinese herbal medicines, such as BFC, Stemonae Radix, Eriobotryae Folium, and Scutellariae Radix. Wang (Wang et al., 2017c) used Feitai

FIGURE 7 | The mechanism of BFC in the treatment of pulmonary tuberculosis.
Capsule to evaluate the clinical efficacy for retreated pulmonary tuberculosis. The results showed that Feitai Capsule combined with anti-tuberculosis chemotherapy drugs in the treatment of retreated pulmonary tuberculosis could effectively promote the absorption of the lesions and the closure of cavities and accelerate the conversion of sputum bacteria to negative. It was shown that Feitai Capsule could enhance the immunity and promote the inflammation dissipation of patients with pulmonary tuberculosis. The TCM Niubeixiaohe is composed of six kinds of TCM such as BFC, Rhizoma Bletillae, Radix Platycodonis, Fructus Arctii, and so on. Liang (Liang et al., 2017) investigated the effects of Niubeixiaohe powder and Niubeixiaohe extracts on tuberculosis mice models infected with *Mycobacterium tuberculosis* H37Rv *in vivo*. It was found that Niubeixiaohe powder and Niubeixiaohe extracts exhibited anti-tuberculosis effects and in particular the Niubeixiaohe extracts could distinctly improve the pulmonary lesions to return to normal pulmonary structure. It could be concluded from this research that Niubeixiaohe was an effective anti-tuberculosis prescription to treat tuberculosis in clinical practice.

Latent tuberculosis infection (LTBI) is a condition of sustained immunity reaction to irritation by antigens of *Mycobacterium tuberculosis* with no phenomenon of active tuberculosis disease in clinical manifestation (Centers for Disease Control and Prevention [CDC]). Mostly there are no signs or symptoms of tuberculosis disease with no infectivity, but once triggered by some factors, it will develop into active tuberculosis disease and become infectious. The most important factor for active tuberculosis disease after infection is immunological situation (Falzon et al., 2020), combined with the findings of this study that BFC had a good protective effect on lung health, which displayed a strong role in activation of immunomodulation and suppressed lung inflammation. TCM prescriptions containing BFC had a good therapeutic effect on pulmonary tuberculosis. Therefore, BFC is a potential drug for the treatment of pulmonary tuberculosis and LTBI can be prevented effectively by making use of BFC, so that it does not become active tuberculosis disease. The mechanisms of BFC in the treatment of pulmonary tuberculosis are shown in Figure 7.

**IS THERE A POTENTIAL DRUG IN THE TREATMENT OF COVID-19?**

The renin-angiotensin system (RAS) plays a major role in control of electrolyte homeostasis, fluid, and blood pressure. Renin and angiotensin I converting enzyme (ACE) cleave the angiotensinogen, the major precursor protein of RAS into angiotensin I (Ang I) and angiotensin II (Ang II), respectively (Pahlavani et al., 2017). RAS consists of ACE, angiotensin converting enzyme 2 (ACE2), Ang II, and Ang II type 1 receptor (Xia and Lazartigues, 2010). The spike glycoprotein (S protein) on the surface of SARS-CoV-2 is a crucial structural protein. It is a highly glycosylated homotrimer and can mediate the invasion of SARS-CoV-2 into human cells (Zheng et al., 2020a; Xu et al., 2020; Walls et al., 2020; Wrapp et al., 2020; Zhong et al., 2020). ACE2 is expressed in many other organs such as lung, stomach, kidney, brain, heart, spleen, liver, and intestines, among which the lung and small intestine are the main vulnerable parts (Hamming et al., 2004; Elased et al., 2008; Chen et al., 2020e) with the expression on the surface of many cell membranes like pulmonary alveolar, tracheal, and bronchial epithelial cells, and also the macrophages (Kai and Kai, 2020). ACE2 regulates the RAS by degradation of Ang II produced by ACE, and it is an important regulator of ARDS (Kai and Kai, 2020). ACE2 is identified as the host cell functional receptor of SARS-CoV-2 as well as SARS-CoV and virus enters the host cells by binding the S protein to ACE2 receptor and adsorbing onto it (Wu et al., 2020d; Gheblawi et al., 2020; Hoffmann et al., 2020). When SARS-CoV-2 enters the host, it will replicate, assemble, and release a great quantity of viral particles thus numerous viruses invade the body and cause

![Figure 8](https://example.com/figure8.png)
SARS-CoV-2 utilizes the identical cell entry receptor to SARS-CoV. That is to say, the two viruses SARS-CoV-2 and SARS-CoV both use their expressed S protein to bind to ACE2 and enter the host cells. But the affinity of SARS-CoV-2 for ACE2 is 10–20 times that of SARS-CoV, which improves its transmission ability (Li et al., 2020b). Significantly, ACE is markedly different from ACE2. ACE also targets on Ang I to generate Ang II involved in the pathogenesis of ARDS, which leads to vasoconstriction and bronchoconstriction, increases blood vessel permeability, and triggers inflammation, fibrosis, and apoptosis. Thus it accelerates the progress of ARDS and lung failure in COVID-19 patients and SARS-CoV infection patients (Wang et al., 1999; Li et al., 2003; Suzuki et al., 2003; Wösthen-van Asperen et al., 2008; Rossi et al., 2020). However, ACE2 targets on Ang II to generate Ang (1–7), which improves ARDS and ACE gene deletion aggravates ARDS (Imai et al., 2005) and thus enzyme ACE2 provides a new therapeutic method for the syndrome (Wösthen-van Asperen et al., 2011). ACE2 converts Ang I to Ang (1–9) (Donoghue et al., 2000) and Ang (1–7) and Ang (1–9) will result in reduction of inflammation and fibrosis (Wigén et al., 2020). Studies confirmed that it could decrease inflammation and mitigate lung injury through inhibiting ACE, or blocking the Ang II receptor in ARDS and the risk could not be increased by administration with ACE inhibitors after being infected by SARS-CoV-2, even more ACE inhibitors can increase ACE2 (Hagiwara et al., 2009; Wösthen-van Asperen et al., 2010; Wysocki et al., 2020). Preoperative serum ACE activity was suggested as a useful prognostic indicator in lung cancer (Danilov et al., 2019). Therefore, the RAS plays an important part in the process of COVID-19 and other pulmonary diseases, and quickly it becomes a hot spot to apply RAS blockers to treat COVID-19 (Danser et al., 2020; Fang et al., 2020; Grasselli et al., 2020; Vaduganathan et al., 2020). In Oh’s study, it was found that verticinone, verticine, and peimisinine could inhibit the activity of ACE in a dose-dependent manner, exhibiting as high as 50% inhibitory concentration of 165.0, 312.8, and 526.5 μM, respectively (Oh et al., 2003). Moreover, many other Fritillaria alkaloids were also found to have inhibitory activity against ACE significantly (Kang et al., 2002; An et al., 2010). The RAS that BFC compounds influence is shown in Figure 8.

Second, the systemic symptoms of COVID-19 patients showed that the levels of C-reactive protein, D-dimer, lactic dehydrogenase (LDH), leukocyte, and neutrophil-lymphocyte ratio (NLR) were elevated but the levels of lymphocytes and platelets were decreased (Chan et al., 2020; Guan et al., 2020; Henry et al., 2020; Qin et al., 2020; Çolak et al., 2021). In severe COVID-19 patients there was dramatically lower number of CD4+ and CD8+ T cells in the peripheral blood accompanied by the reduced lymphocytes in the spleen and lymph nodes as well as the lymphocyte degeneration, necrosis (Li et al., 2020b). Xiong (Xiong et al., 2020) found that the reason for patients’ lymphopenia might be associated with activation of apoptosis and P53 signaling pathway in lymphocytes induced by SARS-CoV-2. Interestingly, with the increasing age the function of naïve CD4+ and CD8+ T cells may be damaged, which should be responsible for declined immunoregulation in the elderly (Rane et al., 2018; Li et al., 2019) and it might be one of the reasons why the severity is worse in older COVID-19 patients. Thus, the SARS-CoV-2 infection will trigger an immune response and mainly impact on T lymphocytes, especially CD4+ and CD8+ T cells, and potential immunological markers are related to COVID-19 (Chen et al., 2020). Initially, adaptive immunoreaction is generated to purge the virus and halt disease process in the immune cell response (Shi et al., 2020). If the protective immunoreaction is damaged, the virus will replicate and impair tissue, particularly in apparatus with more expression of ACE2, just like lungs. The impaired pulmonary cells lead to innate inflammation, which is mainly arranged by macrophages and granulocytes mediating inflammation. With the aggravation of the disease, the potentially lethal lung inflammation occurs, accompanied by the appearance of high fever and myalgia (De Virgiliis and Di Giovanni, 2020), suggesting a serious immune imbalance. Consequently, the systemic immune system is abnormally activated and dysregulated and this immune response results in the cytokine release syndrome (CRS), namely “cytokine storm” that is an excessive immune response (Sinha et al., 2020; Ye et al., 2020). In the “cytokine storm” of SARS-CoV-2 infection there is an intense inflammatory response with the release of abundant increased pro-inflammatory cytokines such as IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α, and VEGF in both ICU and non-ICU COVID-19 patients (Liu et al., 2020c; Ragab et al., 2020). Along with the “cytokine storm” expanding, the monocytes/macrophages exhibit overactivation followed by acute lung injury, contributing to ARDS (Zhang et al., 2020b), which are the important factors of the COVID-19 transition from mild to severe diseases. Therefore, due to the reduced CD4+ and CD8+ T cells, the “cytokine storm” is mediated by leukocytes other than T cells and severe COVID-19 is related to excessive immune response bound up with CRS such as high levels of CXCL-10, CCL-7, and IL-1, which then result in loss of lung function, lung tissue injury, repair imbalance, and respiratory failure (Vaninov, 2020). Furthermore, the viral infection-immunity-inflammation of SARS-CoV-2 are throughout the whole process of COVID-19 even in the recovery stage or after hospital discharge (Wen et al., 2020). A report showed that through immunohistochemistry the expression of IL-4 and M2 macrophages scores of lung tissue were markedly increased in the patients with COVID-19, accompanied by the higher participation of the Th2 (Vaz de Paula et al., 2020). Hence, effective immunization and inflammation therapy can commendably reduce the transition from initial and advanced stages to severe and critical illness, and decrease the incidence of critical illness to lower the mortality. BFC was confirmed to possess a strong inhibitory effect on immunity-inflammation by reducing the production of Th2 cytokines such as IL-4 and IL-13, as well as acting on antagonists of selective muscarinic M2 receptor subtype.

Besides, the complications of serious COVID-19 involve severe pneumonia, pulmonary edema, ARDS, and organ failure (Wu and Mcgoogan, 2020). The pulmonary pathology primarily exerts distinct alveolar injury, such as alveolar edema
FIGURE 9 | BFC exhibits the characteristics of regulating the “cytokine storm”.

TABLE 2 | The clinical characteristics and corresponding pathological or potential treatment mechanisms of COVID-19 intervened by BFC

| NO. | Type      | Nucleic acid tests | Clinical characteristics | Pathological/treatment mechanisms                                                                 | Population trend | BFC intervention |
|-----|-----------|--------------------|--------------------------|---------------------------------------------------------------------------------------------------|------------------|------------------|
| 1   | Asymptomatic | positive          | No clinical symptoms     | • Immune responses                                                                                 | Young            | Yes              |
|     |           |                    | Others                   | • Antiviral therapy                                                                               |                  |                  |
|     |           |                    |                          | • Others                                                                                         |                  |                  |
| 2   | Mild      | positive           | Mild clinical symptoms   | • Clinical symptom treatment                                                                       | Adult or elderly |                  |
|     |           |                    | Others                   | • Lung inflammation                                                                               |                  |                  |
|     |           |                    |                          | • Immune responses                                                                                |                  |                  |
| 3   | Moderate  | positive           | Clinical symptoms       | • Inflammatory responses                                                                           |                  |                  |
|     |           |                    | Mild pneumonia           | • Cytokine storm                                                                                  |                  |                  |
|     |           |                    | Others                   | • Renin-angiotensin system (RAS), ACE2/ACE target                                                |                  |                  |
| 4   | Severe    | positive           | Clinical features        | • STAT, NF-κB, and MAPK signaling pathways                                                         |                  |                  |
|     |           |                    | Hypoxia                  | • Others                                                                                         |                  |                  |
|     |           |                    | Rapid breath             | • Others                                                                                         |                  |                  |
|     |           |                    | Vital organs injuries    | • Others                                                                                         |                  |                  |
|     |           |                    | Others                   | • Others                                                                                         |                  |                  |
| 5   | Critical  | positive           | Respiratory failure      | • Mechanical ventilation                                                                           |                  |                  |
|     |           |                    | ARDS                     | • ICU monitoring treatment                                                                         |                  |                  |
|     |           |                    | Shock                    | • Medication                                                                                     |                  |                  |
|     |           |                    | Other organ failure      | • Others                                                                                         |                  |                  |
|     |           |                    | Others                   |                                                                                                  |                  |                  |
and protein exudation meanwhile exhibits vascular congestion and inflammatory infiltration, along with local fibrin clusters mixed with mononuclear inflammatory cells and multinucleated giant cells (Tian et al., 2020). Thus, COVID-19 is usually associated with inflammation and characterized as acute inflammatory disease (Manjili et al., 2020). Recent reports indicated that severe COVID-19 patients had numerous evidently higher proinflammation cytokines levels of IL-6, TNF, IL-1, IL-2, IL-17, IFN-γ, G-CSF, MCP-1, IFN-γ-induced protein 10/IP-10, and so on, which was similar to that discovered in patients infected with SARS-CoV and MERS-CoV (Wong et al., 2004; Jiang et al., 2005; Lau et al., 2013; Wang et al., 2020c). Especially, severe forms of COVID-19 mainly refer to inflammatory cytokines IL-1β, TNF, and IL-6 (Fauter et al., 2020). Increased levels of inflammatory cytokines may influence lung function and elevate levels of specific cytokines in the pulmonary alveolar microenvironment may lead to respiratory distress. COVID-19 pneumonia is more prevailing in the elderly than in the younger (Yuki et al., 2020). With the increase of age, the ability to resist infection and protect immune responses reduces and the activity of macrophages declines. The level of pro-inflammatory cytokines increases, so that the severity of SARS-CoV-2 infection will worsen in the elderly (Linehan and Fitzgerald, 2015; Zhou et al., 2020b; De Virgiliis and Di Giovanni, 2020). Therefore, blocking these inflammatory cytokines can benefit patients with COVID-19. Victoriously suppressing inflammation may be a promising therapy for the treatment of COVID-19. What makes sense is that the preliminary try to ameliorate COVID-19 by blocking IL-6 reveals hope (Yang et al., 2020a; Liu et al., 2020; Wang et al., 2020d). Pacha (Pacha et al., 2020) put forward that IL-17 was also a plausible target to decrease the recruitment of neutrophil. Through targeting on IL-17, some factors in ARDS would be suppressed. Studies found that the numbers of neutrophils and macrophages in the airways and blood of COVID-19 patients were increased (Wu et al., 2020a; Du et al., 2020) and the proliferation of macrophages was usually found. Meanwhile, COVID-19 patients showed infiltration of monocytes, lymphocytes, and neutrophils. Bridgewood (Bridgewood et al., 2020) suggested that severe inflammation in COVID-19 could be treated by blocking infiltration of neutrophils, monocytes, and lymphocytes, and decreasing inflammatory cytokines such as TNF-α, IL-6, IL-1β, and chemokines such as IFN, CCL-2 produced by immune cells, and airway epithelial cells. The alkaloids from BFC such as imperaline, verticinone, verticine, peimisine, and delavine could inhibit IL-1β, TNF-α, and IL-6 production, and suppress inflammatory response in the lung, which might help to alleviate ARDS associated with COVID-19 and fibrosis development. The characteristics of regulating the “cytokine storm” that BFC exhibits is shown (Figure 9).

COVID-19 cases have different types such as mild, moderate, severe, and critical cases (Saied et al., 2021). However, there are many COVID-19 patients who tested positive on the RT-PCR test for SARS-CoV-2 but with no typical clinical symptoms or signs (Wu et al., 2020a; Schuetz et al., 2020; Torres et al., 2021). These infections are asymptomatic but they can also transmit the virus to others (Luo et al., 2020a; Huang et al., 2020b). Studies have shown that the viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients and asymptomatic or mild cases combined represent about 40–50% of all infections (Qiu, 2020; Zou et al., 2020). It is a great importance to prevent and control this specific type of asymptomatic infection. Some asymptomatic infections may develop into symptomatic cases, and some will recover by themselves (Gáo et al., 2021). Young cases (<15 years old) of COVID-19 such as children had milder clinical manifestations and nearly half of them were prone to be asymptomatic (Hu et al., 2020; Qiu et al., 2020). The pathological mechanism shows that adults have a much higher prevalence of increased C-reactive protein than do children, and there is less immune damage in children with a much milder immunological response (Qiu et al., 2020). Thus, in asymptomatic patients, SARS-CoV-2 invasion causes only a specific mild immune response. Besides, some researchers supported that antiviral therapy could fasten viral clearance on asymptomatic infections (Hu et al., 2020; Lu et al., 2021). BFC is natural drug sources for respiratory diseases from Fritillaria, and Fritillaria displays antiviral activities such as influenza viruses that cause respiratory diseases (Wang et al., 2021). Therefore, in nucleic acid screening for SARS-CoV-2 positive, diagnosed as asymptomatic infection, it is necessary to intervene by giving BFC for treatment the first time. Age and body condition may play an important role in the severity of COVID-19, which is related to different immune responses and other potential factors. BFC may have a benefit for COVID-19 patients with treatment of typical clinical symptoms such as fever, cough, sore throat, dyspnea, etc., exerting antiviral activities, and regulating of immune responses, inflammatory responses, STAT, NF-kB, and MAPK signaling pathways, the “cytokine storm”, and RAS (Table 2).

SUMMARY AND OUTLOOK

In order to successfully defeat the life-threatening COVID-19, many efforts should be made to target ACE, block the cytokines storm, inhibit inflammation, modulate immunity, improve the symptoms, alleviate lung damage, and prevent pulmonary fibrosis. However, up to now, there is no strong clinical evidence to support the efficacy of any other drugs against COVID-19. Namely, there is still lack of specific drugs as well as therapeutic regimens for the treatment of COVID-19 except for the existing chemical drugs such as intravenous remdesivir and dexamethasone, which have modest effects and can only alleviate some symptoms (Zamla et al., 2016; Bailly and Vergoten, 2020; Li and De Clercq, 2020; Asselah et al., 2021). Nowadays, natural products are attracting more and more attention because they are the source of drugs for the prevention and treatment of many diseases. TCM is considered to be an essential source for discovering natural products with biological activity exerting minimal side effects and showing good results in many difficult problems. Through long-term research on different TCM, numerous valuable compounds have been discovered, such as artemisinin (Klayman, 1985; Tu, 2016), paclitaxel
(Rowinsky and Donehower, 1995; Ma and Hidalgo, 2013), curcumin (Heger et al., 2013; Mirzaei et al., 2016; Shafabakhsh et al., 2019), berberine (Kong et al., 2004; Ortiz et al., 2014; Kong et al., 2020), phloretin (Aliomrani et al., 2016; Ye et al., 2018), and so on. Besides, TCM has achieved good clinical effects in the prevention and treatment of SARS-CoV, MERS-CoV, H1N1, H7N9, Ebola, and other epidemics (Liu et al., 2004; Li and Peng, 2013; Luo et al., 2019b; Lu et al., 2020b; Huang et al., 2021). It was worth noting that in 2003, TCM could shorten the hospitalization, reduce drug side effects, and improve symptoms of patients with SARS (World Health Organization, 2004; Leung, 2007). Furthermore, the genomic and in silico structural characterization of SARS-CoV-2 showed that SARS-CoV-2 and SARS-CoV were closely interrelated. It reminds us that TCM may have potential application value in the current COVID-19 epidemic, and it is a resource for drug discovery against SARS-CoV-2 (Ling, 2020). Currently, in the SARS-CoV-2 pandemic, TCM has played a big role in China’s fight against COVID-19 and in China more than 70,000 patients, or 92% of all confirmed cases on the mainland have received TCM treatment, which has been effective for over 90% of them (Zhang, 2020). In addition to conventional remedy, the intervention of TCM as a complementary therapy has also made a difference. Various medicines applied in TCM system have been recommended for the treatment of COVID-19, and the TCM therapy is on account of the different period of disease and symptoms (National Health Commission of the People's Republic of China; Yang et al., 2020b). TCM is characterized by multiple components, multi-targets, multiple pathways, and exerts poly-pharmacological synergistic effect on the human body (Wang et al., 2012b; Guo et al., 2020b). The secondary plant metabolites in herbal TCM play a comprehensive therapeutic role and have participated in dealing with many complex diseases (Hussein and El Ansary, 2019). As the result of analogous chemical structure of secondary metabolites, there is a synergistic or similar pharmacological effect probably and compounds with similar activities can act on the same targets such as protein family in a synergistic manner against the redundancy of the biological network. Besides, compounds without common targets can also produce similar therapeutic effects on the same disease because different targets could be involved in the same signaling pathway, which is closely related to the pathological process (Ye et al., 2012). Therefore, it is of great significance to find potential Chinese medicines of anti-COVID-19 based on the chemical database of TCM (Luo et al., 2020b; Zhang et al., 2020c; Zhang and Liu, 2020). Even, it is believed, that the combination of
| Pharmacological effects | Components | Models | Details | Positive/negative control | Dose | Application | Ref. |
|-------------------------|------------|--------|---------|---------------------------|------|-------------|------|
| Anti-tussive | Extraction with 80% ethanol solvent | KM mice were exposed to 25% NH4OH produced by a sprayer | Enhanced the latent period of cough and inhibited the cough frequency of mice | Dexamethasone, 15 mg/kg | 0.098–1.475 g/kg | in vivo | Xu et al. (2019) |
| Impatiens, chuanbeoreone, verticinone, verticine | Classical mouse cough model induced by ammonia liquor | Inhibited cough frequency and increased latent period of cough in mice induced by ammonia | Godine phosphate, 30 mg/kg | 1.5–3.0 mg/kg | in vivo | Wang et al. (2011) |
| Impatiens, impenetrable-N-oxide, isoverticine, isoverticine-N-oxide | Mouse cough model induced by ammonia liquor | Inhibited cough frequency and increased latent period of cough in mice induced by ammonia | Godine phosphate, 30 mg/kg | 1.5–4.5 mg/kg | in vivo | Wang et al. (2012a) |
| Verticinone | Computerized target fishing combined with manual database mining | | | | 5.25–10.50 mg/kg | in vivo | Zhang et al. (2020a) |
| Expectorant | Extraction with 80% ethanol solvent | KM mice were exposed to 25% NH4OH produced by a sprayer | Enhanced tracheal phenol red output | Ambroxol hydrochloride, 15 mg/kg | 0.098–1.475 g/kg | in vivo | Xu et al. (2019) |
| Impatiens, verticinone, verticinone | KM mice were treated with intraperitoneal injection of phenol red solution | | | | 1.475 g/kg | in vivo | Wang et al. (2011) |
| Impatiens, impenetrable-N-oxide, isoverticine, isoverticine-N-oxide | KM mice were treated with intraperitoneal injection of phenol red solution | | | | 1.5–4.5 mg/kg | in vivo | Wang et al. (2011) |
| Anti-inflammatory | Verticine | Rat model of lactic acid-induced lung inflammation | Ameliorated inflammation of alveolar and lung interstitial, suppressed pulmonary fibrosis, down-regulated TNF-α levels in serum and TGF-β, NF-κB, CTGF, ERK1/2, and Ral, | Dexamethasone 0.00045 g/kg | 0.005 g/kg | in vivo | Guo et al. (2013) |
| | Verticine | NO-H2S2 cells induced by EGF, PMA, or TNF-α | Inhibited the production of NO, PGE2, COX-2, TNF-α, iNOS, and NOX-5 | | | | |
| | Extractions with 80% ethanol solvent | Xylene was applied to the anterior and posterior surfaces of mice ear | | | | | |
| Impatiens, chuanbeoreone | Ear edema model was induced by the xylene | | | | | | |
| Impatiens, impenetrable-N-oxide, isoverticine, isoverticine-N-oxide | Ear edema model was induced by the xylene | | | | | | |
| Total alkaloid fraction | Models of acetic acid-induced capillary permeability alteration, cotton pellet-induced granuloma formation | | | | | | |
| Verticine, Impatiens | LPS-stimulated RAW 264.7 macrophages | Inhibited the production of NO, TNF-α, IL-1β and the expressions of iNOs and COX-2, decreased NF-κB phosphorylated activation of MAPK signaling pathways, included ERK1/2, p38 MAPK, and JNK/SAPK | Dexamethasone, 10 mg/kg | 0.098–1.475 g/kg | in vivo | Xu et al. (2019) |
| Impatiens, verticinone, verticine, palmitine, dalavine | LPS-induced RAW264.7 macrophage cells | Lowered the production of NO, TNF-α and IL-6, and inhibited the mRNAs expressions of TNF-α and IL-6, inhibited the phosphorylation activation of MAPKs signaling pathways, included ERK1/2, p38 MAPK, and JNK/SAPK | Dexamethasone, 10 mg/kg | 0.098–1.475 g/kg | in vivo | Xu et al. (2019) |
| Verticine | PMA-stimulated human mast-cell (HM-1)1, SD rats were injected anti-DNP IgE and DNP-HA5 | Attenuated the production of pro-inflammatory cytokines IL-6, IL-8 and TNF-α, reduced the expression of MAPKs and the expression of NF-κB, decreased PCA reactions | | | | |
| Verticine | Isolated HKV-23 cells were voltage clamped using a PC 535B patch clamp amplifier in the whole-cell configuration | Inhibited KV1.3 ion channel and blocked the Nav1.7 ion channel | | | | |
| Verticine | Murine models of inflammatory and neuropathic pain induced by acetic acid and rat model of paclitaxel-induced neuropathic inflammatory pain | Inhibited acetic acid-induced writhing response, and the nociceptive responses | 200 mg/kg, 15–60 mg/kg | | | |
| Verticine | IL-1β-induced inflammatory response in mouse articular chondrocytes and animals murine osteoarthritis model | Inhibited the expression of NO, PGE2, COX-2, TNF-α, iNOS, and NOX-5 | | | | |
| | LPS-stimulated RAW264.7 macrophages | Inhibited the production of NO, TNF-α, IL-1β, and the expressions of iNOs and COX-2, decreased NF-κB phosphorylated activation of MAPK signaling pathways | | | | |
| | LPS-induced mastitis model mice and the mouse mammary epithelial cells (MMECs) model stimulated with LPS | Lowered the MPO activity, decreased the production of pro-inflammatory mediator TNF-α, IL-1β, COX-2, and iNOS, Suppressed phosphorylation of AKT, NF-κB, ERK1/2, and p38 signaling pathways | | | | |
| Anti-oxidant | Verticine, verticine, impenetrable-β-D-glucoside, dalavine, palmitine | Down-regulated the production of ROS, up-regulated the level of GSH and expression of HO-1 and Nrf2 | | | | |
| Anti-pulmonary fibrosis | Verticine | LPS-stimulated RAW264.7 macrophages | Ameliorated inflammation of alveolar and lung interstitial, suppressed pulmonary fibrosis, down-regulated TNF-α levels in serum and TGF-β, NF-κB, CTGF, ERK1/2, and Ral, | Dexamethasone 0.00045 g/kg | 0.005 g/kg | in vivo | Guo et al. (2013) |
| Anti-cancer | Verticine | GBM cells model and BALB/c nude mice model was established by the injection of U251 cells into the right hips of each mouse | Inhibited glioblastoma via arresting the cell cycle and blocked autophagy flux, downregulated p-AKT and p-GSK3β, p-AMPK and p-ULK1 | | | |
| | Verticine | Colorectal cancer HT-116 cell | | | | |

(Continued on following page)
### TABLE 3 (Continued) The pharmacological activities of BFC with details.

| Pharmacological effects | Components | Models | Details | Positive/negative control | Dose | Application | Ref. |
|-------------------------|------------|--------|---------|---------------------------|------|-------------|------|
| Verticinone             | Human promyelocytic leukemia HL-60 cells | Inhibited colorectal cancer cell proliferation by inducing apoptosis and autophagy and modulating key metabolic pathways | All-trans retinoic acid (ATRA), 0.1–1.0 μM | 1–10 μg/ml | in vitro | Zheng et al. (2017) |
| Verticinone             | Immortalized keratinocytes and oral cancer cells | Inhibited growth, induced apoptosis and G0–G1 cell cycle arrest, downregulated Bcl-2 and up-regulated Bax, activated caspase-3 through a caspase pathway mediated by mitochondrial damage | | -1–10 μM | in vitro | Yu et al. (2006) |
| Water extraction        | Ovarian and endometrial cancer cells | Decreased in expression of TGF-β isoforms, TGF-β receptors, and SMADs. Inhibited basal and TGF-β1 induced cancer cell proliferation and invasion, with abrogation of stromal, stromal MMPs, NF-κB, and p-FAK expression | | | | Kavandi et al. (2015) |
| Verticinone, verticine  | KM mice model bearing a 7-day tumor with injection subcutaneously in the right axilla of mice for the solid form | Inhibited growth of the solid type of hepatoma in mice | 5-fluorouracil, 10 mg/kg | 1.25–5 mg/kg | in vivo | Li et al. (1996) |
| Water extraction        | Human endometrial cancer cell lines Ishikawa and HEC-1B | Decreased cell growth on soft agar and decreased the invasive potential of cancer cells. Activated caspase-3, G0/G1 phase cell-cycle arrest, and downregulated cyclins D1 and D3 and induction of p27. Downregulated NF-κB, suppressed in LPS-induced ARDS in C57 mice | Dexamethasone sodium phosphate (DMP), 1.0 mg/kg | 3.5–7.0 mg/kg | in vivo | Yeum et al., 2007 |
| Anti-asthma              | BFC extracted by water | Down-regulated the levels of IL-5, IL-13, and IL-4 in the bronchoalveolar lavage fluid and reduced the level of ovalbumin-specific IgE in serum. Lowered the number of eosinophils by inhibiting the recruitment of eosinophil and airway inflammation | Cyclopentolate A, 20 mg/kg | 300 mg/kg | in vivo | Li et al., 2007 |
| Impensine, sinapine A, 3β-sulfoxycumarin | OHO-HM2 and OHO-HM3 cells | AUC as the antagonist of selective mu-selective M3 receptor subtype and selective muscarinic M3 receptor subtype antagonist | 100 μg/ml | 1–10 μg/ml | in vivo | Lin et al. (2006) |
| Anti-COPD               | Impensine | Increased IL-4 expression in the lung by regulating the expression of IL-4, IL-6, TGF-β, TNF-α, NF-κB, TGF-β1, MMP-9, and TIMP-1 | Dexamethasone sodium phosphate (DPS), 1.0 mg/kg | 3.5–7.0 mg/kg | in vivo | Wang et al. (2016) |
| Anti-ARDS               | Total alkaloid fraction of BFC | Suppressed inflammatory cells recruitment and cytokine (TNF and IL-6) production in the bronchoalveolar lavage fluid, and attenuated pathological changes in the lung tissues of ARDS mice | DEX, 5 mg/kg | 15–60 mg/kg | in vivo | Wang et al., 2016 |
| Anti-lung cancer        | Total alkaloids of BFC, perimine, impensine, chuanbeinone | Antiproliferative effect, suppressed tumor angiogenesis and promoted apoptosis through increasing the level of caspase-3 expression | | -10 μM | in vitro | Li et al. (2014) |
| Impensine               | A549 tumor-bearing BALB/c nude mouse model | Suppressed both NSCLC tumor and associated inflammation through an inflammation-cancer feedback loop, inhibited NF-κB activity | | -10 μg/ml | in vivo | Lin et al. (2020) |
| Aqueous extract         | NSCLC A549 cells model and xenograft model of nude mice | Inhibited A549 cells proliferation and colony formation and increased the expressions of STAT 1 and STAT 4 and their target genes IFN-γ and IL-12, triggered Bcl-2/Bax protein ratio of cellular apoptosis, decreased the size of the tumor and induced cytostasis IL-12 and IFN-γ secretion | | -100 μg/ml | in vivo | Li et al. (2020) |
| Total alkaloids of BFC, perimine, impensine, chuanbeinone | Lewis lung carcinoma cells (LLC) model, the mice models were constructed by inoculating LLC cells suspension into the left axilla of C57BL/6 J mice | Inhibited tumor angiogenesis and induced apoptosis through activating caspase-3 | Cyclophosphamide, 20 mg/kg | 30–60 mg/kg | in vivo and in vivo | Wang et al., 2014 |
| Chuanbeinone            | Lewis lung carcinoma cells (LLC) model and LLC cells were subcutaneously inoculated into the left axilla of the mice model | Inhibited tumor angiogenesis and induced apoptosis through activating caspase-3 | | | | Wang et al., 2014 |
| Anti-pulmonary tuberculosis | Fatal Capsule containing BFC | Promoted the absorption of the lesions and the closure of cavities, and accelerated the conversion of sputum bacteria to negative, enhanced the immunity, and promoted the inflammation | | | | Wang et al. (2017) |
|Nidebeixia containing BFC | Tuberculosis mice models infected with Mycobacterium tuberculosis H37Rv | Improved the pulmonary lesions to return to normal pulmonary structure | 22.5 μg/M. vaccae vaccine | 1.5–66 mg/kg | in vivo | Liang et al. (2017) |
### TABLE 4 | The main related compounds of BFC’s effect on respiratory diseases

| Components | No. | Compounds | 2D structure | No. | Compounds | 2D structure | No. | Compounds | 2D structure |
|------------|-----|-----------|--------------|-----|-----------|--------------|-----|-----------|--------------|
| Alkaloids  | 1   | Verticinone | ![2D structure](image1) | 2   | Imperialine | ![2D structure](image2) | 3   | Isoverticine-β-N-oxide | ![2D structure](image3) |
|            | 4   | Verticine  | ![2D structure](image4) | 5   | Chuanbeinone | ![2D structure](image5) | 6   | Imperialine-β-N-oxide | ![2D structure](image6) |
|            | 7   | Isoverticine | ![2D structure](image7) | 8   | Peimisine  | ![2D structure](image8) | 9   | Imperialine-3-β-D-glucoside | ![2D structure](image9) |
|            | 10  | Delavine  | ![2D structure](image10) | 11  | Sinperine A | ![2D structure](image11) |     |                       |               |

(Continued on following page)

### TABLE 5 | The main related targets of BFC effect on respiratory diseases

| No. | Targets (PDB ID) | 3D structure | No. | Targets (PDB ID) | 3D structure | No. | Targets (PDB ID) | 3D structure | No. | Targets (PDB ID) | 3D structure |
|-----|------------------|--------------|-----|------------------|--------------|-----|------------------|--------------|-----|------------------|--------------|
| 1   | IL-1β (2WRY)     | ![3D structure](image12) | 2   | TNF-α (5MU8)     | ![3D structure](image13) | 3   | IFN-γ (6F1E)     | ![3D structure](image14) | 4   | STAT1 (1YVL)     | ![3D structure](image15) |
| 5   | IL-4 (2B8U)      | ![3D structure](image16) | 6   | STAT4 (1BGF)     | ![3D structure](image17) | 7   | AKT (8S9W)       | ![3D structure](image18) | 8   | iNOS (1DD7)      | ![3D structure](image19) |
| 9   | IL-5 (1HUL)      | ![3D structure](image20) | 10  | MMP-9 (2OW1)     | ![3D structure](image21) | 11  | MAPK (3UI6)      | ![3D structure](image22) | 12  | TGF-β1 (1KLD)    | ![3D structure](image23) |
| 13  | IL-6 (7NXZ)      | ![3D structure](image24) | 14  | MMP-13 (1FLS)    | ![3D structure](image25) | 15  | HO-1 (1N6)       | ![3D structure](image26) | 16  | Caspase-3 (1RHJ) | ![3D structure](image27) |
| 17  | IL-8 (1ICW)      | ![3D structure](image28) | 18  | TIMP-1 (1UEA)    | ![3D structure](image29) | 19  | Nrf2 (7K2L)      | ![3D structure](image30) | 20  | Bcl-2 (5JSN)     | ![3D structure](image31) |
| 21  | MUC5AC mucin gene (5AJO) | ![3D structure](image32) | 22  | PGE2 (2PBu)      | ![3D structure](image33) | 23  | COX-2 (5FDQ)     | ![3D structure](image34) | 24  | Bax (4BD6)       | ![3D structure](image35) |

(Continued on following page)
TCM and Western medicine might be a potent therapeutic approach for COVID-19 (Zhang et al., 2004; Liu et al., 2020e). BFC, as an important edible and medicinal plant, has strong bioactive material basis. Modern pharmacological research shows that the extracts, alkaloid, or monomer alkaloids of BFC have extraordinary anti-inflammatory properties, which are helpful for the treatment of inflammation of the respiratory system. For example, BFC alkaloids imperialine, chuanbeinone, verticine, verticinone, and peimisine are used to treat lung-related diseases such as lung inflammation, COPD, ARDS, tuberculosis, and lung cancer. BFC has also been developed into herbal dietary supplement products such as the most popular Nin Jiom Pei Pa Koa used to relieve sore throat, cough, etc., which is mainly Fritillaria-based herbal extracts of sucrose syrup (Cunningham et al., 2018; Drugs.com, 1064b). Through this review, it is found that the therapeutic mechanism of BFC on respiratory diseases exerts the characteristics of multi-components, multi-targets, and multi-signaling pathways. The main related signaling pathways of BFC’s effect on respiratory diseases are shown (Figure 10). The pharmacological activities of BFC with details are summarized and shown in Table 3. The main related compounds and targets of BFC effect on respiratory diseases are shown as follows (Tables 4, 5). SARS-CoV-2 will cause inflammatory responses characterized by damage of deep airway and alveolar; meanwhile, the patients develop symptoms such as fever, dry cough, and fatigue, and the lungs eventually show fibrosis and exudative lesions. BFC has a good therapeutic effect on

| No. | Targets (PDB ID) | 3D structure | No. | Targets (PDB ID) | 3D structure | No. | Targets (PDB ID) | 3D structure | No. | Targets (PDB ID) | 3D structure |
|-----|----------------|-------------|-----|----------------|-------------|-----|----------------|-------------|-----|----------------|-------------|
| 25  | IL-12 (1F42)   |             | 26  | p38 (1WFC)     |             | 27  | ERK1/2 (6G9A)  |             | 28  | NF-κB (p65/ P50) (1LES) |             |
| 29  | IL-13 (1IJZ)   |             | 30  | FasL (SL19)    |             | 31  | MDR (3G5U)    |             | 32  | Aggrecan (1TDQ) |             |
| 33  | ACE (1O86)     |             | 34  | MPO (7LAG)     |             | 35  | ERCC1 (2A1I)  |             | 36  | Kv1.3 ion channel (4BG3) |             |
| 37  | JNK/SAPK (4UX9) |             | 38  | IgE (1FP5)     |             | 39  | ADAMTS-5 (3B82) |             | 40  | Nav1.7 ion channel (6J8G) |             |
| 41  | Collagen-II (6HG7) |         | 42  | muscarinic M2 receptor (5ZK3) |             | 43  | Muscarinic M3 receptor (4DAJ) |             | 44  | Collagen-II (SNfR) |             |
| 45  | GSH            |             | 46  | histamine      |             | 47  | ROS O2-, H2O2, OH |             | 48  | PCA reactions |             |
| 49  | LRP            |             | 50  | CTGF           |             | 51  | PPKCB         |             | 52  | ECM            |             |
respiratory diseases to treat cough, sputum, asthma, bronchial inflammation, ARDS, COPD, and pneumonia due to its beneficial antitussive, expectorant, anti-inflammatory, anti-asthma, anti-oxidant, and anti-pneumonic effects. Then, we speculate that by utilizing the alkaloids in BFC to act on lung injury, lung inflammation, ACE target, immunoregulation, oxidative stress, and so on, is there a potential drug in the treatment of COVID-19? The reasons BFC may become a potential drug and be beneficial for COVID-19 are as follows:

1. The diseases of the elderly and the patients with basic diseases, such as the immunocompromised are often serious and dangerous after being infected, and the mortality rate of the elderly over 65 years old is distinctly higher (Zheng et al., 2020b), while BFC is considered to be effective for the treatment of the elderly and children.

2. The clinical manifestations of COVID-19 are fever, dry cough, phlegm, shortness of breath, etc., while BFC can manage the symptoms such as fever, dry cough, phlegm, asthma, and sore throat. Even as for the asymptomatic infections, it is necessary to intervene by giving BFC to treat the first time due to its antiviral activities, and regulation of immune responses in the early stage.

3. SARS-CoV-2 virus infection mainly affects the lungs, and the infected patients begin with flu-like symptoms, quickly developing to ARDS, while BFC exhibits significantly therapeutic effects on ARDS.

4. Lung inflammation is one of the characteristics of COVID-19, while BFC has evidently anti-inflammatory activity and obviously alleviates lung inflammation.

5. In the “cytokine storm” of SARS-CoV-2 infection, there is an intense inflammatory response with the release of abundant increased pro-inflammatory cytokines such as IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α, and VEGF in COVID-19 patients, while BFC can inhibit IL-1β, IL-8, IFN-γ, TNF-α, IL-6, IL-13, IL-4, NO, PGE2, COX-2, and iNOS production to suppress inflammatory response.

6. There is a serious immune imbalance in COVID-19 patients and the immune response is dysregulated and abnormally activated, while BFC has an effect on immunomodulation with regulating the immune related pathways, involving STAT, NF-kB, and MAPK signaling pathways.

7. ACE is involved in the disease process of COVID-19 and ACE inhibitors are considered to be a promising drug to treat COVID-19, while the alkaloids in BFC can inhibit the activity of ACE in a dose-dependent manner.

In summary, BFC has unique advantages in the prevention and treatment of respiratory diseases, which is worthy of in-depth excavation and application. For COVID-19, may it be a potential drug? This review expounds the potentiality theoretically, but it still needs to be verified by a large number of experiments. COVID-19 has become a major threat to the health of people all over the world; we hope this review can provide insights on the drug discovery of anti-COVID-19.

**AUTHOR CONTRIBUTIONS**

YQ and JZ contributed the conception of the review. YQ, LL, ZY, SC, JY, JL, LZ, and QY summarized and analyzed the literatures. YQ drafted the manuscript, prepared tables, and drew the figures. JZ critically revised the manuscript. All authors read and approved the submitted version of the manuscript.

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