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Review article

Xuanfei Baidu decoction in the treatment of coronavirus disease 2019 (COVID-19): Efficacy and potential mechanisms

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide and become a major global public health concern. Although novel investigational COVID-19 antiviral candidates such as the Pfizer agent PAXLOVID™, molnupiravir, baricitinib, remdesivir, and favipiravir are currently used to treat patients with COVID-19, there is still a critical need for the development of additional treatments, as the recommended therapeutic options are frequently ineffective against SARS-CoV-2. The efficacy and safety of vaccines remain uncertain, particularly with the emergence of several variants. All 10 versions of the National Health Commission's diagnosis and treatment guidelines for COVID-19 recommend using traditional Chinese medicine. Xuanfei Baidu Decoction (XFBD) is one of the "three Chinese medicines and three Chinese prescriptions" recommended for COVID-19. This review summarizes the clinical evidence and potential mechanisms of action of XFBD for COVID-19 treatment. With XFBD, patients with COVID-19 experience improved clinical symptoms,

Abbreviations: 3CLpro, 3-Chymotrypsin-like protease; ACE2, angiotensin converting enzyme 2; ALI, acute lung injury; ALPs, atractylodes polysaccharides; AO-I, atractylenolide I; ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; CCL, CC-chemokine ligand; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CXCL, chemokine ligand; DPPH, 1,1-diphenil-2-picrylhydrazyl; ERK, extracellular signal-regulated kinase; ESEs, Ephedra sinica extracts; ICU, intensive care unit; IFV, inhibit influenza virus; IL, interleukin; JAK/STAT, Janus kinase/signal transducer and activator of transcription; JAK2, Janus kinase 2; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; MIC, minimum inhibitory concentration; MPO, myeloperoxidase; NF-κB, nuclear factor-kappa B; NK, natural killer; NLRP3, nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3; NO, nitric oxide; PA, patchouli alcohol; PD-1, programmed death-1; PGE2, prostaglandin E2; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; PM2.5, particulate matter 2.5; RCT, randomized controlled trial; RdRp, RNA-dependent RNA polymerases; ROS, reactive oxygen species; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOD, superoxide dismutase; STAT3, signal transducer and activator of transcription 3; TCM, traditional Chinese medicine; TFs, total flavonoids; Th, T helper; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; WBC, white blood cell; XFBD, Xuanfei Baidu Decoction.

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shorter hospital stay, prevention of the progression of their symptoms from mild to moderate and severe symptoms, and reduced mortality in critically ill patients. The mechanisms of action may be associated with its direct antiviral, anti-inflammatory, immunomodulatory, antioxidative, and antimicrobial properties. High-quality clinical and experimental studies are needed to further explore the clinical efficacy and underlying mechanisms of XFBD in COVID-19 treatment.

1. Introduction

Since December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which began to spread worldwide, has become a major global public health challenge [1–3]. As of December 31st, 2022, the number of COVID-19 cases was growing continuously, with more than 657 million confirmed cases, more than 6 million deaths and approximately 631 million recovered individuals across 223 countries or territories [4]. The main clinical symptoms of patients with COVID-19 are fever, fatigue, and dry cough, which can progress to pneumonia, acute respiratory distress syndrome (ARDS), acid-base imbalance, and even death from multiorgan failure [5–9].

Despite intense research efforts worldwide, only a few novel investigational COVID-19 antiviral candidates, such as the Pfizer agent PAXLOVID™ (PF-07321332) [10], molnupiravir (MK-4482/EIDD-2801) [11,12], baricitinib [13,14], remdesivir [15], and favipiravir [16], are currently used to treat patients with COVID-19. There is still a great need to develop additional treatments, as the current recommended therapeutic options are insufficient against SARS-CoV-2 in many cases [10,17–20]. Although *in vitro* studies [21–24] have identified some compounds that act against SARS-CoV-2, their efficacy and safety in treating patients with COVID-19 remain to be confirmed [25–27]. Vaccines against COVID-19 have been approved in several countries; however, there is still a lack of convincing evidence regarding the efficacy and safety of these vaccines, particularly with the emergence of several SARS-CoV-2 variants [28]. Therefore, there is an urgent need to develop new therapeutic strategies for the effective management of COVID-19.

Traditional Chinese medicine (TCM) has a history of more than 2000 years and is currently gaining popularity as an alternative therapy for various communicable and noncommunicable diseases [29]. TMC has played a significant role in combating the COVID-19 pandemic, with the advantage of multiple organ protection [30]. In China, the National Health Commission has released 10 versions of COVID-19 diagnosis and treatment protocols, all of which recommend TCM treatment. Xuanfei Baidu Decoction (XFBD) is one of the "three Chinese medicines and three Chinese prescriptions" recommended for COVID-19. It has been reported that XFBD has significant advantages in accelerating clinical symptom relief, shortening hospital stay, and delaying the progression of patients with COVID-19 from mild or moderate to severe symptoms [31]. Recently, several published reports have suggested that XFBD can inhibit viral infection and reduce the inflammatory response in patients with severe COVID-19 [32,33].

Network pharmacological analysis revealed that XFBD has antiviral, anti-inflammatory, immunomodulatory, and antioxidant properties [34–36]. However, the underlying mechanisms of XFBD in treating COVID-19 remain unclear. This review summarizes the available clinical evidence on the use of XFBD in the treatment of COVID-19 and explores its potential mechanisms.

2. Methods

2.1. Search strategy

Two independent reviewers searched for relevant studies in the following seven databases up to December 2022: Embase, PubMed, the Cochrane Library, the Chinese Science and Technology Journals Database (VIP), the Chinese National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (SinoMed), and the Wanfang Database. The search terms included Xuanfeibaidu, Xuanfei Baidu, Xuan Fei Bai Du, TCM herbs contained in XFBD (such as *Ephedra sinica* Stapf, ephedra, Ma Huang, Mahuang, etc.), antiinflammat*, anti-inflammat*, antioxida*, anti-oxida*, antiviral, anti-viral, antimicrobial, anti-microbial, antibacteria*, anti-bacteria*, and immun*. There were no language restrictions.

2.2. Eligibility criteria

Inclusion criteria: (1) XFBD and the 13 TCM herbs it contains; (2) mechanisms of action: antiviral, anti-inflammatory, immunomodulatory, antioxidative, antibacterial, and antifungal properties. Exclusion criteria: (1) conference proceedings; (2) irrelevant to the study topic.

2.3. Study selection and data extraction

After excluding duplicate literature, two independent reviewers (TM and JD) screened for eligible literature first by title or abstract and then by full text. Two other reviewers (SX and LY) independently extracted relevant information from the included studies. Any disagreement regarding the study selection and data extraction was resolved by consulting the third reviewer (SS).

3. Results

3.1. Study selection

Initially, a total of 7972 potential documents were identified, of which 3314 were removed due to duplication. Then, 3360 papers were excluded by reading the title and abstract, and 1191 papers were excluded by reading the full text. The PRISMA flowchart of the study selection process is shown in Fig. 1.

3.2. The composition of XFBD

XFBD is a novel TCM prescription for COVID-19 that was proposed by academician Zhang Boli and Professor Liu Qingquan. The prescription is composed of 13 TCM herbs [37] and originated from four classic TCM recipes, including Maxing Shigan decoction, Maxing Yigan decoction, Qianjin Weijing decoction, and Tingli Dazao Xiefei decoction [38]. The TCM herbs and dosages used were as follows: *Ephedra sinica* Stapf (Ma Huang; Stem), 6 g; *Prunus armeniaca* L (Xing Ren; Seed), 15 g; *Gypsum fibrosum* (Sheng Shi Gao; inorganic substance), 30 g; *Coix lacryma-jobi* L (Yi Ren; Seed), 30 g; *Atractylodes lancea* (Thunb.) DC. (Cang Zhu; Root), 10 g; *Pogostemon cablin* (Blanco) Benth (Huo Xiang; Root), 15 g; *Artemisia annua* L (Qing Hao; Whole plant except root), 12 g; *Reynoutria japonica* Houtt (Hu Zhang; Root), 20 g; *Verbena officinalis* L (Ma Bian Cao; Whole plant except root), 30 g; *Phragmites communis* Trin (Lu Gen; Root), 30 g; *Lepidium apetalum* Willd (Ting Li Zi; Seed), 15 g; *Citrus* × *reticulata* Blanco (Ju Hong; Fruit), 15 g; *Glycyrrhiza uralensis* Fisch. ex DC. (Zhi Gan Cao; Root), 10 g. Fig. 2 shows the processed raw materials of XFBD.

3.3. Clinical evidence of XFBD in COVID-19 treatment

An observational study investigated the clinical efficacy of XFBD in 41 patients with severe or critical COVID-19 [39]. All 41 patients received XFBD (150 ml twice daily) combined with conventional western medicine for 14 days. The results showed that the patients experienced an improvement in their clinical symptoms, including fever (17.0% vs. 1.0%), cough (37.0% vs. 15.0%), chest tightness/shortness of breath (26.0% vs. 9.0%), wheezing (19.0% vs. 5.0%), bodily pain (10.0% vs. 0.0%), fatigue (18.0% vs. 6.0%), and poor appetite (28.0% vs. 7.0%), after 14 days of treatment. Moreover, hematological markers improved compared to those before treatment, including white blood cell (WBC) counts (5.6 [4.3–7.2] vs. 6.1 [5.5–7.8], $P < 0.05$), C-reactive protein (CRP) (21.5 [5.3–56.6] vs. 5.0 [1.4–13.2], $P < 0.05$), fibrinogen (3.6 [3.1–4.4] vs. 2.8 [2.3–3.2], $P < 0.05$), and lactate dehydrogenase (LDH) (246.3 [175.3–357.4] vs. 201.5 [120.3–233.5], $P < 0.05$). In one randomized controlled trial (RCT), 42 patients with COVID-19 were enrolled and randomly assigned to the XFBD (22 patients received XFBD plus conventional medicine, XFBD: 200 ml twice per day) and control groups (20 patients received conventional medicine alone) [40]. All patients were treated for seven days. The results showed that the rate of clinical symptom disappearance was significantly higher in the XFBD group than in the control group, such as fever (90.0% vs. 72.3%, $P = 0.043$), cough (76.5% vs. 38.9%, $P = 0.028$), fatigue (78.9% vs. 42.9%, $P = 0.039$), and poor appetite (75.0% vs. 22.2%, $P = 0.024$). The reduction rate of CRP levels (83.3% vs. 29.4%, $P = 0.002$) and erythrocyte sedimentation rate (84.2% vs. 37.5%, $P = 0.006$) in the XFBD group were significantly superior to those in the control group. Based on XFBD prescriptions, XFBD granule, an oral Chinese patent medicine, was approved for marketing by the China State Food and Drug Administration in March 2021. In patients with COVID-19 infected with the omicron variant, a recent study investigated the clinical efficacy of XFBD granule [41]. Forty Patients with mild or moderate COVID-19 omicron variant were administered XFBD granule (one dose of the study drug, twice per day). The results showed that XFBD granule could improve clinical symptoms (such as cough, fever, headache, fatigue, and sore throat), reduce the serum level of the inflammatory marker procalcitonin, and shorten hospital stay. Another trial involving 180 patients with COVID-19 omicron strain evaluated the efficacy and safety of XFBD granule [42]. In the XFBD group, 120 patients received XFBD granule in combination with conventional treatment, whereas 60 patients in the control group received conventional

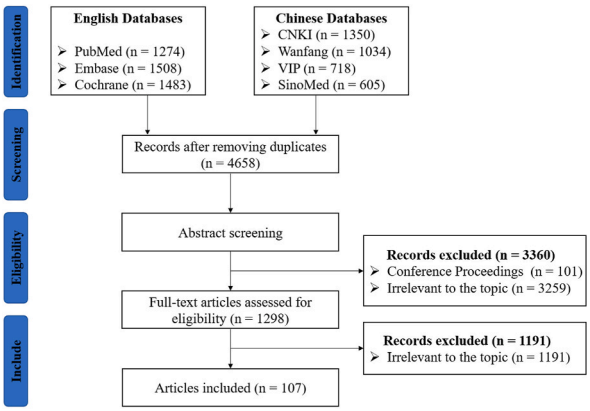

Fig. 1. PRISMA flowchart of the study selection process.

Fig. 2. The processed raw materials of the Xuanfei Baidu Decoction (the images are collected from the Internet, with no conflict of interest).

treatment. Both the viral nucleic acid-negative conversion time (8 [6,10] vs. 10 [7,11], $P < 0.05$) and the length of hospital stay in the XFBD group were shorter than those in the control group (11 [9,13] vs. 12 [10.5, 13.5], $P < 0.05$). TCM syndrome (including cough, coughing sputum, sore throat, and dry throat) was more prevalent in the XFBD group than in the control group. Table 1 shows the characteristics of the clinical trials of XFBD.

3.4. Potential mechanisms of XFBD for COVID-19

3.4.1. Antiviral effects

SARS-CoV-2 is a single-stranded RNA virus that can encode four structural proteins, 16 nonstructural proteins, and 9 accessory proteins. The main structural proteins include the spike (S), envelope, membrane, and nucleocapsid proteins [43]. SARS-CoV-2 enters host cells by binding its spike protein to the angiotensin converting enzyme 2 (ACE2) receptor and subsequently releases viral RNA for replication and transcription [44]. A variety of nonstructural proteins, including papain-like protease (Nsp 3), main protease (Nsp 5), 3-Chymotrypsin-like protease (3CLpro), and RNA-dependent RNA polymerases (RdRp, Nsp 12), are translated under the action of host cell proteases. RdRp is responsible for replicating SARS-CoV-2 RNA and is regulated by 3CLpro [45,46].

XFBD exerts anti-SARS-CoV-2 effects via multiple pathways (Fig. 3 and Table 2 show the potential antiviral mechanisms of XFBD). Network pharmacology suggested that XFBD strongly binds to 3CLpro and ACE2, indicating that XFBD may directly suppress SARS-CoV-2 by blocking its entry into host cells and inhibiting its replication [35,36]. In addition, some *TCM herbs* present in XFBD exhibit potential activity against SARS-CoV-2. Lv et al. identified three active ingredients of *Ephedra sinica* Stapf, ephedrine, pseudoephedrine, and methylephedrine, with potential anti-SARS-CoV-2 activity by surface plasmon resonance analysis. Binding assays revealed that these three active ingredients could specifically bind with ACE2 [47]. Mei et al. demonstrated that quinoline-2-carboxylic acids in *Ephedra sinica* Stapf could block the infectivity of SARS-CoV-2 S protein-pseudoviruses to human airway epithelial cells and 293T cells transfected with ACE2 *in vitro* [48]. Several *Ephedra sinica* Stapf-related drug pairs also have potential anti-SARS-CoV-2 activity.

Table 1
Characteristics of the clinical trials of XFBD[a].

Studies	Design	Sample Size (T[b]/C[c])	Intervention		Disease Stage	Outcome Measures	Trial Identification Numbers
			T	C			
Li et al., 2022 [39]	before and after comparison	41/-	XFBD (Decoction) + CWM[d]	/	severe or critical severe	① cure rate ② length of hospital stay ③ improvement of pulmonary CT[e] ④ laboratory indicators at day 14 (WBC[f], NEUT%[g], LYM[h], PLT[i], CRP[j], D-dimer, FIB[k], LDH[l], PCT[m], PT[n], CK[o], AST[p], ALT[q], TBiL[r], Cr[s], and BUN[t]) ⑤ improvement of TCM[u] symptoms at days 7 and 14 ⑥ AE[v]	/
Xiong et al., 2020 [40]	RCT[w]	22/20	XFBD (Decoction) + CWM	CWM	mild or severe	①disappearance rate of main symptoms (fever, fatigue, and cough) ②disappearance rate of secondary symptoms (loss of appetite, shortness of breath, chest tightness, insomnia, pharyngalgia, chill, headache, nausea, vomiting, and diarrhea) ③ laboratory indicators (WBC, LYM, CRP, and ESR[x]) ④ safety outcomes	ChiCTR2000034795
Feng et al., 2022 [41]	before and after comparison	40/-	XFBD (Granule)	/	mild or moderate	① improvement of TCM symptoms ② laboratory indicators (WBC, NEUT%, LYMPH%[y], LYM, PLT, CRP, IL-6[z], PCT, D-Dimer, and ABG[aa]) ③ duration of nucleic acid turn negative ④ length of hospital stay ⑤ improvement of pulmonary CT ⑥safety outcomes (liver function and renal function)	/
Pang et al., 2022 [42]	non-RCT	120/60	XFBD (Granule) + CWM	CWM	mild or moderate	① duration of nucleic acid turn negative ② length of hospital stay ③ symptom disappearance rate at day 7 (fever, fatigue, cough, coughing sputum, sore throat, and dry throat) ④ incidence of severe cases ⑤ case-fatality rate ⑥ safety outcomes (AE, liver function, and renal function)	/

[a] XFBD: Xuanfei Baidu.
[b] T: test group.
[c] C: control group.
[d] CWM: conventional western medicine.
[e] CT: computed tomography.
[f] WBC: white b*lood cells.*
[g] NEUT%: neutrophil percentage.
[h] LYM: absolute lymphocyte value.
[i] PLT: platelet count.
[j] CRP: C-reactive protein.
[k] FIB: fibrinogen.
[l] LDH: lactate dehydrogenase.
[m] PCT: procalcitonin.
[n] PT: prothrombin time.
[o] CK: creatine kinase.
[p] AST: aspartate aminotransferase.
[q] ALT: alanine aminotransferase.
[r] TBiL: total bilirubin.
[s] Cr: creatinine.
[t] BUN: blood urea nitrogen.
[u] TCM: traditional Chinese medicine.
[v] AE: adverse event.
[w] RCT: randomized controlled trial.
[x] ESR: erythrocyte sedimentation rate.
[y] LYMPH%. lymphocyte percentage.

[z] IL: interleukin.
[aa] ABG: arterial blood gas.

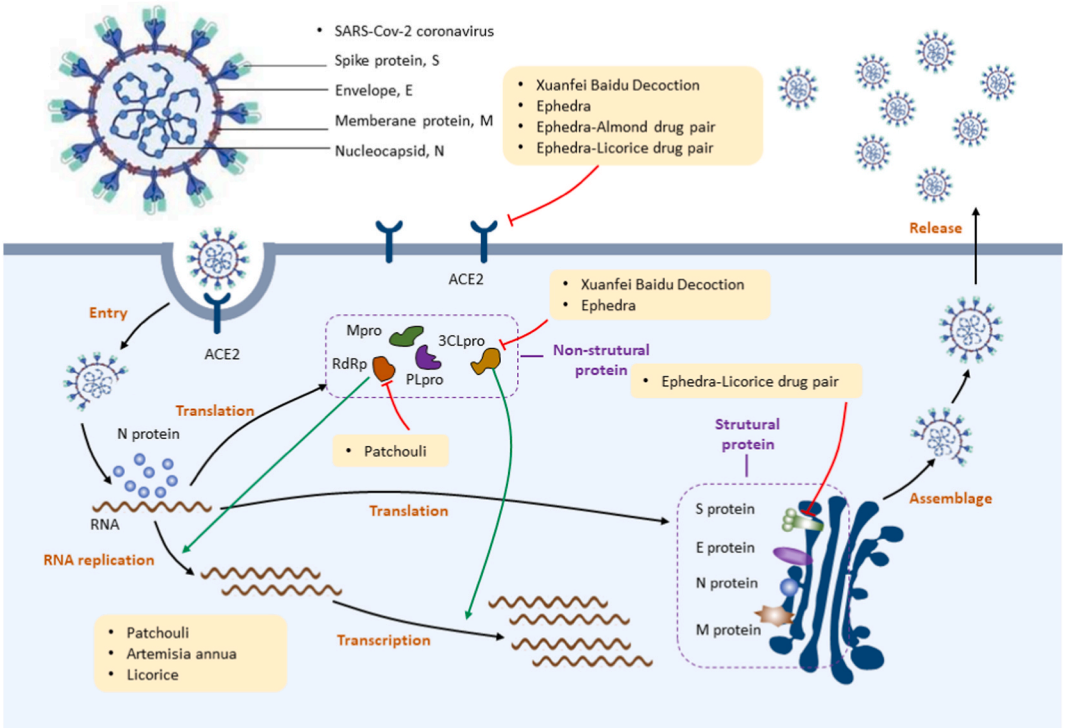

Fig. 3. Anti-SARS-CoV-2 mechanisms of Xuanfei Baidu Decoction and its traditional Chinese medicine herbs.

Molecular docking showed that both *Ephedra sinica* Stapf-*Glycyrrhiza uralensis* Fisch.ex DC. and *Ephedra sinica* Stapf-*Prunus armeniaca* L drug pairs had a high affinity for 3CLpro and ACE2. The *Ephedra sinica* Stapf-*Glycyrrhiza uralensis* Fisch.ex DC. drug pair also showed strong binding to the 3CLpro S protein [49,50]. *Pogostemon cablin* (Blanco) Benth, *Artemisia annua* L, and *Glycyrrhiza uralensis* Fisch.ex DC. have been shown to exert potential anti-SARS-CoV-2 activity by inhibiting replication of the virus [51,52]. Molecular docking results revealed good binding ability of patchouli alcohol (PA) and RdRp, suggesting an anti-SARS-CoV-2 effect of PA [51]. Michaelis et al. found that glycyrrhizin exerted antiviral activity in verum cell models infected with plasma samples from SARS patients by inhibiting viral replication and blocking viral adsorption and penetration in the early stages of the replication cycle [53]. A recent *in vitro* study assessed the anti-SARS-CoV-2 effect of nine artemisinin-related compounds and found that arteannuin B, artesunate, and dihydroartemisinin showed high anti-SARS-CoV-2 potential. Arteannuin B could inhibit SARS-CoV-2 replication in a dose-dependent manner at the postentry step of its infection [52].

Furthermore, TCM herbs have shown antiviral activity against several respiratory viruses. *Ephedra sinica* Stapf and its active ingredients have antiviral properties against influenza and respiratory syncytial virus [54–56]. Hou et al. found that ephedrannin B suppressed the expression of the respiratory syncytial virus infection fusion gene and viral replication in RSV-infected BEAS-2B cells [56]. Glycyrrhizin and its metabolite, glycyrrhizic acid, have been experimentally proven to exert antiviral activity against human parainfluenza virus type 2 and influenza A virus (such as H1N1 and H5N1) by inhibiting viral replication [53,57–61]. PA was found to strongly inhibit influenza virus (IFV) replication by directly inactivating virus particles and interfering with the early stages of virus adsorption [62–64]. Yu et al. discovered that the anti-IFV actions of PA might occur through the cellular phosphatidylinositol-3-kinase/protein kinase B (PI3K/Akt) and extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) signaling pathways [62]. In addition, PA also showed an anti-IFV effect *in vivo*. In a mouse model infected with influenza A virus, PA (20–80 mg/kg, five days) reduced the quantity of IFV in the lungs [65].

3.4.2. Anti-inflammatory effects

Intensive care unit (ICU) patients had higher plasma levels of inflammatory factors, such as interleukin (IL)-2, IL-7, IL-10, tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), than non-ICU patients, indicating that the "cytokine storm" was correlated with the severity of COVID-19 [7]. Cytokine storms lead to extensive pulmonary edema, capillary leakage, and alveolar structure destruction, eventually developing into acute lung injury (ALI), ARDS, and even respiratory and circulatory failure or death [7,66].

Network pharmacology revealed that XFBD exhibits anti-inflammatory properties by regulating the MAPK, Janus kinase/signal

Table 2
Antiviral effects of XFBD[a] and its major herbs.

Herbal Medicine	Components	Targets/ Pathway	Virus Type	Model	Mechanisms	Source
Ephedra sinica Stapf	Ephedrine PseudoephedrineMethylephedrine	/	SARS-CoV-2[b] pseudovirus	ACE2[c] cells	Binding to ACE2 and inhibiting SARS-CoV-2 spike pseudovirus into ACE2 cells	Lv et al., 2021 [44]
Ephedra sinica Stapf	Quinoline-2-carboxylic acids	/	SARS-CoV-2 S protein-pseudoviruses	Calu-3[d] and 293T-ACE2[e]	Reducing the ability of SARS-CoV-2 S protein-pseudoviruses to infect Calu-3 and 293T-ACE2	Mei et al., 2021 [48]
Ephedra sinica Stapf	Ephedrannin B	/	RSV[f]	RSV-infected BEAS-2B cells	Suppressing the expression of RSV infection fusion gene and viral replication	Hou et al., 2020 [56]
Artemisia annua L	Arteannuin B Artesunate Dihydroartemisinin	/	SARS-CoV-2	African green monkey kidney Vero E6 cells	Inhibiting SARS-CoV-2 replication at the postentry step of its infection	Cao et al., 2020 [52]
Glycyrrhiza uralensis Fisch.ex DC.	Glycyrrhizin	/	SARS-associated coronavirus (FFM-1 and FFM-2)	Vero cells	Inhibiting viral replication and blocking viral adsorption and penetration in the initial stages of the replication cycle	Cinatl et al., 2003 [53]
Glycyrrhiza uralensis Fisch.ex DC.	Glycyrrhizin	NF-κB[g], JNK[h], and p38 signaling pathways	H5N1 virus	Lung epithelial (A549) cells	Interfering with H5N1 virus replication	Michaelis et al., 2011 [57]
Pogostemon cablin (Blanco) Benth	Patchouli alcohol	PI3K/Akt[i] and ERK/MAPK[j] signaling pathways	Influenza virus	MDCK cells infected with Vir 09, NWS or PR8	Inactivating virus particles directly and interfering with the initial phase after virus adsorption	Yu et al., 2019 [62]
Pogostemon cablin (Blanco) Benth	Patchouli alcohol	/	Influenza virus	Pneumonia mice infected with IAV[k]	Inhibiting IAV multiplication in mice lungs	Li et al., 2012 [65]

[a] XFBD: Xuanfei Baidu Decoction.
[b] SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
[c] ACE2: angiotensin-converting enzyme 2.
[d] Calu-3: human airway epithelial cells.
[e] 293T-ACE2: 293T cells transfected with ACE2.
[f] RSV: respiratory syncytial virus.
[g] NF-κB: nuclear factor kappa B.
[h] JNK: Jun N-terminal kinase.
[i] PI3K/Akt: phosphatidylinositol-3-kinase/protein kinase B.
[j] ERK/MAPK: extracellular signal-regulated kinase/mitogen-activated protein kinase.
[k] IAV: influenza A virus.

transducer and activator of transcription (JAK/STAT), nuclear factor-kappa B (NF-κB), and PI3K/Akt signaling pathways [34–36]. XFBD has been experimentally proven to exert anti-inflammatory effects both *in vivo* and *in vitro* (Fig. 4 and Table 3 show the potential anti-inflammatory mechanisms of XFBD). In lipopolysaccharide (LPS)-induced ALI mice, Wang et al. discovered that XFBD could improve pulmonary injury by inhibiting inflammatory cell infiltration and the release of IL-6, TNF-α, and IL1-beta (IL1-β). This mechanism may be related to regulation of the programmed death-1 (PD-1)/IL-17A signaling pathway [67]. Another experiment demonstrated that XFBD could reduce bleomycin-induced pulmonary fibrosis and macrophage-induced inflammation by inhibiting the IL-6/STAT3 signaling pathway [68]. Additionally, modulation of the NF-κB signaling pathway is crucial because inhibition of NF-κB improves survival in SARS-coronavirus-infected mice [69]. Li et al. investigated the anti-inflammatory effect of XFBD *in vitro*, focusing on A549 cells and THP1-derived macrophages. XFBD showed little anti-inflammatory effect in A549 cells. In the THP1-derived macrophage model, XFBD showed no apparent cytotoxicity at concentrations up to 10% (v/v). In contrast, at either 1% (v/v) or 5% (v/v) concentration, XFBD markedly inhibited the production of proinflammatory markers, including IL-6, TNF-α, CCL2, and chemokine ligand 10 (CXCL-10), which could be due to inhibition of the NF-kB signaling pathway. The aforementioned results suggested that XFBD might exert a protective effect in patients with COVID-19 by regulating the macrophage inflammatory response [70]. Some TCM herbs present in XFBD, such as *Artemisia annua* L, *Pogostemon cablin* (Blanco) Benth, *Glycyrrhiza uralensis* Fisch.ex DC., *Reynoutria japonica* Houtt, *Prunus armeniaca* L, *Phragmites communis* Trin, and *Atractylodes lancea* (Thunb.) DC., were also found to exhibit an inhibitory effect on the NF-κB signaling pathway [71–82].

Furthermore, these herbs have a wide range of anti-inflammatory effects in various inflammatory models. Some alkaloids and their derivatives from *Ephedra sinica* Stapf have been demonstrated to exert anti-inflammatory effects both *in vivo* and *in vitro* [55,56,83–85]. Additionally, Ephedra polysaccharides have also been reported to exhibit anti-inflammatory properties. Liang et al. demonstrated that

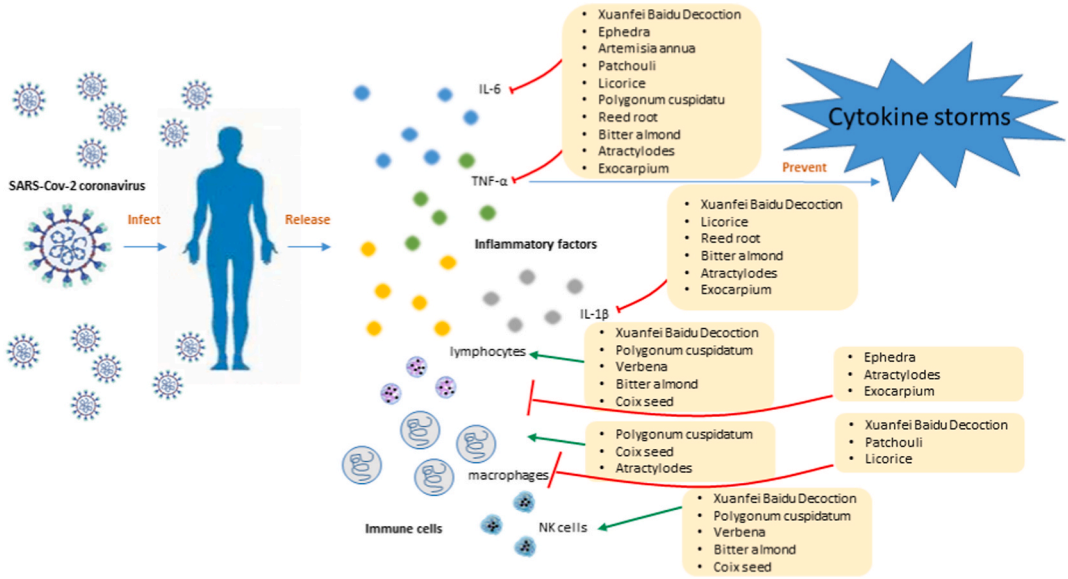

Fig. 4. Anti-inflammatory effects and immunomodulatory effects of Xuanfei Baidu decoction and its traditional Chinese medicine herbs.

polysaccharides from *Ephedra sinica* Stapf alleviated airway and pulmonary inflammation by decreasing inflammatory cells in serum (neutrophils and lymphocytes) and inflammatory factors (IL-6, IL-8, and TNF-α) in the lung [86]. Hunt et al. found that extracts of *Artemisia annua* L dose-dependently suppressed the LPS-induced production of TNF-α and prostaglandin E2 (PGE2) in neutrophils [87]. In a mouse model of LPS-induced lung injury, artesunate showed protective effects on lung injury by inhibiting inflammation. Further study revealed that artesunate exerted anti-inflammatory effects against LPS-induced ALI by inhibiting the Toll-like receptor 4 (TLR4)/NF-κB signaling pathway [72]. The active ingredients in *Pogostemon cablin* (Blanco) Benth, including PA, β-patchoulene, and patchoulene epoxide, have been shown to exhibit anti-inflammatory activity in LPS-induced macrophages [73–77]. Interestingly, patchoulene epoxide, as the oxidative product of β-PAE, appeared to have better anti-inflammatory effects than β-patchoulene [76]. Yu et al. demonstrated that PA significantly decreased the number of inflammatory cells (neutrophils and macrophages) and the production of inflammatory cytokines (TNF-α, IL-1β, and IL-6) by inhibiting the NF-κB signaling pathway in an LPS-induced ALI mouse model [88]. As the main active ingredient of *Glycyrrhiza uralensis* Fisch.ex DC., glycyrrhizin has been reported to exhibit anti-inflammatory properties both *in vivo* and *in vitro* [57,78,89–95]. Yao et al. found that glycyrrhizin significantly ameliorated the inflammatory state by inhibiting the NF-κB and p38/ERK pathways and pyroptosis in an ALI mouse model [78]. Michaelis et al. revealed that glycyrrhizin suppressed H5N1-induced inflammatory factors, including CXCL-10, IL-6, CC-chemokine ligand (CCL) 2, and CCL5, by inhibiting the expression of proinflammatory genes *in vitro* [57]. A clinical study showed that the extract of *Reynoutria japonica* Houtt containing resveratrol exerted an anti-inflammatory effect by suppressing the intranuclear binding of NF-κB and the expression of TNF-α and IL-6 in normal subjects [79]. In an LPS-induced ALI murine model, amygdalin reduced the infiltration of inflammatory cells and the expression of inflammatory factors (TNF-α, IL-1β, and IL-6) in bronchoalveolar lavage fluid (BALF) by inhibiting the NF-κB and nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) signaling pathways [80]. *Phragmites communis* Trin and its main active ingredients have been shown to exhibit anti-inflammatory properties both *in vitro* and *in vivo* [81,96–98]. The acidic polysaccharide PRP-2 isolated from *Phragmites communis* Trin inhibited the production of nitric oxide (NO) in RAW246.7 macrophages induced by LPS [96]. Stigmasta-3,5-dien-7-one, an anti-inflammatory steroid from *Phragmites communis* Trin, effectively reduced the expression of NO, PGE2, and proinflammatory cytokines, which might be attributed to blocking the NF-κB signaling pathway [81]. *Lepidium apetalum* Willd has been shown to have significant anti-inflammatory effects [99–102]. Zhao et al. found that aqueous extracts of *Lepidium apetalum* Willd reduced pulmonary edema and improved lung inflammatory cell infiltration in ALI rats, which might be attributed to the reduction in aquaporin 5 [101]. Atractylenolide I (AO-I) suppressed the inflammatory response induced by LPS by decreasing the production of inflammatory cells (lymphocytes and neutrophils) and the expression of inflammatory cytokines (such as TNF-α, IL-6, IL-1β, IL-13, and macrophage migration inhibitory factor) in the BALF of ALI mice. Its mechanisms might be attributed to the inhibition of TLR4 expression and NF-κB activation by AO-I [82]. Moreover, a similar anti-inflammatory effect was observed in ALI mice treated with atractylodin. Atractylodin significantly attenuated LPS-induced ALI by inhibiting the NLRP3 inflammasome and TLR4 signaling pathways [103]. Both aqueous and ethanolic extracts of *Citrus* × *reticulata* Blanco exerted significant anti-inflammatory activities [104]. Total flavonoids (TFs) from *Citrus* × *reticulata* Blanco markedly alleviated the particulate matter 2.5 (PM2.5)-induced inflammatory response in lung tissues via the inhibition of the production of WBCs, neutrophils, lymphocytes, and monocytes and the expression of TNF-α, IL-1β, IL-6, and IL-18 [105]. Its mechanisms of action could involve the suppression of the MARK and NF-κB signaling pathways [106].

Table 3
Anti-inflammatory effects of XFBD[a] and its major herbs.

Herbal Medicine	Components	Targets/ Pathway	Model	Mechanisms	Source
XFBD	/	PD-1/IL-17A[b] signaling pathway	LPS[c]-induced ALI[d] mice	Improving pulmonary injury by decreasing the expression of IL-6[e], TNF-α[f], and IL-1β as well as the infiltration of macrophages and neutrophils	Wang et al., 2022 [67]
XFBD	/	PD-1/IL-17A signaling pathway	LPS-stimulated RAW264.7 macrophages	Inhibiting the expression of IL-6, TNF-α, and iNOS[g]	Wang et al., 2022 [68]
XFBD	/	IL-6/STAT3[h] signaling pathway	BLM[i]-induced lung fibrosis mice model	Reducing pulmonary fibrosis by inhibiting macrophage infiltration	Wang et al., 2022 [68]
XFBD	/	NF-κB[j] signaling pathway	LPS-induced M1 macrophages derived from THP-1[k]	Suppressing the expression of IL-6, TNF-α, MCP-1, and CXCL-10[l]	Li et al., 2021 [70]
Ephedra sinica Stapf	Ephedra polysaccharide	TGF-β1/Smad2 signaling pathway	SD[m] rats intratracheal instilled with LPS	Alleviating airway and pulmonary inflammation by decreasing neutrophil and lymphocyte cells in serum and IL-6, IL-8, and TNF-α in lung homogenization buffer	Liang et al., 2018 [86]
Artemisia annua L	Extracts of *Artemisia annua* L	TLR4[n]/NF-κB and Nrf2[o] signaling pathways	LPS-induced A549 cells	Suppressing the production of IL-8, IL-6, TNF-α and PGE2[p]	Zhao et al., 2017 [87]
Artemisia annua L	Artesunate	/	LPS-induced lung injury mice model	Protecting against ALI by decreasing the numbers of inflammatory cell infiltration, lung edema, MPO[q] activity, and MDA[r] content	Zhao et al., 2017 [72]
Pogostemon cablin (Blanco) Benth	Patchouli alcohol	NF-κB signaling pathway	LPS-induced ALI mice model	Decreasing the infiltration of neutrophils and macrophages cells Reducing the expression of TNF-α, IL-1β, IL-6	Yu et al., 2015 [88]
Glycyrrhiza uralensis Fisch.ex DC.	Glycyrrhizin	NF-κB and p38/ ERK[s] signaling pathways	S. aureus[t]-induced ALI mice model	Reducing IL-6, TNF-α, IL-8, IL-1β, and HMGB1[u] production Decreasing neutrophil and macrophage infiltration	Yao et al., 2019 [78]
Glycyrrhiza uralensis Fisch.ex DC.	Glycyrrhizin	NF-κB, JNK[v], and p38 signaling pathways	H5N1-infected A549 cells	Suppressing CXCL-10, IL-6, CCL2[w], and CCL5 by inhibiting the expression of pro-inflammatory genes	Michaelis et al., 2011 [57]
Reynoutria japonica Houtt	Extract of *Reynoutria japonica* Houtt containing resveratrol	NF-κB signaling pathway	Normal-weight healthy subjects	Suppressing the expression of TNF-α and IL-6 and CRP[x] in plasma	Ghanim et al., 2010 [79]
Phragmites communis Trin	Acidic polysaccharide (PRP-2)	/	LPS-induced RAW246.7 macrophages	Inhibiting the production of NO[y]	Zhou et al., 2020 [96]
Phragmites communis Trin	Stigmasta-3,5-dien-7-one	NF-κB and p38 signaling pathways	LPS-induced inflammation in macrophages	Reducing the expression of NO and PGE2 Inhibiting the synthesis of TNF-α, IL-1β, and IL-6	Park et al., 2016 [81]
Prunus armeniaca L	Amygdalin	NF-κB and NLRP3[z] signaling pathways	LPS-induced ALI murine model	Reducing the infiltration of inflammatory cells and the expression of TNF-α, IL-1β, and IL-6 in the BALF[aa]	Zhang et al., 2017 [80]
Lepidium apetalum Willd	Aqueous extracts of *Lepidium apetalum* Willd	AQP5[ab]	Endotoxin-induced ALI rat	Reduced pulmonary edema and improved lung inflammatory cells infiltration	Zhang et al., 2016 [101]
Atractylodes lancea (Thunb.) DC.	Atractylenolide I	TLR4/NF-κB signaling pathway	LPS-induced ALI mice	Decreasing the production of lymphocytes and neutrophils, the expression of TNF-α, IL-6, IL-1β, IL-13, and MIF[ac] in BALF	Zhang et al., 2015 [82]
Atractylodes lancea (Thunb.) DC.	Atractylodin	TLR4 signaling pathway	LPS-induced ALI mice	Inhibiting NLRP3 inflammasome Decreasing the TNF-α, IL-6, IL-1β and MCP-1 secretion in BALF	Tang et al., 2018 [103]
Citrus × reticulata Blanco	Total flavonoids	/	PM2.5[ad]-induced lung injury mice	Inhibiting the production of WBCs[ae], neutrophils, lymphocytes, and monocytes Decreasing the TNF-α, IL-1β, IL-6, and IL-18	Zhu et al., 2019 [105]
Citrus × reticulata Blanco	Flavonoids	MAPK[af] and NF-κB signaling pathways	LPS-induced Raw264.7 Cell	Downregulating the mRNA of TNF-α, IL-1β, and IL-6 Upregulating the mRNA of IL-10	Hu et al., 2017 [106]

[a] XFBD: Xuanfei Baidu Decoction.
[b] PD-1/IL-17A: Program death receptor-1/interleukin-17.
[c] LPS: lipopolysaccharide.

[d] ALI: acute lung injury.
[e] IL: interleukin.
[f] TNF-α: tumor necrosis factor-α.
[g] iNOS: inducible nitric oxide synthase.
[h] STAT3: signal transducer and activator of transcription 3.
[i] BLM: bleomycin.
[j] NF-κB: nuclear factor kappa B.
[k] THP-1: human myeloid leukemia mononuclear cells.
[l] CXCL-10: chemokine ligand 10.
[m] SD: Sprague Dawley.
[n] TLR4: toll-like receptor 4.
[o] Nrf2: nuclear factor erythroid 2 related factor 2.
[p] PGE2: prostaglandin E2.
[q] MPO: myeloperoxidase.
[r] MDA: malondialdehyde.
[s] ERK: extracellular signal-regulated kinase.
[t] *S. aureus*: *Staphylococcus aureus*.
[u] HMGB1: High Mobility Group Box 1.
[v] JNK: Jun N-terminal kinase.
[w] CCL: CC-chemokine ligand.
[x] CRP: C-reactive protein.
[y] NO: nitric oxide.
[z] NLRP3: nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.
[aa] BALF: bronchoalveolar lavage fluid.
[ab] AQP5: aquaporin 5.
[ac] MIF: macrophage migration inhibitory factor.
[ad] PM2.5: particulate matter 2.5.
[ae] WBCs: white blood cells.
[af] MAPK: mitogen-activated protein kinase.

3.4.3. Immunomodulatory effects

Immunosuppressed status is one of the representative symptoms of COVID-19. A retrospective clinical study of 522 patients with COVID-19 and 40 healthy subjects found that the numbers of $CD4^+$ (less than 300/μL), $CD8^+$ (less than 400/μL), and total T lymphocytes (less than 800/μL) were significantly reduced in patients with COVID-19 compared with healthy subjects, especially in severe patients. T lymphocyte count was inversely associated with patient survival. Additionally, the level of PD-1, a depletion marker, in T lymphocytes of patients with COVID-19 was significantly elevated, indicating functional failure of surviving T lymphocytes [107].

Network pharmacology has revealed that XFBD exhibits immunomodulatory properties by modulating T helper (Th) 1, Th 2, and Th 17-cell differentiation and regulating the T-lymphocyte receptor signaling pathway [34–36]. Yan et al. found that XFBD significantly enhanced the immune response of immunosuppressed mice induced by cyclophosphamide by increasing the immune organ index, improving spleen and thymus pathology, facilitating the proliferation of $CD4^+$ and $CD8^+$ T lymphocytes, and upregulating the expression of IgG and IgM [108]. In addition, the TCM herbs in XFBD also have immunomodulatory effects (Fig. 4 and Table 4 show the potential immunomodulatory mechanisms of XFBD). An *in vivo* study demonstrated that PA promoted phagocytic activity and serum IgM and IgG levels and subsequently enhanced humoral immunity [109]. Glycyrrhizin could effectively activate multiple immune cell activities, including those of natural killer (NK) cells and macrophages, via the MAPK and TLRP signaling pathways [110,111]. Moreover, Bordbar et al. demonstrated that glycyrrhizin upregulated major histocompatibility complex class II, CD86, and CD40 levels, suggesting that glycyrrhizin could induce phenotypic maturation of dendritic cells [110]. The crude extract of *Reynoutria japonica* Houtt showed immunomodulatory effects by promoting the proliferation of T and B lymphocytes, enhancing the phagocytic activities of macrophages, and increasing the cytotoxic effects of NK cells in normal mice. Moreover, crude extract of *Reynoutria japonica* Houtt could also upregulate the blood levels of immunoreactive cell markers, such as CD3, CD11b, and membrane attack complex 3 [112]. The ethanol extract of *Verbena officinalis* L could promote T and B lymphocyte proliferation in healthy Kunming mice at 20 mg/kg [113]. Apricot kernel oil significantly improved immune function by increasing the levels of immunoglobulin IgA, IgM, and IgG in a rat model of cyclophosphamide-induced immunosuppression [114]. Amygdalin could promote the activity of T lymphocytes by regulating the JAK2/STAT3 signaling pathway [115]. Water extracts of *Phragmites communis* Trin effectively enhanced the immune function of immunosuppressed mice by increasing phagocytosis of the reticuloendothelial system, the activity of NK cells, and the percentage of lymphocytes [116,117]. Ethanol sediments of *Lepidium apetalum* Willd significantly improved the phagocytic capacities of phagocytes, enhanced thymus and spleen coefficients, and increased the expression of interferon-gamma and IL-4 in immunosuppressed mice [118]. Both *Coix lacryma-jobi* L and its active ingredients, such as Coix seed polysaccharide and Coix seed oil, possess immunomodulatory properties, including boosting the phagocytic capacities of phagocytes and promoting lymphocyte proliferation [119–121]. Atractylodes polysaccharides (ALPs), including neutral polysaccharides, ALP-1, and acidic polysaccharides, ALP-3, also showed immunomodulatory activity on macrophage functions, while ALP-3 showed stronger activity than ALP-1 in promoting macrophage proliferation and phagocytosis [122].

Table 4
Immunomodulatory effects of XFBD[a] and its major herbs.

Herbal medicine	components	Targets/ pathway	Model	Mechanisms	Source
XFBD	/	/	Cyclophosphamide-induced immunosuppress ion in mice	Increasing immune organ index by improving spleen and thymus pathology, facilitating the proliferation of $CD4^+$ and $CD8^+$ T lymphocytes, and upregulating the expression of IgG and IgM	Yan et al., 2021 [108]
Pogostemon cablin (Blanco) Benth	Patchouli alcohol	/	Kunming mice	Enhancing humoral immunity by promoting phagocytic activity and serum IgM and IgG levels	Liao et al., 2013 [109]
Glycyrrhiza uralensis Fisch.ex DC.	Glycyrrhizin	/	Dendritic cells	Promoting phenotypic maturation of dendritic cells by upregulating MHC-II[b], CD86, and CD40 levels	Bordbar et al., 2012 [110]
Reynoutria japonica Houtt	Crude extract of *Reynoutria japonica* Houtt	/	Normal mice	Promoting the proliferation of T and B lymphocytes, enhancing the phagocytic activities of macrophages, and increasing the cytotoxic effects of NK[c] cells Upregulating the blood levels of CD3, CD11b, and MAC-3[d]	Chueh et al., 2015 [112]
Verbena officinalis L	Ethanol extract of *Verbena officinalis* L	/	Healthy Kunming mice	Promoting T and B lymphocyte proliferation	Wang et al., 2008 [113]
Prunus armeniaca L	Apricot kernel oil	/	Cyclophosphamide-induced immunosuppression in rat	Increasing the levels of IgA, IgM, and IgG	Tian et al., 2016 [114]
Prunus armeniaca L	Amygdalin	JAK2/STAT3[e] signaling pathway	Human peripheral blood T lymphocytes	Promoting the activity of T lymphocytes	Wang et al., 2021 [115]
Phragmites communis Trin	Water extracts of *Phragmites communis* Trin	/	Immunosuppressed mice	Increasing the phagocytosis of the reticuloendothelial system and the activity of NK cells	Sun et al., 2016 [117]
Lepidium apetalum Willd	Ethanol sediments of *Lepidium apetalum* Willd	/	Cyclophosphamide-induced immunosuppression in mice	Improving the phagocytic capacities of phagocytes, enhancing thymus and spleen coefficients, and increasing the expression of IFN-γ[f] and IL-4[g]	Zheng et al., 2015 [118]
Coix lacryma-jobi L	Coix seed oil	/	Health mice	Promoting splenic lymphocyte proliferation and antibody generation Enhancing NK cell activity	Zhou et al., 2018 [120]
Coix lacryma-jobi L	Water extracts of *Coix lacryma-jobi* L	/	Cyclophosphamide-induced immunosuppression in mice	Improving the phagocytosis of macrophages and increasing the serum hemolysin level	Ye et al., 2006 [121]
Coix lacryma-jobi L	Coix seed polysaccharide	/	Cyclophosphamide-induced immunosuppression in mice	Improving the phagocytosis of macrophages and promoting the formation of hemolysin and hemolytic plaque	Miao et al., 2002 [119]
Atractylodes lancea (Thunb.) DC.	Atractylodes polysaccharides	/	Murine RAW264.7 macrophage cell line	Promoting macrophages proliferation and phagocytosis	Qin et al., 2019 [122]

[a] XFBD: Xuanfei Baidu Decoction.
[b] MHC-II: major histocompatibility complex class II.
[c] NK: natural killer.
[d] MAC-3: membrane attack complex 3.
[e] JAK2/STAT3: Janus kinase 2/signal transducer and activator of transcription 3.
[f] IFN-γ: interferon-γ.
[g] IL-4: interleukin-4.

3.4.4. Antioxidative properties

Normally, an oxidative-antioxidative balance is maintained between the production and removal of reactive oxygen species (ROS), which plays an important role in regulating signaling pathway transduction, cell proliferation, and apoptosis [123]. When this balance is disrupted by an excessive immune response and cytokine storm associated with COVID-19, ROS are overproduced, and oxidative stress is activated, leading to damage to the mitochondrial respiratory chain in cells and degeneration of macromolecular substances such as lipids, sugars, proteins, and DNA, eventually resulting in oxidative damage to cells [124,125].

Most TCM herbs used in XFBD have excellent antioxidant properties (Fig. 5 and Table 5 show the potential antioxidative mechanisms of XFBD). Extracts of *Ephedra sinica* Stapf showed significant antioxidant activity by reducing oxidative stress markers (H_2O_2 and NO) in a fipronil-induced liver damage rat model [126]. However, the antioxidant activities of the different solvent Ephedra sinica extracts (ESEs) varied. The scavenging activity of ESEs in different solvent ESEs for H_2O_2 was in the order of methanol (IC50 = 251 μg/ml) > aqueous (IC50 = 290 μg/ml) > chloroform (IC50 = 325 μg/ml) > ethyl acetate (IC50 = 342 μg/ml) > n-hexane (IC50 = 521 μg/ml), and that for NO was aqueous (IC50 = 250 mg/ml) > ethyl acetate (IC50 = 270 mg/ml) > methanol (IC50 = 312 mg/ml) > chloroform (IC50 = 386 mg/ml) > n-hexane (IC50 = 826 mg/ml) [127]. Zhao et al. found that artesunate possesses antioxidant

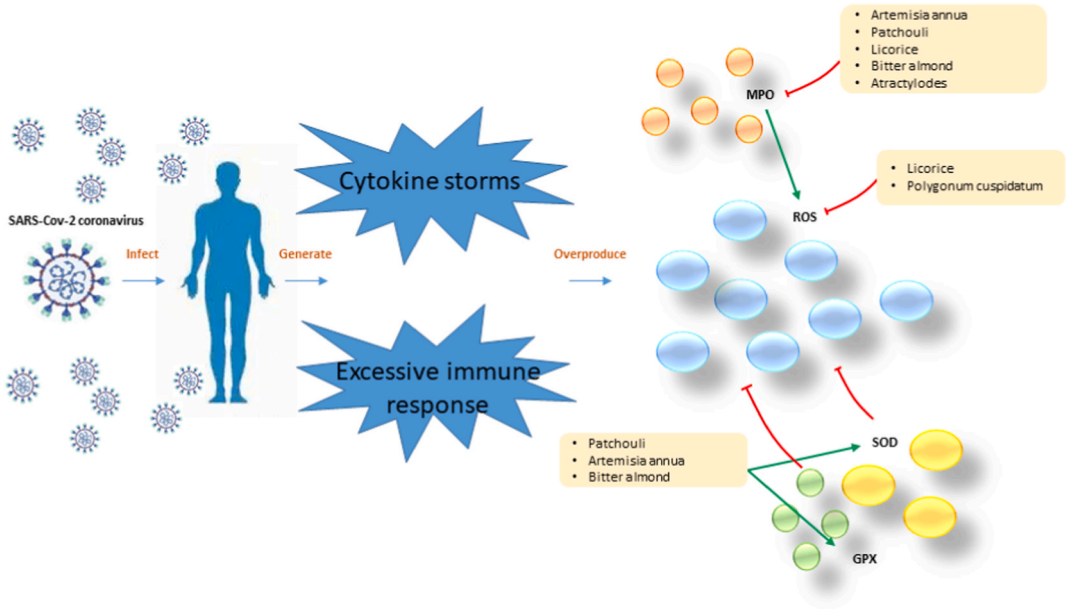

Fig. 5. Antioxidative properties of Xuanfei Baidu decoction and its traditional Chinese medicine herbs.

properties against LPS-induced ALI by activating the nuclear factor erythroid 2 related factor 2/heme oxygenase 1 signaling pathway [72]. A previous study showed that PA exerted antioxidative effects by upregulating superoxide dismutase (SOD) and glutathione peroxidase (GPX) and downregulating myeloperoxidase (MPO) and malondialdehyde in the lung tissue, which in turn increased the survival rate of LPS-induced ALI mice [128]. Michaelis et al. found that glycyrrhizin interfered with H5N1-induced redox-sensitive signaling pathways, including NF-κB, MAPKs p38, and Jun N-terminal kinase, subsequently inhibited viral replication and cellular production [57]. An *in vivo* study showed that licorice flavonoids alleviated oxygen radical-mediated pulmonary injury by enhancing SOD activity and suppressing MPO activity [129]. Phenolic compounds present in *Reynoutria japonica* Houtt are the main antioxidant constituents [130]. A clinical study showed that resveratrol in the extract of *Reynoutria japonica* Houtt exerted an antioxidant effect by suppressing ROS generation and nicotinamide adenine dinucleotide phosphate oxidase subunit expression in normal subjects [79]. The three solvent extracts (50% methanol, ethyl acetate, and chloroform) of *Verbena officinalis* L showed the scavenging activity of 1, 1-diphenil-2-picrylhydrazyl (DPPH), among which the 50% methanol extract showed the strongest antioxidant activity. Further studies have revealed that flavonoids (EC50 = 2.20 μg/ml) and caffeoyl derivatives (EC50 = 7.23 μg/ml) in the methanol extract are the main active components responsible for DPPH scavenging [131]. In an LPS-induced ALI murine model, amygdalin reduced MPO levels in lung tissues by inhibiting the NF-κB and NLRP3 signaling pathways [80]. Phragmitis rhizoma polysaccharides scavenged DPPH, hydroxyl, and nitrite radicals in a dose-dependent manner [132]. Chemical composition analysis of Phragmitis rhizoma polysaccharide revealed that (−)-lyoniresinol 9′-O-β-D-glucopyranoside showed the highest scavenging activity against DPPH [133]. PA markedly alleviated LPS-triggered oxidative stress in lung tissues by upregulating SOD and GPX and downregulating myeloperoxidase and malondialdehyde. Thus, the survival rate of ALI mice was improved [128]. Both AO-I and atractylodin exert antioxidant effects in LPS-induced ALI mice by decreasing the expression of MPO in BALF [82,103]. TFs from *Citrus* × *reticulata* Blanco significantly alleviated PM2.5-induced oxidative stress in lung tissues by inhibiting the expression of total protein, malondialdehyde, and NO [105].

3.4.5. Antibacterial and antifungal properties

Bacterial and fungal infections are well-known complications of COVID-19 and are significantly associated with poor prognosis [134–141]. A pooled study containing 171 trials with 171,262 patients with COVID-19 discovered that the prevalence of combined bacterial infections was 5.1%, and secondary bacterial infections were 13.1%. Patients in the ICU had a higher chance of bacterial infection at 18.8% [135]. The common bacteria included *Staphylococcus aureus*, *coagulase-negative staphylococci*, and *Klebsiella species*. One additional study, including 38 trials with 17,695 patients with COVID-19, found 1,182, or 6.7%, coinfections with fungi. The common fungi included *Aspergillosis* and *Candidiasis* [141]. Despite antibiotic treatment, patients with COVID-19 with bacterial and fungal infections still show a poor prognosis. Increasing antimicrobial resistance has exacerbated this crisis [142,143], thus requiring alternative treatment options.

Several TCM herbs present in XFBD exhibit antibacterial and antifungal properties. Khan et al. performed an *in vitro* experiment to test the antibacterial activity of different ESE solvents. The methanol extract of *Ephedra sinica* Stapf had strong antibacterial activity against *Bacillus subtilis, Kleibsiella pneumoniae, Pseudomonas aeruginosa,* and *Bacillus atrophaeus*, whereas the aqueous extract of *Ephedra sinica* Stapf could only kill *Bacillus atrophaeus* [144]. Multiple studies have shown that volatile organic components of *Artemisia annua* L. have inhibitory effects on both gram-positive *(Staphylococcus aureus* and *Streptococcus pneumoniae*) and gram-negative bacteria (*Klebsiella pneumoniae, Haemophilus influenzae*, and *Pseudomonas aeruginosa*) [145–149]. Adhavan et al. found that patchouli oil had an

Table 5
Antioxidative properties of XFBD[a] and its major herbs.

Herbal medicine	components	Targets/pathway	Model	Mechanisms	Source
Ephedra sinica Stapf	Ephedra sinica extract	/	Fipronil-induced liver damage rat model	Reducing H_2O_2 and NO[b]	Seif et al., 2021 [126]
Artemisia annua L	Artesunate	Nrf2[c]/HO-1[d] signaling pathway	LPS[e]-induced lung injury in mice	Decreasing MPO[f] activity, and MDA[g] content	Zhao et al., 2017 [72]
Pogostemon cablin (Blanco) Benth	Patchouli alcohol	/	LPS-triggered ALI[h] mice	Upregulating SOD[i] and GPX[j] and downregulating MPO and malondialdehyde in lung tissue	Su et al., 2016 [128]
Glycyrrhiza uralensis Fisch.ex DC.	Glycyrrhizin	NF-κB[k], MAPKs[l] p38, and JNK[m] signaling pathways	H5N1-infected A549 cells	Inhibiting the formation of ROS[n]	Michaelis et al., 2011 [57]
Glycyrrhiza uralensis Fisch.ex DC.	Licorice flavonoids	/	LPS-induced acute pulmonary inflammation in mice	Alleviating pulmonary injury by enhancing SOD activity and suppressing MPO activity	Xie et al., 2009 [129]
Reynoutria japonica Houtt	Resveratrol	/	Normal subject	Suppressing the generation of ROS and the expression of p47phox[o]	Ghanim et al., 2010 [79]
Prunus armeniaca L	Amygdalin	NF-κB and NLRP3[p] signaling pathways	LPS-induced ALI murine model	Reducing the MPO in lung tissues	Zhang et al., 2017 [80]
Prunus armeniaca L	Amygdalin	Nrf2 signaling pathway	Ang II[q]-induced H9c2 cells	Upregulating the expression of Nrf2, catalase, SOD-2, and GPX-4	Kung et al., 2021 [180]
Atractylodes lancea (Thunb.) DC.	Atractylenolide I	TLR4[r]/NF-κB signaling pathway	LPS-induced ALI mouse model	Decreasing the expression of MPO in BALF[s]	Zhang et al., 2015 [82]
Atractylodes lancea (Thunb.) DC.	Atractylodin	TLR4/NF-κB signaling pathway	LPS-induced ALI mice model	Decreasing MPO activity	Tang et al., 2018 [103]
Citrus × *reticulata* Blanco	Total flavonoids	/	PM2.5[t]-induced mice model	Inhibiting the expression of TP[u], MDA, and NO, the activities of LDH[v], iNOS[w], GSH-Px[x], and SOD, and the ratio of reduced GSH[y] to GSSG[z]	Zhu et al., 2019 [105]

[a] XFBD: Xuanfei Baidu Decoction.
[b] NO: nitric oxide.
[c] Nrf2: nuclear factor erythroid 2 related factor 2.
[d] HO-1: heme oxygenase 1.
[e] LPS: lipopolysaccharide.
[f] MPO: myeloperoxidase.
[g] MDA: malondialdehyde.
[h] ALI: acute lung injury.
[i] SOD: superoxide dismutase.
[j] GPX: glutathione peroxidase.
[k] NF-κB: nuclear factor kappa B.
[l] MAPKs: mitogen-activated protein kinases.
[m] JNK: Jun N-terminal kinase.
[n] ROS: reactive oxygen species.
[o] p47phox: nicotinamide adenine dinucleotide phosphate oxidase subunit.
[p] NLRP3: nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3.
[q] Ang II: angiotensin II.
[r] TLR4: toll-like receptor 4.
[s] BALF: bronchoalveolar lavage fluid.
[t] PM2.5: particulate matter 2.5.
[u] TP: total protein.
[v] LDH: lactate dehydrogenase.
[w] iNOS: inducible nitric oxide synthase.
[x] GSH-Px: glutathione peroxidase.
[y] GSH: glutathione.
[z] GSSG: oxidized glutathione.

antimicrobial effect on *isolates of Streptococcus mutans*, *Shigella flexneri*, and *Staphylococcus aureus* [150]. Wang XY et al. reported that pogostone also exhibited a bacteriostatic effect on *Staphylococcus aureus*. Further investigations have revealed that the antibacterial action of pogostone may be exerted by altering cell membrane permeability [151]. Previous studies have shown that multiple active ingredients of *Glycyrrhiza uralensis* Fisch.ex DC., such as glycyrrhizin, liquiritigenin, isoliquiritigenin, and some flavonoids, have broad-spectrum antimicrobial activities [152]. These potential mechanisms are related to the inhibition of bacterial genes, bacterial growth, and the reduction of bacterial toxins [153–156]. *In vitro* studies have shown that the methanol extract from the root of *Reynoutria japonica* Houtt significantly inhibits *Streptococcus mutans* and *Streptococcus sobrinus* [157–159]. Phytochemical analysis showed that the antibacterial activities of isolated fractions of *Reynoutria japonica* Houtt root might be associated with the presence of

anthraquinones, cardiac glycosides, terpenoids, and phenolics [157]. Methanol extracts of *Prunus armeniaca* L exhibited significant antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, and *Candida albicans*, whereas aqueous extracts showed activity against *Escherichia coli*, *Proteus mirabilis*, and *Staphylococcus aureus* [160]. *Verbena officinalis* L. exerted a marked inhibitory effect on both bacteria and fungi. Casanova et al. found that the methanolic crude extract of *Verbena officinalis* L. significantly inhibited *Penicillium expansum* (32.55%) and *Rhizopus stolonifer* (28.98%) [131]. Zhao et al. found that the aqueous extract of *Verbena officinalis* L markedly inhibited *Escherichia coli* and *Staphylococcus aureus*, with minimum inhibitory concentrations of 500.0 mg/mL and 250.0 mg/mL, respectively [161]. Table 6 shows the antibacterial and antifungal properties of XFBD.

4. Discussion

Recent decades have seen the emergence of several new viruses, such as SARS-CoV, Middle East respiratory syndrome coronavirus, Ebola virus, and the most recent SARS-CoV-2, causing pandemic infectious diseases. TCM is well established to play an important role in preventing and treating communicable diseases [30,38,162–164], particularly in the fight against SARS-CoV-2. Numerous studies have been conducted on the use of TCM treatment for COVID-19, suggesting that TCM can improve clinical symptoms and halt disease

Table 6
Antibacterial and antifungal properties of XFBD[a] and its major herbs.

Herbal medicine	components	Type of microorganism	Mechanisms	Source
Ephedra sinica Stapf	Methanol extract of *Ephedra sinica* Stapf	*B. subtilis*[b], *K. pneumoniae*[c], *P. aeruginosa*[d], and *B. atrophaeus*[e]	/	Khan et al., 2017 [144]
Ephedra sinica Stapf	Aqueous extract of *Ephedra sinica* Stapf	*B. atrophaeus*	/	Khan et al., 2017 [144]
Artemisia annua L	Essential oil of *Artemisia annua* L	*E. coli*[f], *F. oxysporum*[g], *A. niger*[h], and *C. albicans*[i]	Infiltrating into bacteria cells through the lipophilic nature	Khalid et al., 2019 [181]
Artemisia annua L	Essential oil of *Artemisia annua* L	*E. hirae*[j], *C. albicans*, and *S. cerevisiae*[k]	Inhibiting the growth of bacteria and fungi	Juteau et al., 2002 [145]
Pogostemon cablin (Blanco) Benth	Patchouli oil	*S. mutans*[l], *S. flexneri*[m], and *S. aureus*[n]	Eradicating the biofilm	Adhavan et al., 2017 [150]
Pogostemon cablin (Blanco) Benth	Pogostone	*S. aureus*	Altering cell membrane permeability	Wang et al., 2018 [151]
Glycyrrhiza uralensis Fisch.ex DC.	18β-Glycyrrhetinic acid	*S. aureus*	Reducing the expression of key virulence genes (saeR and hla)	Long et al., 2013 [156]
Glycyrrhiza uralensis Fisch.ex DC.	Liquiritigenin	*S. aureus*	Decreasing the production of α-hemolysin	Dai et al., 2013 [155]
Glycyrrhiza uralensis Fisch.ex DC.	Licochalcone E	*S. aureus*	Reducing the production of α-toxin	Zhou et al., 2012 [154]
Glycyrrhiza uralensis Fisch.ex DC.	Glabridin and licochalcone A	*C. albicans*	Inhibiting the formation of biofilm and hyphal	Messier et al., 2011 [153]
Reynoutria japonica Houtt	Methanol extract of *Reynoutria japonica* Houtt	*S. mutans* and *S. sobrinus*[o]	Inhibiting biofilm formation	Song et al., 2007 [157]
Prunus armeniaca L	Methanol extracts of *Prunus armeniaca* L	*E. coli*, *S. aureus*, and *C. albicans*	/	Yiğit et al., 2009 [160]
Prunus armeniaca L	Aqueous extracts of *Prunus armeniaca* L	*E. coli*, *P. mirabilis*[p], and *S. aureus*	/	Yiğit et al., 2009 [160]
Verbena officinalis L	Methanolic crude extract of *Verbena officinalis* L	*P. expansum*[q] and *R. stolonifer*[r]	/	Casanova et al., 2008 [131]
Verbena officinalis L	Aqueous extract of *Verbena officinalis* L	*E. coli* and *S. aureus*	Inhibiting the growth of bacteria	Zhao et al., 2012 [161]

[a] XFBD: Xuanfei Baidu Decoction.
[b] *B. subtilis*: *Bacillus subtilis*.
[c] *K. pneumoniae*: *Klebsiella pneumoniae*.
[d] *P. aeruginosa*: *Pseudomonas aeruginosa*.
[e] *B. atrophaeus*: *Bacillus atrophaeus*.
[f] *E. coli*: *Escherichia coli*.
[g] *F. oxysporum*: *Fusarium oxysporum*.
[h] *A. niger*: *Aspergillus niger*.
[i] *C. albicans*: *Candida albicans*.
[j] *E. hirae*: *Enterococcus hirae*.
[k] S. cerevisiae: *Saccharomyces cerevisiae*.
[l] *S. mutans*: *Streptococcus mutans*.
[m] *S. flexneri*: *Shigella flexneri*.
[n] *S. aureus*: *Staphylococcus aureus*.
[o] *S. sobrinus*: *Streptococcus sobrinus*.
[p] *P. mirabilis*: *Proteus mirabilis*.
[q] *P. expansum*: *Penicillium expansum*.
[r] *R. stolonifer*: *Rhizopus stolonifer*.

progression in patients with COVID-19 [165–170]. This review illustrates the clinical efficacy and potential mechanisms of XFBD in COVID-19 by summarizing the current clinical evidence of XFBD treatment for COVID-19 and the experimental studies on the antiviral, anti-inflammatory, immunoregulatory, antioxidant, and antimicrobial properties of XFBD and its herbal components.

In addition to pneumonia, SARS-CoV-2 can also damage multiple organs, such as the heart, liver, and kidney, which might be attributed to inflammation, immune regulation, oxidative stress, and infection of multiple systems [171]. In a pooled analysis of 1198 patients with COVID-19, 11.5% had acute myocardial injury with elevated creatine kinase levels [172]. In a case series, arrhythmia was reported in 10 of 137 patients with COVID-19 (7.3%) [173]. An epidemiological study revealed that of the 5449 patients hospitalized with COVID-19, 1993 (36.6%) developed acute kidney injury [174]. According to a meta-analysis of 16 studies, 1254 of the 6253 patients with COVID-19 experienced acute liver injury, with an incidence of up to 22.8% [175]. Additionally, organ injuries were significantly associated with a poor clinical prognosis in patients with COVID-19. Forty-two compounds and nine analytes were identified in rat-fed XFBD granule, of which nine compounds were detected in the lung and liver, six in the kidney, five in the spleen, and three in the heart. The extensive *in vivo* distribution indicated that the XFBD granule exerted multicomponent, multitargeted, and multipathway comprehensive regulatory and potential protective effects on multiple organs.

However, there are some caveats worth noting when using XFBD to treat COVID-19, such as its use in critically ill patients and in combination with western medicines. Critically ill patients are susceptible to septic shock, liver failure, and renal failure, which decrease drug metabolism and excretion. Therefore, caution is advised when prescribing XFBD and other TCMs to critically ill patients. In patients with COVID-19, the combination of TCM and western medicines may have either a synergistic or antagonistic effect. For example, *Ephedra sinica* Stapf in XFBD may induce elevated blood pressure and heart rate [176,177]. Thus, it is necessary to monitor blood pressure and heart rate when using XGBD, and antihypertensive or antiarrhythmic drugs should be used in combination, if necessary.

There were several limitations associated with the present review. First, the published clinical studies on XFBD for COVID-19 included small sample sizes, were single-center, poorly designed, and had no long-term follow-up of patients after discharge [39,40,178]. Recently, a cohort study published in *The Lancet* followed 1733 discharged patients with COVID-19 for six months and found that 63% suffered from muscle weakness or fatigue, 26% had insomnia, and 23% had depression or anxiety [179]. Therefore, future studies investigating the potential long-term efficacy of XFBD for the treatment of COVID-19 are warranted. Second, some research on the mechanisms of XFBD in COVID-19 has been based on virtual screening or network pharmacological prediction; thus, direct experimental evidence is urgently needed. Third, this study reviewed the effects of the individual components of XFBD in the treatment of COVID-19. However, when an individual component is combined with others, their interactions may lead to a series of biochemical reactions. No prior studies have reported whether the individual components, when combined as XFBD, may exert inhibitory effects on others. Therefore, future research should focus on exploring the changes in the chemical composition of the TCM herbs and their compatibility to identify the main active ingredients through which XFBD plays a role.

5. Conclusion

XFBD, an effective TCM prescription for COVID-19, provides distinct advantages in improving clinical symptoms, preventing disease progression, and reducing mortality in critically ill patients. Its mechanisms of action may be associated with its direct antiviral, anti-inflammatory, immunomodulatory, antioxidant, and antibacterial effects, which are mainly attributed to the multicomponent, multitarget, and multipathway properties of TCM. Additional high-quality clinical and experimental studies are required to further explore the clinical efficacy and underlying mechanisms of XFBD in COVID-19.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article. </p>

Author statement

Tiantian Meng: conceptualization, methodology, data selection, data extraction, supervision, visualization, writing-original draft, writing-reviewing, and editing; Jingyi Ding: conceptualization, methodology, data selection, data extraction, visualization, writing-original draft, writing-reviewing, and editing; Shujie Shen: conceptualization, data selection, supervision, writing-reviewing and editing; Yingzhi Xu: supervision, validation; Peng Wang: supervision; Xinbin Song: data extraction, data curation, investigation; Yixiang Li: data extraction, data curation, investigation; Shangjin Li: investigation; Minjie Xu: validation; Ziyu Tian: validation; Qingyong He: conceptualization, project administration, writing-reviewing and editing.

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Data availability

The data of this review are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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