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Xuanfei Baidu granule alleviates coronavirus-induced pneumonia in low-temperature and high-humidity environments

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Abstract

Objective: Our study aimed to investigate the action of Xuanfei Baidu granules (XFBD) and their mechanism of action in a model of coronavirus pneumonia under cold and damp conditions.

Methods: A total of 60 Bagg Albino (BALB/c) mice were randomly assigned to different groups, including the control, model, low-dose XFBD (1.84 g/kg), medium-dose XFBD (3.67 g/kg), and high-dose XFBD (7.34 g/kg) groups. To simulate the model of coronavirus infection, a combination of cold and damp stimuli and coronavirus strain 229E (CoV 229E) was employed. Subsequently, XFBD was administered on the fifth day and lasted for 3 days. To evaluate the efficacy of XFBD in BALB/c mice, various parameters, including behavior, lung index, viral load, and pulmonary pathology, were observed. Levels of interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) were measured using enzyme-linked immunosorbent assay (ELISA). The fractions of $CD4^+$ T cells, $CD8^+$ T cells, and B cells were measured using flow cytometry.

Results: The mice in the control group were active, in good condition, and exhibited shiny hair. After modeling, the mice demonstrated less activity, low energy levels, messy and less shiny hair, poor appetite, and soft stools. The symptoms of coronavirus pneumonia were all significantly improved after the administration of different doses of XFBD. At three dosage levels, XFBD effectively increased gastrin (GAS) content, whereas medium and high doses of XFBD reduced motilin (MTL) content. The high-dose XFBD group showed a significant reduction in pathological damage to lung tissue. Treatment with three doses of XFBD demonstrated significant downregulation of inflammatory factors and regulation of $CD4^+$ and $CD8^+$ T cell and B cell expression. The high-dose XFBD group exhibited enhanced efficacy compared to the other doses.

Conclusions: XFBD showed a therapeutic effect on coronavirus pneumonia under cold and damp conditions, improved the behavioral characterization and gastrointestinal index, and reduced the lung virus titer and histopathology. This may be associated with the inhibition of inflammation and an increase in the number of lymphocytes.

Keywords: Chinese medicine, Coronavirus, Inflammation, Xuanfei Baidu granule

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Introduction

Coronavirus Disease 2019 (COVID-19) primarily affects humans and is caused by the SARS-CoV-2 virus. However, it is important to note that there are certain coronaviruses that can affect animals as well. These animal coronaviruses may cause a variety of diseases in pets, wild animals, birds, and rodents. The severity of these diseases can vary, ranging from mild gastrointestinal issues to more severe respiratory and systemic conditions[1]. Moreover, domestic animals may serve as intermediary hosts for the transmission of viruses from their native wild animal hosts to humans[1-2], causing common cold or pneumonia. The first human coronavirus, human respiratory virus 229E, was discovered in 1966[3]. To date, six known human coronaviruses (HCoVs) have been identified. These include 229E, NL63, HKU1, OC43, MERS-CoV, SARS-CoV, and SARS-CoV-2[4]. Communicable diseases not only pose a threat to human health, but also cause great economic damage[5].

While certain coronaviruses, like SARS-CoV, have shown higher prevalence at lower ambient temperatures, SARS-CoV-2, the virus responsible for COVID-19, has been observed to occur year-round. However, there have been observations that SARS-CoV-2 tends to reach its peak transmission rates during late winter and spring seasons[4]. In both humans and animals, freezing temperatures decrease the immune response by altering cell and molecular defenses to prevent infection of the upper airway, facilitating viral survival[6].

Qianru Zhao and Ronghua Zhao contributed equally to this work.

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Physical activity and environmental stress, including exposure to both cold and hot weather, can have an impact on various aspects of the immune system. These factors can influence the number and function of immune cells, such as T cells and natural killer cells. They can also affect processes like cytolysis, cytokine secretion, lymphocyte proliferation, and immunoglobulin levels[7]. The CoV protein envelope serves as a defense mechanism. As proteins and nucleic acids are sensitive to environmental shifts, the environment affects CoV activity. CoVs thrive in cold environments, whereas their activity is negatively affected by high temperatures[8]. In addition to cold environments, viral survival is also influenced by high-humidity environments. These environmental factors are also important considerations when evaluating the potential medicinal efficacy of drugs for the treatment of pneumonia caused by CoVs[8].

Traditional Chinese medicine (TCM) has historically consisted of utilizing a wide variety of herbs. Various substances, which may contain known or unknown active components, have shown the potential to target different pathways or mechanisms to address specific therapeutic indications. These substances can be adapted to suit a particular patient's symptoms and needs[9]. Xuanfei Baidu granules (XFBD) is a TCM herbal medicine formulation that has been widely studied as an effective treatment of CoVs and has demonstrated a significant improvement of clinical symptoms in patients with COVID-19[10]. In a clinical trial of 280 hospitalized patients treated with XFBD, none of the patients progressed to a serious or critical status[11]. Previous research has shown that XFBD has an anti-inflammatory effect through the inhibition of neutrophils and macrophages[12], reduces macrophage-induced inflammation[13], and suppresses the activation of the NLRP3 inflammasome[14]. While previous studies have established XFBD as a potential therapeutic agent, supporting its clinical application, limited research has specifically investigated its therapeutic potential in treating pneumonia caused by CoVs under cold and damp conditions.

In this study, a model of CoV-induced pneumonia under cold and damp conditions was used to study the protective influence and mechanism of XFBD against CoV-induced pneumonia in low- and high-humidity environments. We found that XFBD had a therapeutic effect on CoV-induced pneumonia, improves behavioral characteristics, and gastrointestinal index, whereas it decreases the viral load in lung tissue under cold and damp conditions. This mechanism may be associated with the inhibition of inflammation and decreased lymphocyte count.

Methods

Animals

Bagg Albino (BALB/c) mice were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China). The mice were kept under specific pathogen free (SPF) environmental conditions with a 12-hour light-dark cycle at (22 ± 1) °C and 40% to 50% relative humidity. The experiments followed the guidelines established by the Animal Care and Use Committee of Tianjin University of Traditional Chinese Medicine.

Drugs

XFBD was provided by Tianjin Modern Innovative TCM Technology Co. Ltd. (Tianjin, China). The manufacturer listed a dosage of 10 g twice daily. It was produced on March 6, 2020, and was valid for 24 months. Recombinant human interferon alpha-2b injections were acquired from Tianjin Sinobioway Biomedicine Co., Ltd. (Tianjin, China). The recommended clinical usage can be found in the 7th edition of the "Novel Coronavirus Pneumonia Treatment Protocol." The suggested dosage is 5 million IU dissolved in 2 mL of sterilized injectable water, to be administered twice daily *via* nebulized inhalation. It was produced on November 26, 2019, and was valid for 12 months.

Reagents

The ELISA kits were purchased from Biotechne (Minneapolis, Minnesota, USA). The human Coronavirus (HCoV-229E) real-time reverse transcription-polymerase chain reaction (RT-PCR) kit was obtained from Shanghai ZJ Bio-Tech Co., Ltd. (Shanghai, China). Phycoerythrin (PE)-labeled anti-mouse CD4, anti-mouse CD8, and erythrocyte lysates (10×) were purchased from TONBO Biosciences (Foster City, Santiago, USA).

Model establishment

Mice were placed inside a controlled climatic chamber with specific conditions, including a relative humidity of (90 ± 3) %, no airflow, and a temperature of (4 ± 2) °C. This setup was repeated daily, and the mice were exposed to these conditions for 4 h each day, over a period of seven consecutive days. Mice were infected with 100 $TCID_{50}$ HCoV-229E virus solution *via* nasal drops.

Grouping and drug intervention

On days 5 and 6 of stimulation, BALB/c mice were subjected to light anesthesia. Subsequently, they were randomly divided into control, model, low-dose XFBD (1.84 g/kg/d), medium-dose XFBD (3.67 g/kg/d), high-dose XFBD (7.34 g/kg/d), and recombinant human interferon α-2b injection groups. On the day of the initial infection, both the XFBD and positive control groups received the drug. In the XFBD dose groups, the drug was administered *via* oral gavage at a dosage of 0.2 mL per 10 g of body weight. The drug was administered in the positive drug group *via* aerosol inhalation. This treatment regimen lasted 20 min a day and spanned across 3 d. The same quantity of distilled water was administered to the control and model groups *via* oral gavage.

Histopathological preparation and analysis

The tissues from the dissected lungs were rapidly frozen in liquid nitrogen and kept at −80°C. The samples were fixed in a formaldehyde solution for 12 h before

being embedded in paraffin. Samples were dehydrated using various alcohol concentrations. Dehydrated samples were serially sectioned after fixing in paraffin. The sections were then stained for histological analysis with hematoxylin and eosin to examine the lung tissue's pathological state at 400× magnification. Lung damage was evaluated using a quantitative scoring system that assessed immune cell infiltration, alveolar wall thickening, and lung parenchymal destruction[15]. The scoring of lung injury was independently conducted by three researchers based on a standard protocol.

Reverse transcription-polymerase chain reaction

The TRIzol reagent was used to extract total RNA from mouse lung tissues in accordance with the manufacturer's instructions (Osaka, Japan). RT-PCR analysis was performed using the SYBR Premix Ex Taq Kit from Takara (Osaka, Japan). Reactions were performed using the StepOneTM platform from Applied Biosystems (Foster City, California, USA). To normalize the expression of the target gene, GAPDH was used as the internal standard and its expression levels were measured alongside the target gene.

ELISA assay

Blood samples were extracted and interleukin-6 (IL-6), IL-10, and tumor necrosis factor-α (TNF-α) levels were determined thrice using ELISA in accordance with the manufacturer's protocols.

Flow cytometry assay

Each sample received a cell suspension and locker before receiving either the CD4 or CD8 surface antibody and being incubated at 4°C for 30 min in the dark. Subsequently, the cells were rinsed with PBS and 250 μL of a membrane rupture agent was added to each sample. The samples were then incubated at 4°C for 20 min before being rinsed again and resuspended in 100 μL of the intracellular antibody, Foxp3. After 30 min of incubation in the dark, the samples were washed and filtered using a staining buffer. FlowJo software was used to analyze the data.

Statistical analysis

All values are displayed as the mean ± SD. GraphPad Prism software was used for the statistical analysis. One-way analysis of variance (ANOVA) was used to test the statistical significance of group differences. Statistical significance was defined as $P < 0.05$.

Results

XFBD effectively protects mice induced by coronavirus

To study the therapeutic effect in mice infected with CoV, we intranasally infected HCoV-229E ($TCID_{50}$ = 100) virus on days 5 and 6. XFBD was administered *via* oral gavage on the fifth, sixth, and seventh day, before being analyzed on the eighth day (Figure 1A). Compared to the model, XFBD reduced the viral load in the mouse lung tissue (Figure 1B). The administration of all three doses of XFBD resulted in a significant increase in gastrin (GAS) content (Figure 1C). Furthermore, the medium and high doses of XFBD led to a reduction in motilin (MTL) content (Figure 1D). Throughout the experiment, the activity, stool status, and skin hair condition of the mice in each group were observed on a daily basis. The experimental results revealed that XFBD had a more favorable effect on the mice compared to the model group.

XFBD attenuates lung injury induced by coronavirus in mice

The model group did not receive any medication, and as a result, the shade density and visual pulmonary quality were higher in the mice. However, after administering XFBD for 3 d, there was a significant reduction in the shaded area within the pulmonary field (Figure 2A). Pathological examination plays a crucial role in the diagnosis of inflammation. To assess changes in alveolar morphology and inflammatory cell infiltration, lung sections were stained with hematoxylin and eosin. Figure 2B shows that compared to the control group, the model mice exhibited slight destruction of the normal alveolar structure and infiltration of inflammatory cells within the tissues. Conversely, with the administration of XFBD, inflammation tended to decrease, and the lesions were significantly attenuated.

XFBD regulates the immune system of mice induced by coronavirus

When a pathogen breaks through the first barrier of the skin or mucosa, the immune system is activated, and an inflammatory reaction is rapidly initiated[16]. Most viral infections can be managed by the adaptive immune system. B cells, $CD4^+$ T cells, and $CD8^+$ T cells are essential components of the adaptive immune system. B cells are responsible for producing antibodies, which are crucial for immune defense. $CD4^+$ T cells have diverse functions, including assisting other immune cells and activating immune responses. $CD4^+$ T cells can differentiate into subsets with specific roles in fighting different types of viruses and responding to vaccines, whereas $CD8^+$ T cells are involved in cell-mediated immunity and play a vital role in eliminating infected or cancerous cells. Together, these cell types work in coordination, providing help and activating immune responses to combat pathogens and maintain immune function[17]. To investigate the effect of XFBD on immunity in mice infected with CoV, we studied inflammation and immunity. Compared to the model group, the three doses of XFBD reduced IL-6 and TNF-α expression. Furthermore, a high dose of XFBD (7.34 g/kg) effectively reduced the expression of IL-10 (Figure 3A). Moreover, all three XFBD doses significantly increased the number of $CD8^+$ T cells and high doses of XFBD (7.34 g/kg) effectively increased the numbers of $CD4^+$ T cells and B cells (Figure 3B).

Discussion

Low-temperature and high-humidity environments can lead to a reduction in human immunity against various infections. In this study, we developed a mouse model

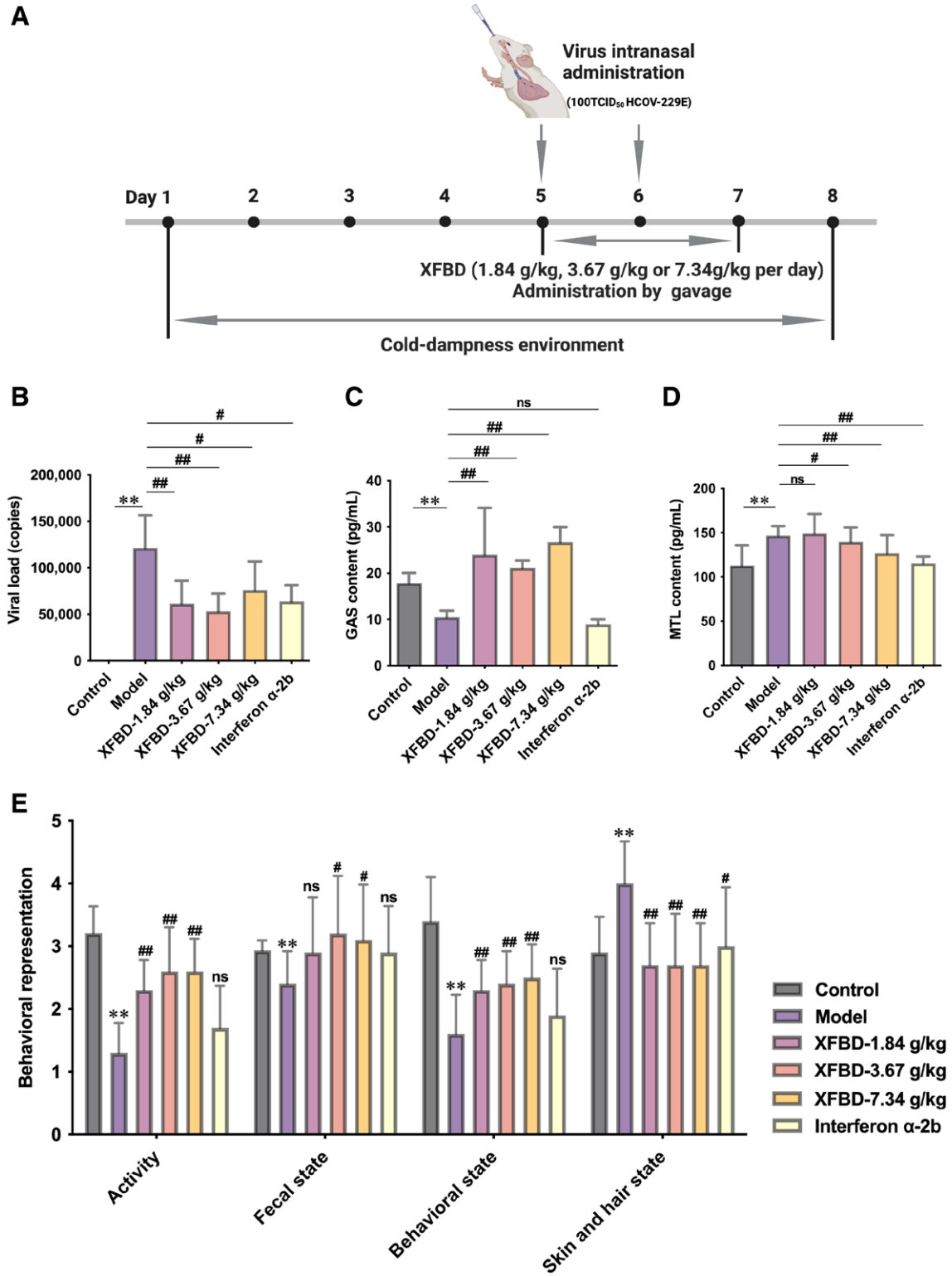

Figure 1. XFBD effectively protects mice induced by coronavirus. BALB/c mice were infected with virus (100TCID50 HCOV-229E) *via* intranasal administration, followed by oral administration of XFBD (1.84, 3.67, 7.34 g/kg) for 3 d. Mice were sacrificed on day 8. Throughout the experiment, the state of the mice was observed, and on the eighth day, blood and lung tissue samples from the mice were obtained for testing. (A) Experimental flowchart (B) viral load. (C, D) The content of GAS and MTL in serum. (E) Activity, fecal state, behavioral state, skin, and hair state of mice. GraphPad Prism software 5.0 was used for statistical analysis. Results are shown as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$, versus control group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, versus model group, $n = 10$. BALB/c: Bagg Albino; GAS: Gastrin; MTL: Motilin; XFBD: Xuanfei Baidu granules.

of human CoV pneumonia by infecting BALB/c mice with HCoV-229E in a cold and humid environment. After modeling, some of the mice demonstrated less activity and energy, messy and less shiny hair, a decrease in appetite, and soft stools, consistent with the clinical symptoms of CoV infections[18]. The symptoms induced by CoV infections under cold and damp conditions are more severe than those caused by a single CoV infection or exposure to cold and damp conditions alone[19]. Our findings demonstrated that XFBD is highly effective in

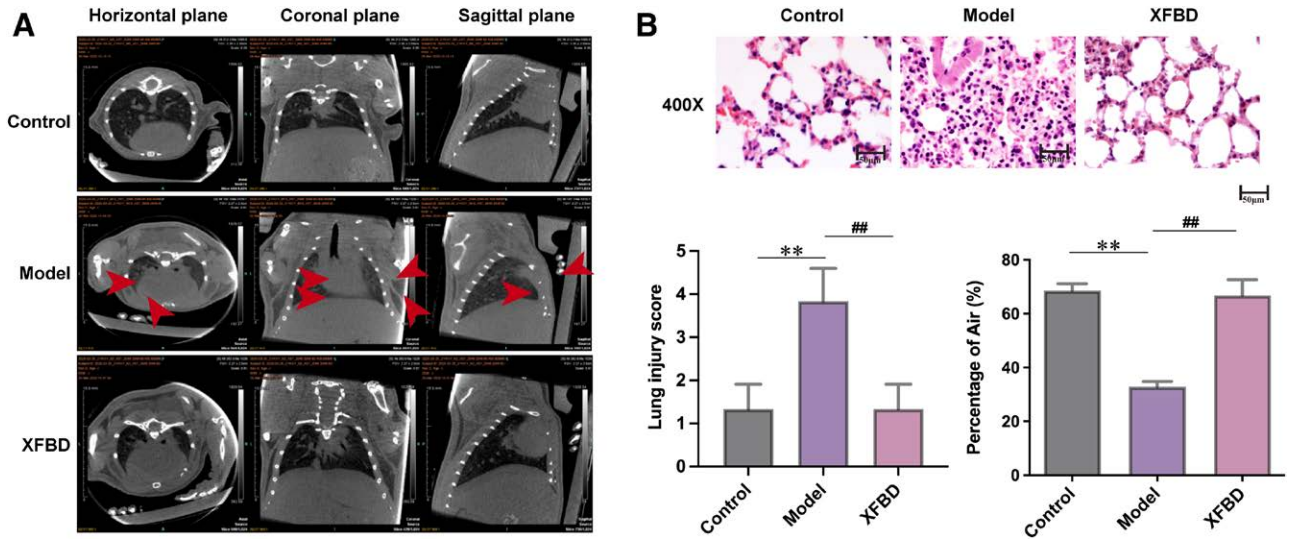

Figure 2. Observation of lung imaging and pathological staining. Mice were scanned with a μCT scanner on the eighth day. Each mouse underwent only one CT imaging session and was thereafter euthanized. Lung sections were stained with H&E staining on the eighth day to check the changes of alveolar morphology and inflammatory cell infiltration. (A) The horizontal, coronal, and sagittal fields of microscopic CT in XFBD high-dose group mice. (B) Representative pictures of H&E staining of lung tissue and the quantitative analysis of XFBD high-dose group mice. Scale bar stands for 50 μm. GraphPad Prism software 5.0 was used for statistical analysis. Results are shown as mean ± SD. $^{**}P < 0.01$, versus control group, $^{\#\#}P < 0.01$, versus model group, $n = 3$. μCT: Micro computed tomography; H&E: Hematoxylin and eosin; XFBD: Xuanfei Baidu granules.

treating human CoV pneumonia, even under cold and damp conditions. XFBD administration resulted in significant improvements in behavioral characteristics, gastrointestinal index, and lung virus titer in our model. Moreover, XFBD demonstrated a notable alleviation of lung injury in the mice.

Once a pathogen passes through the first layer of the skin or mucous membrane, both soluble and cellular innate defensive systems are activated, causing rapid inflammation[16]. Innate immune cells such as neutrophils, natural killer cells, and monocytes are drawn to the infection site by soluble inflammatory chemokines and activated complements that are produced in response to pathogens[16,20–21]. The pathogen is initially contained in innate inflammatory cytokines and cell clusters, but is ultimately eliminated by highly specialized, stimulated cells of the adaptive immune response[22]. Clinical illness can follow if the coordinated recruitment of both innate and adaptive immunity cannot keep the pathogen under control[16]. Research suggests that PD-1/IL17A is involved in the regulation of neutrophil infiltration, and that macrophages are a mechanism for XFBD treatment of lipopolysaccharide (LPS)-induced pulmonary injury. In addition, XFBD protects macrophages from inflammatory responses and lung fibrosis by inhibiting IL-6/STAT3[13]. Moreover, through multimodal screening, it was found that XFBD components, such as *Polygoni cuspidati Rhizoma*, *Phragmitis Rhizoma*, and *Citri grandis Exocarpium rubrum*, significantly reduced macrophage activation. Certain components of *Artemisia annua* and *Ephedra* herbs have shown significant inhibitory effects on endogenous macrophages[23]. Nevertheless, it remains uncertain whether these active ingredients would exhibit effectiveness in this particular model. Therefore, additional research is needed to validate this hypothesis. Herbal medicines are widely used to treat various ailments worldwide. However, their effectiveness and applications are not yet fully recognized, primarily due to their unclear mechanisms of action and the unknown active ingredients they contain[24]. It is particularly important to elaborate on the active ingredients and their mechanisms of action.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Qianru Zhao and Ronghua Zhao performed the experiments and wrote the manuscript. Zihan Geng and Shanshan Guo established a mouse model and analyzed *in vivo* data. Qianru Zhao and Lei Bao analyzed the data. Yu Wang and Xiaolan Cui designed the study. All the authors have read and approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

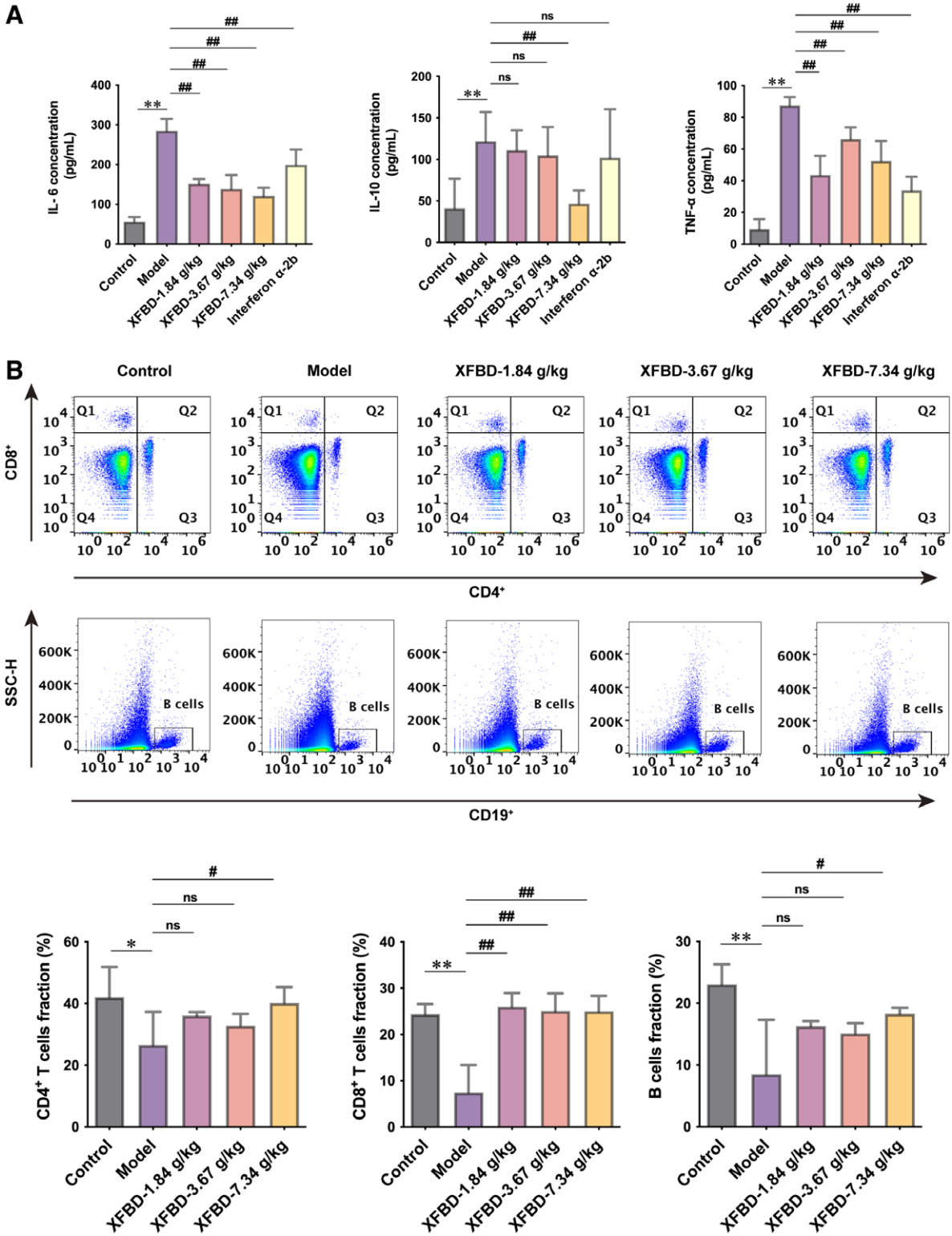

Figure 3. Effect of XFBD on immunological functioning. The release of proinflammatory cytokines brought on by viral infection was stopped by the administration of XFBD. On day 8, blood samples were collected and cytokine concentration was calculated using ELISA. Using flow cytometry, the fractions of $CD4^+$ T cells, $CD8^+$ T cells, and B cells were calculated. (A) The concentration of IL-6, IL-10, and TNF-α in serum. (B) The fraction of $CD4^+$ T cells, $CD8^+$ T cells, and B cells in peripheral blood. GraphPad Prism software 5.0 was used for statistical analysis. Results are shown as mean ± SD. $^*P < 0.05$, $^{**}P < 0.01$, versus control group, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, versus model group, $n = 6$. ELISA: Enzyme-linked immunosorbent assay; IL: Interleukin; TNF-α: Tumor necrosis factor-α; XFBD: Xuanfei Baidu granules.

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