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Yunpi Xiefei Huatan Tang decoction reduces airway inflammation and airway remodeling in asthmatic mice through Wnt/ β -catenin signaling pathway

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Abstract

Background: Asthma is one of the most prevalent chronic respiratory diseases among children, markedly impairing patient's health and imposing an increasing burden on the healthcare system. Several traditional Chinese medicines have demonstrated efficacy in alleviating asthma symptoms through studies conducted on animal models. Recent studies have shown that the Yunpi Xiefei Huatan Tang decoction (YPD) exhibits significant therapeutic outcomes in treating phlegm-obstructed pulmonary asthma. However, the precise regulatory effects of YPD on the progression of asthma require additional investigation.

Objective: To explore the functions of YPD in asthma progression.

Material and Methods: The asthma rat model triggered by ovalbumin (OVA) was established successfully. The pathological changes of lung tissues were examined through Hematoxylin and Eosin (H&E) staining. The levels of Interleukin 6 (IL-6) and IL-1 β were tested through Enzyme-Linked-Immunosorbent Serologic Assay (ELISA). The number of total cells or eosinophils in bronchoalveolar lavage fluid was confirmed through cell counter. The collagen deposition in bronchi was assessed through Masson staining. The protein expressions were measured through western blot.

Results: This study demonstrated that YPD could mitigate airway inflammation in an OVA-triggered asthma rat model. Furthermore, YPD was found to decrease the production of inflammatory cytokines in the lungs and suppress the infiltration of inflammatory cells into bronchoalveolar lavage fluid. Additionally, the airway remodeling stimulated by OVA could be suppressed following YPD treatment. Finally, it was disclosed that YPD inhibited the wingless-related integration site-beta-catenin (Wnt/ β -catenin) signaling pathway in the OVA-stimulated asthma rat model.

Conclusion: YPD alleviated airway inflammation and remodeling in asthmatic mice via the Wnt/ β -catenin signaling pathway. This research offers significant insights into the potential application of YPD in the treatment of asthma.

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Introduction

Asthma is a heterogeneous condition characterized by variable and progressively intensifying respiratory symptoms, such as cough, chest tightness, and wheezing.¹ The prolonged exposure to aeroallergens can lead to increased type 2 cytokines, eosinophilia, elevated allergen-specific immunoglobulin E (IgE), and airway hyperresponsiveness, resulting in airway inflammation and remodeling in asthma.² The annual global prevalence of asthma is on an upward swing, probably attributed to its complex pathogenesis. Currently, the worldwide prevalence stands at 4%, with a notably higher prevalence of 14% among children aged <5 years.^{3,4} Diseases such as COVID-19, lung cancer, chronic obstructive pulmonary disease (COPD), and lung fibrosis are known to adversely affect airway inflammation, airway remodeling, and lung function.⁵⁻⁷ Glucocorticoids have traditionally been regarded as the primary pharmacological intervention for asthma management. Nonetheless, their efficacy in the clinical setting is compromised in instances of severe asthma, and their utilization is constrained by the adverse effects associated with high-dose or prolonged treatment.⁸ Consequently, the primary focus is to discover more effective medications to mitigate asthma.

Recent studies have demonstrated that various traditional Chinese medicines effectively alleviate asthma symptoms in animal models. Notably, the *Soufeng Yuchuan* decoction has shown promise in ameliorating lung damage in mice subjected to ovalbumin (OVA)-induced asthma mode.⁹ Granules of *Yanghe Pingchuan* showed promise in preventing airway remodeling in asthma.¹⁰ Furthermore, extracts of *Salvia miltiorrhiza Bunge (Danshen)* demonstrated to alleviate allergic asthma in mice induced by OVA through the modulation of airway inflammation and remodeling.¹¹ *Suhuang* antitussive capsule could protect against airway inflammation and remodeling in chronic asthma.¹²

Yunpi Xiefei Huatan Tang (YPD) comprises a formulation of several traditional Chinese medicinal components, such as *Dan Nan Xing*, *Quan gua lou*, *Zhe beimu*, *Faxia*, almond, *Scutellaria baicalensis*, *Poria cocos*, *Chenpi*, betel nut, *jiao hawthorn*, *Fructus aurantii*, *Citrus aurantium*, and licorice. This prescription originated from *Qingqi Huatan* pill, as documented in the “*Yi fang kao*” It was developed by Professor Chen Zhu in collaboration with traditional Chinese medicine practitioner Huang Jianye by incorporating his many years of clinical experience. Previous studies demonstrated that YPD has had significant therapeutic effects in treating asthma with phlegm obstruction in the lungs. However, more research is needed to understand the specific regulatory impacts of YPD on the progression of asthma and to determine whether YPD can be used to treat asthma patients.

This study disclosed that YPD mitigates airway inflammation and remodeling in asthmatic mice via wingless-related integration site-beta-catenin (Wnt/ β -catenin) signaling pathway. This research indicated that YPD could represent a novel and efficacious therapeutic option for ameliorating asthma in clinical settings.

Materials and Methods

Asthma mice model

Sprague-Dawley (SD) mice (6-week-old males, 180-200 g, n = 30) were bought from Vital River Laboratory Animal Technology Co. (Beijing, China). All mice were deprived of food and water (12-h light/dark cycle, 25±1°C). The animals were randomly divided into the following five groups (six mice in each group): control, OVA, OVA+0.005 mL/g YPD, OVA+0.01 mL/g YPD, and OVA+0.02 mL/g YPD.

The asthma mice model was established by inducing OVA (grade V; Sigma, MA, USA). On day 1, mice were injected intraperitoneally (i.p.) with 1-mL 10% OVA solution (Shanghai Xinyu Biotechnology Pharmaceutical Co., Shanghai, China). From day 14, the mice were treated with 1% OVA solution (diluted in normal saline) by nebulization for 20 min (daily for 3 days, then once every other day) until the mice developed asthma symptoms, such as accelerated respiration, wheezing breathing, sneezing, and abdominal spasm. Mice in the control group were treated with normal saline. Different concentrations (0.005 mL/g, 0.01 mL/g, or 0.02 mL/g) of YPD (*Dan Nan Xing*, *Quan gua lou*, *Zhe beimu*, *Faxia*, almond, *Scutellaria baicalensis*, *Poria cocos*, *Chenpi*, betel nut, *jiao hawthorn*, *Citrus aurantium*, and licorice) were administered orally (daily for 21 days). Then the animals were sacrificed for further experiments.

Hematoxylin and Eosin (H&E) staining

The lung tissues of mice were subjected to dehydration and permeabilization and subsequently embedded in paraffin. Then the tissues were sliced into 4- μ m sections, stained with hematoxylin (5 min) and eosin (2 min), and evaluated for pathological changes using a microscope (Olympus Corporation, Tokyo, Japan).

Enzyme-Linked-Immunosorbent Serologic Assay (ELISA)

Interleukin 6 (IL-6; ab234570; Abcam, Shanghai, China) and IL-1 β (ab255730; Abcam) ELISA kits were employed for assessing the levels of IL-6 and IL-1 β in bronchoalveolar lavage fluid (BALF).

Cell counting

The lavage fluid was centrifuged. Then, the cell sediment was resuspended in phosphate-buffered saline (PBS) solution to create cell suspension. Following the removal of liquid, the cells were stained with Diff-Quik solution. The total number of cells or eosinophils was counted using a cell counter.

Masson staining

The bronchovesicular tissue-embedded paraffin was sectioned into 4- μ m sections. These sections were then

stained using Masson's trichrome staining solution (Sigma, St Louis, MO, USA) and observed under a microscope (Olympus Corporation).

Western blot analysis

The proteins from bronchovesicular tissues underwent separation using 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Subsequently, the proteins were transferred to a polyvinylidene difluoride membrane (PVDF; Millipore, Billerica, MA, USA). The membranes were then incubated with primary antibodies for 12 h, followed by a 2-h incubation with secondary antibodies (1/1000; ab6721). Finally, the bands were visualized using an enhanced chemiluminescence kit (Thermo Fisher Scientific, MA, USA).

Primary antibodies were as follows: α -SMA (1/10,000; ab124964, Abcam), Wnt3a (1/1000; ab219412), β -catenin (1/5000; ab32572), c-Myc (1/1000; ab32072), and glyceraldehyde 3-phosphate dehydrogenase (GAPDH; 1/500; ab8245).

Statistical analysis

The data were presented as mean \pm standard deviation (SD). The statistical analyses were conducted using the GraphPad Prism Software version 9 (GraphPad Software, CA, USA). Differences between groups were assessed through one-way analysis of variance (ANOVA), with $P < 0.05$ considered statistical significance.

Results

Yunpi Xiefei Huatan Decoction Alleviated Airway Inflammation Triggered by OVA

The mice were induced with OVA to simulate asthma. H&E staining revealed increased inflammatory infiltration,

disordered airway epithelial structure, and narrowed airway lumen after OVA treatment. However, these effects lessened following the YPD treatment (Figure 1). In general, YPD alleviates airway inflammation triggered by OVA.

Yunpi Xiefei Huatan Decoction Reduced the Generation of Inflammatory Cytokines in Lung and Restrained the Infiltration of Inflammatory Cells in Bronchoalveolar Lavage Fluid

The concentrations of IL-6 and IL-1 β were elevated following OVA induction; however, this elevation was mitigated following the treatment with YPD (Figure 2A). Furthermore, the total number of cells or eosinophils in BALF increased, but this effect was reduced after YPD treatment (Figure 2B). YPD significantly diminished the production of inflammatory cytokines in the lungs and curtailed the infiltration of inflammatory cells into BALF.

Yunpi Xiefei Huatan Decoction Suppressed Airway Remodeling Stimulated by OVA

The accumulation of collagen fibers increased after OVA stimulation, but this change was reversed following the YPD treatment (Figure 3A). Furthermore, the expression of α -SMA protein was elevated after induction of OVA; however, this elevation was mitigated by YPD treatment (Figure 3B). Concisely, YPD effectively suppressed the airway remodeling stimulated by OVA.

Yunpi Xiefei Huatan Decoction Retarded the Wnt/ β -catenin Signaling Pathway

Following the OVA induction, a notable up-regulation was observed in the protein expressions of Wnt3a, β -catenin, and c-Myc. However, subsequent treatment with YPD neutralized these effects, as evidenced in Figure 4. This

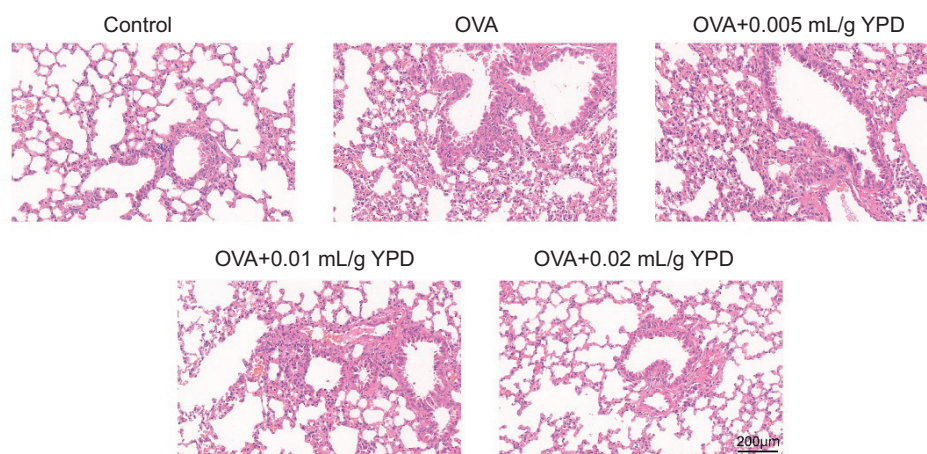


Figure 1 Yunpi Xiefei Huatan decoction alleviates airway inflammation triggered by OVA. Groups were divided into control, OVA, OVA+0.005 mL/g YPD, OVA+0.01 mL/g YPD, and OVA+0.02 mL/g YPD. Pathological changes in lung tissues were examined by H&E staining.

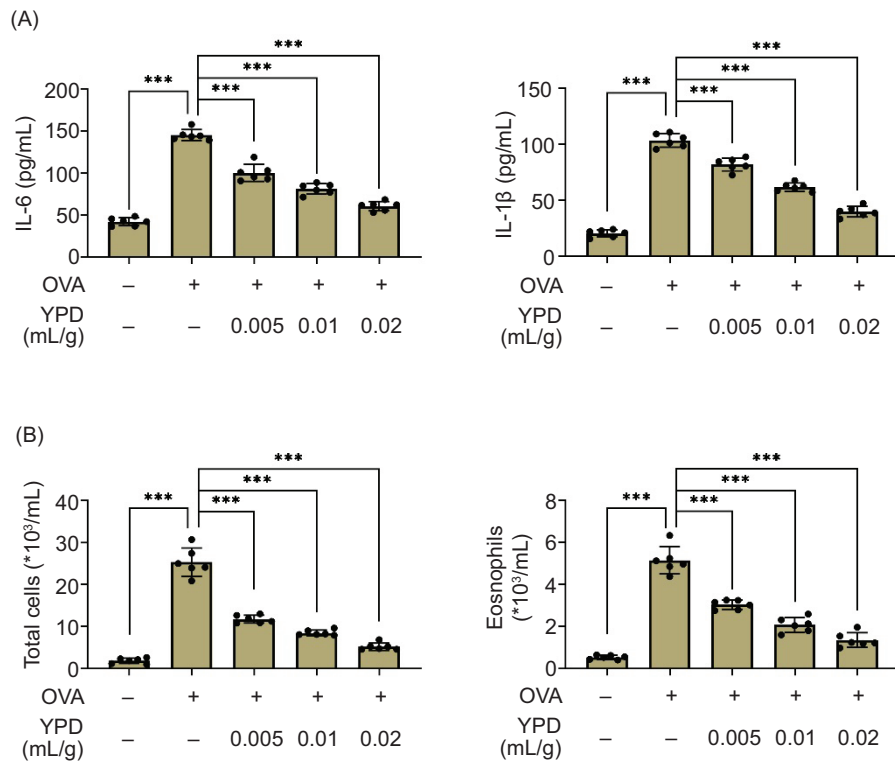


Figure 2 Yunpi Xiefei Huatan decoction reduces the generation of inflammatory cytokines in the lungs and restrains the infiltration of inflammatory cells in BALF. Groups were divided into control, OVA, OVA+0.005 mL/g YPD, OVA+0.01 mL/g YPD, and OVA+0.02 mL/g YPD group. (A) The levels of IL-6 and IL-1 β were tested by using ELISA. (B) The number of total cells or eosinophils in BALF was confirmed by using cell counter. ***P < 0.001.

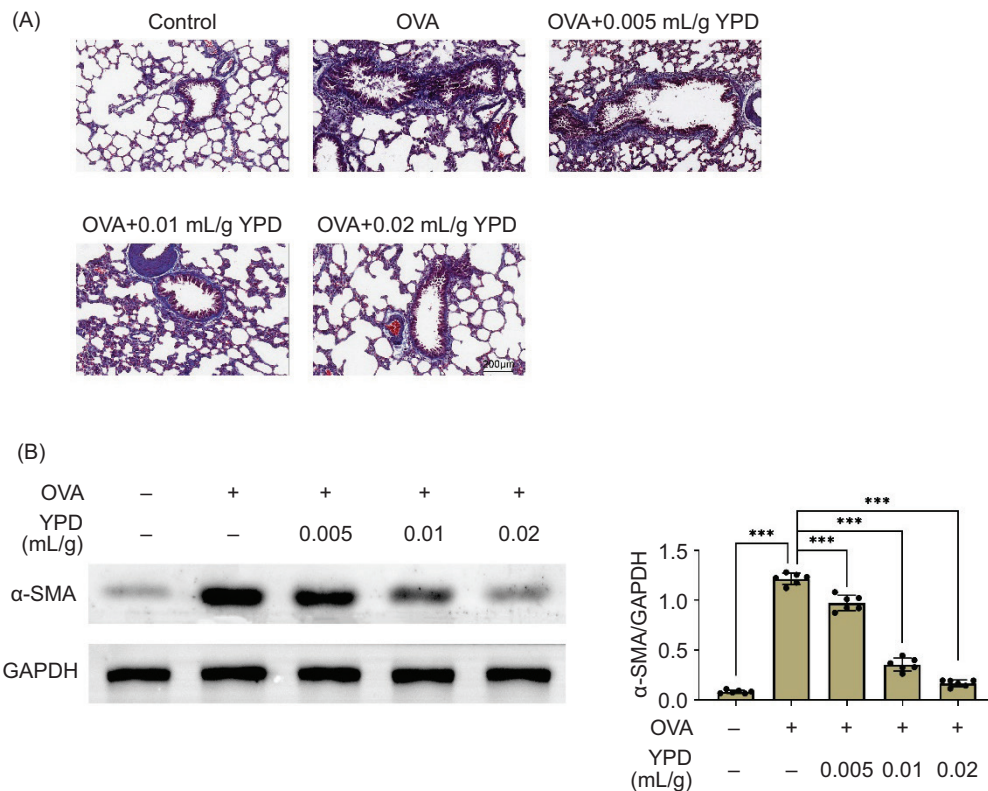


Figure 3 Yunpi Xiefei Huatan decoction suppresses airway remodeling stimulated by OVA. Groups were divided into control, OVA, OVA+0.005 mL/g YPD, OVA+0.01 mL/g YPD, and OVA+0.02 mL/g YPD. (A) Collagen deposition in bronchi was assessed by Masson staining. (B) The α -SMA protein expression was measured by Western blot analysis. ***P < 0.001.

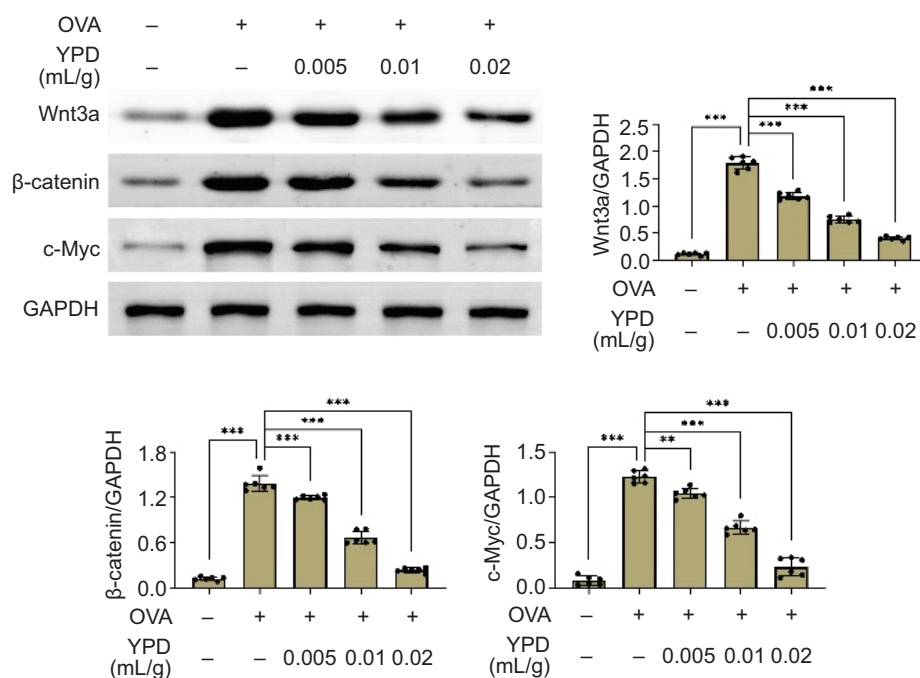


Figure 4 Yunpi Xiefei Huatan decoction retarded the Wnt/ β -catenin signaling pathway. Groups were divided into control, OVA, OVA+0.005 mL/g YPD, OVA+0.01 mL/g YPD, and OVA+0.02 mL/g YPD. The protein expressions of Wnt3a, β -catenin, and c-Myc were evaluated through Western blot analysis. ** $P < 0.01$, *** $P < 0.001$.

observation suggested that YPD effectively inhibited the Wnt/ β -catenin signaling pathway.

Discussion

Several rehabilitation strategies are effectively implemented in asthma management, such as breathing techniques, prescribed exercise regimens, comprehensive health education, psychological support, and nutritional interventions.^{13,14} Some traditional Chinese medicines (*Soufeng Yuchuan* decoction, *Yanghe Pingchuan* granules, *Salvia miltiorrhiza Bunge* extracts, and *Suhuang* antitussive capsule) are proved to relieve symptoms associated with asthma.⁹⁻¹² YPD is also a traditional Chinese medicinal formula that has demonstrated significant therapeutic effects in phlegm obstructive pulmonary asthma. However, the intricate regulatory effects of YPD in the progression of asthma necessitated thorough investigations. Accordingly, this research through a series of experiments aimed to ascertain whether YPD could alleviate asthma progression.

The chronic and long-term presence of airway inflammation is a key pathological feature in the progression of asthma.¹⁵ Many researchers have focused on investigating the modulation of inflammation in asthma. For example, formononetin is found to alleviate airway inflammation and oxidative stress in allergic asthma.¹⁶ Oroxlylin A helps to reduce allergic airway inflammation in OVA-induced asthma.¹⁷ In a rat model of OVA-mediated asthma, flavonoids derived from *Selaginella uncinata* are shown to relieve airway inflammation.¹⁸

Additionally, the root extract of *Adenophora stricta* lessens airway inflammation in mice with OVA-induced asthma.¹⁹ This study showed that YPD could alleviate airway inflammation in an OVA-triggered asthma rat model. Furthermore, YPD reduced the production of inflammatory cytokines in the lungs and inhibited the infiltration of inflammatory cells in BALF.

The chronic inflammatory response within the airways is closely linked to structural alterations known as airway remodeling.^{20,21} This remodeling is a crucial characteristic of severe asthma and has garnered significant attention. For example, quercetin inhibits the transforming growth factor-beta-suppressor of mothers against decapentaplegic homolog 3 (TGF- β 1/Smad3) signaling pathway, attenuating asthma-induced airway inflammation and remodeling.²² In asthma management, bergenin enhances deacetylase sirtuin 1 (SIRT1) to modulate the nuclear factor κ B (NF- κ B) pathway, alleviating airway inflammation and remodeling.²³ Additionally, schisandrin B inhibits oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in asthma, alleviating airway inflammation and remodeling.²⁴ Similarly, this study suggests that YPD treatment can suppress airway remodeling stimulated by OVA, indicating that YPD has the potential to alleviate airway remodeling.

The Wnt/ β -catenin signaling pathway is a critical regulator involved in the progression of asthma. Notably, vitamin D inhibits the Wnt/ β -catenin signaling pathway in asthma to alleviate airway remodeling.²⁵ Curcumin impacts the Wnt/ β -catenin signaling pathway, attenuating lung inflammation in asthmatic mice.²⁶ Additionally, secreted frizzled-related protein 5 (SFRP5) modulates the

Wnt/ β -catenin signaling pathway, restraining cell proliferation and migration in pediatric asthma.²⁷ Moreover, mesenchymal stem cells (MSCs) inhibit the Wnt/ β -catenin signaling pathway, mitigating airway remodeling in asthmatic mice.²⁸ In this study, it was discovered that YPD also inhibited the Wnt/ β -catenin signaling pathway in the OVA-stimulated asthma rat model.

Conclusion

In conclusion, the study found that YPD effectively reduced airway inflammation and airway remodeling in asthmatic mice through Wnt/ β -catenin signaling pathway. However, it's essential to acknowledge the limitations of this project, such as the absence of clinical investigations, cell models, and other animal models. Future research should focus on conducting more comprehensive investigations into the impact of YPD on the progression of asthma.

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Competing Interests

The authors stated that there were no conflicts of interest to disclose.

Ethics Approval

Ethical approval was obtained from the Ethics Committee of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (Approval No. KYW20230022).

Data Availability

The authors declare that all data supporting the findings of this study are available within the paper and any raw data can be obtained from the corresponding author upon request.

Author Contribution

Li Du and Zhu Chen—designed the study and carried out the same. Li Du, Zhu Chen, Qiong Tao, Jianhui Yang, Na Chen, and Qiao Wang—supervised data collection. Li Du, Zhu Chen, Qiong Tao, Jianhui Yang, Na Chen, and Qiao Wang—analyzed the data. Li Du, Zhu Chen, Qiong Tao, Jianhui Yang, Na Chen, and Qiao Wang—interpreted the data. Li Du and Zhu Chen—prepared the manuscript for publication and reviewed its draft. All authors had read and approved the final manuscript.

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