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ORIGINAL RESEARCH

Multi-Target Therapeutic Effects of YuPingTongQiao (YPTQ) in Allergic Rhinitis: A Traditional Chinese Medicine Restoring Dysregulated T_{FR} Cells and Reinforcing Epithelial Barrier Integrity

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Background: Allergic rhinitis (AR) is a prevalent chronic inflammatory disease characterized by immune dysregulation and epithelial barrier dysfunction. Conventional therapies are often limited by side effects and insufficient efficacy in addressing the underlying pathophysiology. To explore alternative approaches, this study investigated the potential of YuPingTongQiao (YPTQ), a novel Traditional Chinese Medicine (TCM) formulation, as a multi-target treatment for AR.

Methods: An ovalbumin-induced AR rat model was established. Nasal allergic symptoms were assessed using a standardized scoring system. Histopathology, FC, RT-qPCR, and ELISA were performed to assess epithelial integrity, cell infiltration, cytokine expression, and immune cell phenotypes.

Results: YPTQ significantly alleviated AR symptoms, including nasal rubbing, sneezing, and rhinorrhea, in a dose-dependent manner. The high-dose YPTQ (YPTQ-H) group demonstrated superior efficacy compared to Loratadine. Mechanistically, YPTQ suppressed T_H2 cytokines (IL-4, IL-5, IL-13) and IL-33, restored follicular regulatory T (T_{FR}) cell balance, and increased CTLA4 expression, thus mitigating IgE-mediated immune responses. Additionally, YPTQ enhanced epithelial barrier integrity by upregulating Claudin1 and reduced mucus hypersecretion by suppressing MUC2 expression. Histological analysis revealed decreased infiltration of eosinophils, mast cells, and goblet cells in the nasal mucosa.

Conclusion: YPTQ offers a safe, effective, and multi-target therapeutic option for AR, addressing both immune dysregulation and epithelial dysfunction. Its superior efficacy compared to Loratadine and excellent safety profile highlight its potential as a novel alternative or adjunct to conventional treatments for AR.

Keywords: allergic rhinitis, traditional Chinese medicine, multi-target therapy

Introduction

Allergic rhinitis (AR), a chronic inflammatory disorder of the nasal mucosa, has shown a rising prevalence globally, leading to significant socioeconomic burdens.[1,2] Central to its pathogenesis is immunoglobulin E (IgE), the least abundant immunoglobulin isotype, which plays a pivotal role in mediating allergic responses.[3] Upon allergen-IgE binding, the high-affinity IgE receptor FcεRI, predominantly expressed on mast cells and basophils, undergoes cross-linking.[4] This process triggers the degranulation of inflammatory mediators, resulting in characteristic allergic symptoms and promoting type 2 T-helper (T_H2) cell polarization.[5]

While conventional paradigms have long emphasized the role of T_H2 cells in IgE regulation, emerging evidence from both murine and human studies highlights the indispensable role of follicular helper T (T_{FH}) cells in IgE synthesis.[6] Notably,

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follicular regulatory T (T_{FR}) cells, characterized by the expression of Foxp3 and Bcl-6, modulate this process through CTLA4-mediated suppression of T_{FH} activity.[7] This immunoregulatory axis effectively limits IgE production and mitigates allergic responses, offering a new perspective on the underlying mechanisms of AR pathogenesis.[8]

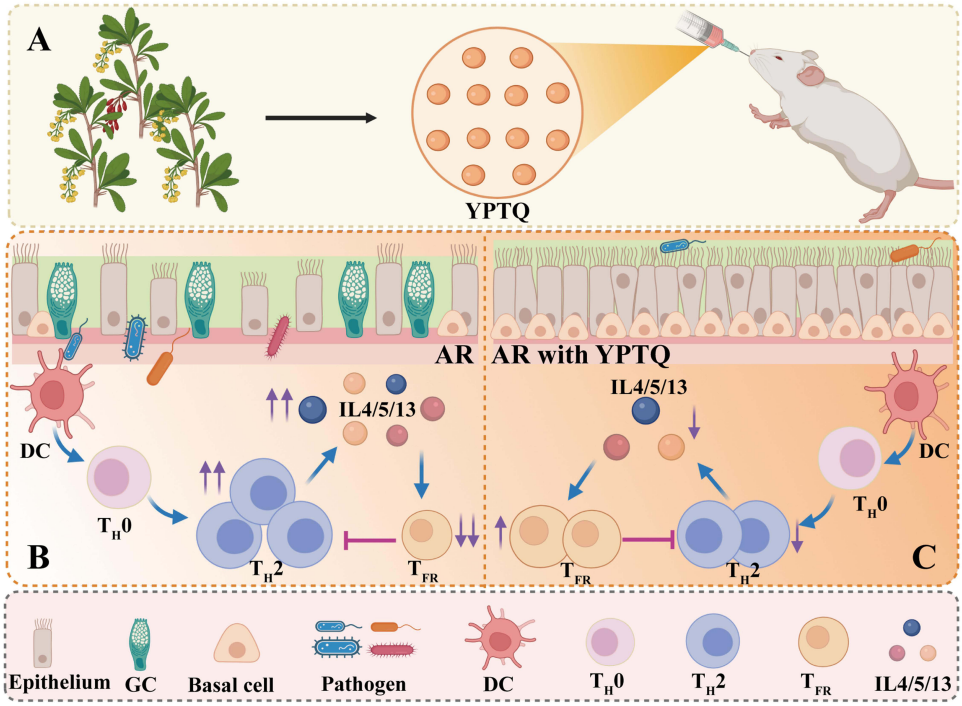
Current therapeutic strategies for AR remain predominantly palliative rather than curative. First-line pharmacological treatments, including antihistamines, corticosteroids, and leukotriene receptor antagonists, provide symptomatic relief but are often associated with adverse effects and high costs. For example, antihistamines may cause central nervous system side effects, such as somnolence and cognitive impairment, while long-term corticosteroid use increases the risk of adrenal suppression and osteoporosis.[9] Although allergen-specific immunotherapy (AIT) has shown efficacy in managing intermittent AR, its clinical application is limited by the need for prolonged subcutaneous regimens and suboptimal outcomes in persistent AR cases.[10] As a result, there is an urgent need to develop safe, effective, and cost-efficient therapeutic alternatives that address the root causes of AR.

Traditional Chinese medicine (TCM) has gained increasing recognition as a complementary therapeutic paradigm for AR management. Classified as "Bi Qiu" in TCM doctrine, this condition has been extensively characterized through historical medical treatises describing its etiology and treatment principles.[11] TCM interventions exhibit distinctive advantages over conventional pharmacotherapy, particularly in symptom amelioration, immune modulation, reduced adverse events, and enhanced treatment accessibility.[12,13] YuPingTongQiao (YPTQ) represents a novel TCM formulation derived from classical theories of "Bi Qiu" treatment, specifically targeting the pathomechanism of "lung-spleen dual deficiency with exogenous pathogen invasion". This study systematically investigates the therapeutic efficacy and mechanistic underpinnings of YPTQ to establish an evidence-based foundation for clinical implementation (Scheme 1).

Materials and Methods

Animals

Sixty male Sprague-Dawley (SD) rats, aged 6–8 weeks, were obtained from the Animal Experiment Center of Ren Ji Hospital (Shanghai, China). The sample size was determined based on the requirements for conducting ELISA, qPCR,



Scheme 1 Schematic diagram of YPTQ treatment mechanism for allergic rhinitis. (**A**) YPTQ is administered to allergic rhinitis rats via gavage. (**B**) In AR rats, the nasal mucosal epithelial barrier is damaged, T_H2 cells are overly activated, and T_{FR} cells are inhibited. (**C**) After YPTQ treatment, the nasal mucosal epithelial barrier is effectively restored, reversing the immune imbalance in the nasal mucosa. Created with Biorender.com.
Abbreviations: GS, goblet cells; DC, dendritic cells; Tn, naive T cells; T_{FR}, follicular regulatory T cells.

and flow cytometry experiments. Experimental units were defined as cages, with three animals housed per cage. Inclusion criteria required that all animals be healthy and of similar age and weight. Animals showing signs of illness or significant weight variance were excluded from the study. The animals were maintained in a controlled environment with a consistent temperature of 22 ± 3°C, relative humidity of 55 ± 5%, and a 12-hour light/dark cycle throughout the study. All experimental procedures were conducted in compliance with the Guide for the Care and Use of Laboratory Animals and approved by the Ethics Committee of RenJi Hospital (approval number: RJ2023-134A).

Analysis of YPTQ Ethanol Extract

The YPTQ tablets, with a specification of 0.47 g per tablet (batch number A2101001), were obtained from Beijing Yiling Pharmaceutical Co., Ltd. The commercially available loratadine (batch number MDJ481J) was obtained from Xi'an Janssen Pharmaceutical Co., Ltd. The ethanol extract of YPTQ was analyzed using a Dionex UltiMate 3000 system coupled with a Thermo Q-Exactive mass spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) for ultra-high-performance liquid chromatography-diode array detection coupled with quadrupole-orbitrap mass spectrometry (UHPLC-DAD-MS/MS). Chromatographic separation was performed on an ACQUITY BEH C18 column (100 × 2.1 mm, 1.7 μm) under a gradient elution system comprising 0.1% formic acid in water and acetonitrile. Spectra were acquired in positive ion mode, and data were processed using Xcalibur v.3.0, Tracefinder v.4.0, and Compound Discoverer 3.1 (Thermo Fisher Scientific, Waltham, MA, USA). Phytochemicals in the YPTQ extract were identified based on their mass spectral profiles and comparisons with databases such as mzCloud (https://www.mzcloud.org). This analysis successfully elucidated the chemical composition of the YPTQ ethanol extract, highlighting its bioactive potential.

Composition and Botanical Verification of YuPingTongQiao (YPTQ)

Huangqi (*Astragalus membranaceus* (Fisch). Bunge), root; Baizhu (*Atractylodes macrocephala* Koidz)., rhizome; Fangfeng (*Saposhnikovia divaricata* (Turcz). Schischk)., root; Xinyi (*Magnolia biondii* Pamp)., flower bud; Baizhi (*Angelica dahurica*), root; Gaoliangjiang (*Alpinia officinarum* Hance), rhizome; Qianghuo (*Notopterygium incisum* Ting ex H. T. Chang), rhizome and root; Mudanpi (*Paeonia suffruticosa* Andr)., root bark; Chantui (*Cryptotympana atrata* (Fabricius)), exuviae; Wumei (*Prunus mume* (Sieb). Sieb. et Zucc)., nearly mature fruit; Gancao (*Glycyrrhiza uralensis* Fisch)., root and rhizome.

Rat AR Model and Treatments

Sixty SD rats (6–8 weeks) were randomly assigned to six groups using a simple random assignment method: Control (Con), Allergic Rhinitis (AR), YPTQ-Low (YPTQ-L), YPTQ-Medium (YPTQ-M), YPTQ-High (YPTQ-H), and Loratadine (n = 10 per group). The study was approved by the Ethics Committee of RenJi Hospital (approval number: RJ2023-134A).

The AR rats model was established as previously described.[14,15] Sensitization was induced by intraperitoneal injections of 50 μg ovalbumin (OVA) mixed with 4 mg aluminum hydroxide (Alum) in 400 μL on days 0, 2, 4, 6, 8, 10, 12, and 14. From days 15–21, the Con group received 20 μL of PBS intranasally, while the remaining groups were administered 20 μL of 5% OVA intranasally once daily for 7 days. From days 22–35, the Con group continued receiving 20 μL of PBS intranasally, whereas the other groups received 20 μL of 5% OVA intranasally every other day for a total of 7 administrations.

Starting on day 15, intragastric treatments were conducted daily. The Con and AR groups received 3 mL of PBS via gavage, while the YPTQ-L, YPTQ-M, and YPTQ-H groups received 3 mL of PBS containing 0.1128 g, 0.2256 g, and 0.4512 g of YPTQ, respectively. The Loratadine group received 3 mL of PBS containing 0.3 mg of loratadine via gavage. Allergic rhinitis was considered successfully induced in rats with allergy scores exceeding 5 (Table S1).

Serum Biochemical Parameter Assessment

AST (aspartate transaminase), ALT (alanine transaminase), and Cr (creatinine) enzyme activities were measured in serum using FUJI DRI-CHEM SLIDE kits (FUJIFILM, Tokyo, Japan) according to the manufacturer's instructions.

Diff-Quick Straining

After euthanasia, the nasal cavity was gently perfused with 1 mL of ice-cold PBS from the trachea to the nasopharynx, and nasal lavage fluid (NALF) was collected immediately. For differential cell count analysis, 100 μL of NALF was centrifuged using a cytospin (Beyotime Biotechnology, China). The resulting slides were stained with Diff-Quick (Sysmex Co., Japan) according to the manufacturer's instructions.

Enzyme-Linked Immunosorbent Assay (ELISA)

Supernatants were collected as described previously. The levels of IL4, IL5, IL13, IL33, IgE, and OVA-specific IgE in the rats were quantified using ELISA kits (Elabscience Biotechnology, China) following the manufacturer's protocols. Absorbance at 450 nm (A450) was measured using a microplate reader. A standard curve (Figure S1) was generated, and the concentration of each sample was calculated accordingly.

Reverse Transcription Quantitative Real-Time Polymerase Chain Reaction (RT-qPCR)

Total RNA was extracted from cells and nasal mucosa using TRIzol reagent (Thermo Fisher, USA) in accordance with the manufacturer's guidance. The RNA was reverse-transcribed into complementary DNA (cDNA) using the miScript II RT Kit (Takara, Japan). RT-qPCR was conducted using the miScript SYBR Green PCR Kit (Novoprotein Scientific, China) on a QuantStudio7 Flex PCR system. Each experiment was performed in triplicate, and primer sequences are provided in Table S2. Gene expression levels were calculated using the $2^{-\Delta\Delta CT}$ method.

Hematoxylin-Eosin (HE), Toluidine Blue (TB), Periodic Acid-Schiff (PAS) Staining and Immunohistochemistry (IHC)

After collecting the nasal lavage fluid (NALF), the rat heads were fixed in 10% neutral buffered formaldehyde solution (Sigma-Aldrich, USA) for 48 hours, decalcified in 0.1 M EDTA buffer (Bio-solution, Korea) for one month, and embedded in paraffin. Coronal sections of 5 μm thickness were prepared from the paraffin blocks, with some sections stained using HE (Sigma-Aldrich, USA), PAS (Sigma-Aldrich, USA), or TB (Sigma-Aldrich, USA), respectively.

Other sections were processed for immunohistochemistry (IHC). These sections were incubated with primary antibodies, including anti-MUC2 antibody (1:200, Abbiotec, USA), anti-Claudin1 antibody (1:200, LifeSpan BioSciences, USA), and anti-CTLA4 antibody (1:200, Abbiotec, USA). Afterward, the sections were incubated with a secondary antibody diluted in antibody buffer for 1 hour at room temperature, followed by several PBS washes. DAB was applied for color development, and nuclei were counterstained with hematoxylin. The proportion of positive cells was calculated by counting all or 100 submucosal cells in each high-magnification field.

The slides were scanned using the Pannoramic DESK digital scanner (NANOZOOMER S360, China) and analyzed with Pannoramic Case software (NANOZOOMER S360, China). Submucosal eosinophil, mast cell, and goblet cell counts, as well as the proportion of positive cells and staining intensity in IHC, were evaluated by two independent pathologists blinded to the sample information. Counts were performed in 10 randomly selected high-magnification fields (×400) for each sample.

Flow Cytometry Analysis

Following euthanasia by carbon dioxide asphyxiation, 20 mg of nasal mucosa was collected and digested in 5 mL of DMEM solution (Biowest, France) containing 5 mg of collagenase type II (Sigma-Aldrich, USA) and 50 μg of DNAase (Sigma-Aldrich, USA) at 37°C for 1.5 hours. The resulting suspension was filtered and centrifuged at 450 g for 5 minutes. The nasal mucosal cells were resuspended in PBS after filtration and centrifugation.

The cell suspension was divided into several portions for analysis. One portion was incubated with IgE-PE (Biolegend, USA), CD3-AF488 (Biolegend, USA), and CD4-BV650 (Biolegend, USA) separately at 4°C in the dark for 60 minutes. Another portion was incubated with CD4-AF488 (Biolegend, USA) and CXCR5-APC (Biolegend, USA) under the same conditions, followed by permeabilization with specific reagents and further incubation with Foxp3-PE

(Biolegend, USA) at 4°C in the dark for 60 minutes. After washing with PBS and resuspension, the samples were analyzed using a flow cytometer (FACS Celesta, USA) and FlowJo software (version 10.6.2, Treestar, USA).

Statistical Analysis

All experiments were conducted in triplicate or more for each group, and the data were expressed as means ± standard deviation (SD). Statistical analysis was performed using SPSS software (version 19.0, USA). Comparisons between groups were made using one-way ANOVA, and a p-value < 0.05 was considered statistically significant.

Results

Untargeted Plant Metabolomics Analysis of YPTQ

To understand the bioactive components of YPTQ, we performed an initial qualitative and quantitative analysis of its overall metabolites. The typical base peak chromatogram (BPC) of the sample revealed the detection of 8614 metabolites, among which 2930 were identified (Figure 1A). Among the metabolites with classification information, 10 compounds exceeded a proportion of 2%, with Lipids being the most abundant at 25.57%. Terpenoids followed, accounting for 10.14% (Figure 1B). By analyzing the KEGG pathways associated with the identified metabolites, it was observed that the metabolites in YPTQ primarily exert their bioactive effects through pathways such as the Biosynthesis of Other Secondary Metabolites, Amino Acid Metabolism, and Xenobiotics Biodegradation and Metabolism (Figure 1C).

Establishment of an Allergic Rat Model and Preliminary Evaluation of YPTQ's Therapeutic Effect via Allergy Scoring and Inflammatory Factor Analysis in Nasal Lavage Fluid

An allergic rhinitis (AR) rat model was established based on previously reported methods,[14,15] involving systemic sensitization via intraperitoneal injection and local nasal stimulation with ovalbumin (OVA) (Figure 2A). The successful establishment of the AR model was confirmed when the nasal allergy score—comprising parameters such as nasal rubbing, sneezing, and rhinorrhea—exceeded 5 points.[16]

As shown in Figure 2B, C and G, the allergy scores in the AR group consistently exceeded 5 points on days 21, 28, and 35, with a progressive increase over time. On day 35, the counts or scores for nasal rubbing, sneezing, and rhinorrhea were recorded for each group (Figure 2D–E). YPTQ treatment demonstrated a dose-dependent reduction in nasal rubbing and sneezing, with the YPTQ-H group exhibiting significantly greater efficacy compared to the Loratadine group (Figure 2D and E). Furthermore, rhinorrhea scores were significantly reduced in the YPTQ-L, YPTQ-M, YPTQ-H, and Loratadine groups compared to the AR group (Figure 2F).

Besides the allergy scoring, we also measured the levels of inflammatory mediators, including Th2-type cytokines, total IgE, and OVA-specific IgE, in nasal lavage fluid (NALF) using ELISA. In the OVA-induced AR group, the levels of IL-4, IL-5, IL-13, and IL-33 in NALF were significantly elevated (Figure 2H–K). Notably, the YPTQ-H group exhibited pronounced inhibition of IL-33 elevation. Additionally, OVA exposure led to increased levels of total IgE (Figure 2L) and OVA-specific IgE (Figure 2M) in NALF, which were suppressed by YPTQ treatment in a dose-dependent manner.

YPTQ Inhibits mRNA Transcription of Th2-Type Cytokines in Nasal Mucosa and Reduces Inflammatory Cell Infiltration in Nasal Lavage Fluid

To further investigate the regulatory effects of YPTQ on Th2-type cytokines IL-4, IL-5, and IL-13 in nasal mucosa, we employed RT-qPCR technology to detect the transcription of their mRNA. The results showed that compared to the Con group, the transcription of IL-4, IL-5, and IL-13 mRNA in the AR group was significantly upregulated (Figure 3A–C). After two weeks of treatment with different doses of YPTQ and Loratadine, the upregulation of the aforementioned cellular factors' transcription was suppressed to varying degrees. Specifically, the YPTQ-L group exhibited similar therapeutic effects to the loratadine group, while the YPTQ-H group showed the most significant effects (Figure 3A–C).

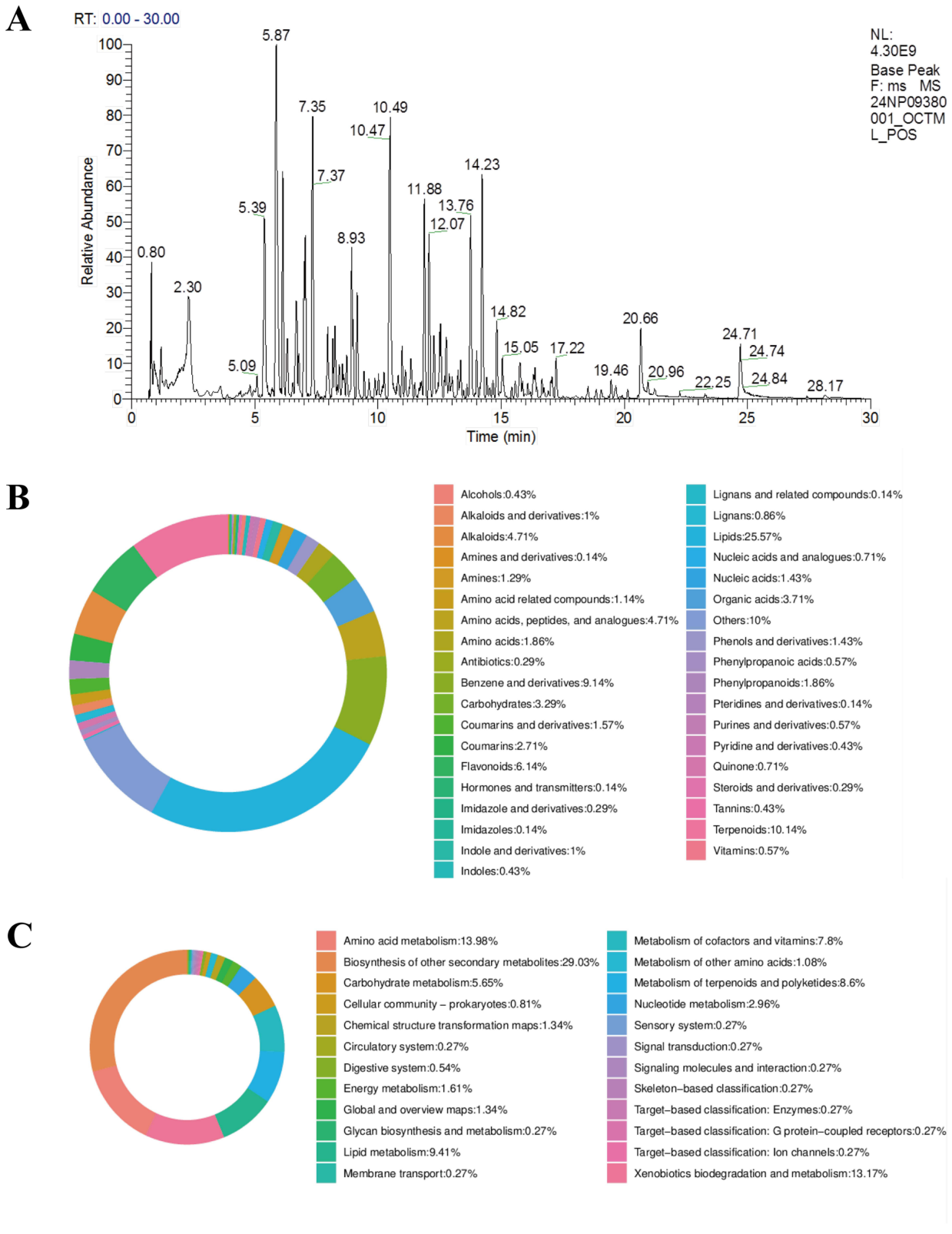


Figure 1 UHPLC-DAD–MS/MS analysis of YPTQ. (**A**) Typical chromatogram of YPTQ: The x-axis represents retention time, and the y-axis represents the signal intensity of the most intense ion detected at each time point. (**B**) YPTQ metabolite classification pie chart: Different colors represent different metabolite classification items, and the percentage indicates the proportion of metabolites in each classification relative to the total number of classified metabolites. (**C**) YPTQ metabolite classification pie chart: Different colors represent different metabolite classification items, and the percentage indicates the proportion of metabolites in each classification relative to the total number of classified metabolites.

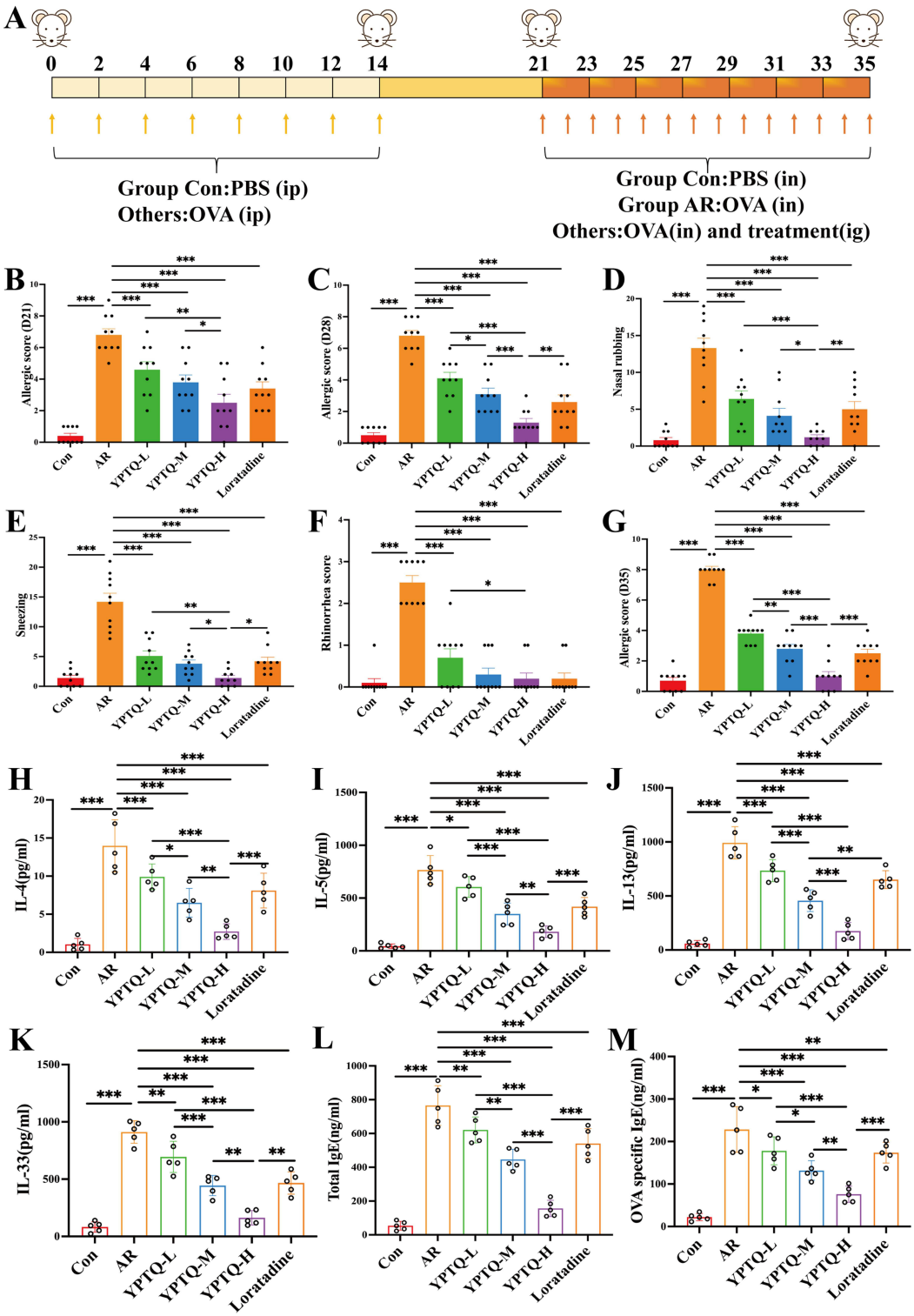


Figure 2 Schematic diagram of OVA-induced AR rat model, with the expression of inflammatory cytokines. (**A**) SD rats were sensitized with 50 μg OVA together with 4 mg Alum (400 μL) by intraperitoneal injection on days 0, 2, 4, 6, 8, 10, 12 and 14. From days 15–21, the Con group received 20 μL of PBS intranasally, while the remaining groups were administered 20 μL of 5% OVA intranasally once daily for 7 days. From days 22–35, the Con group continued receiving 20 μL of PBS intranasally, whereas the other groups received 20 μL of 5% OVA intranasally every other day for a total of 7 administrations. Starting on day 15, intragastric treatments were conducted daily. The Con and AR groups received 3 mL of PBS via gavage, while the YPTQ-L, YPTQ-M, and YPTQ-H groups received 3 mL of PBS containing 0.1128 g, 0.2256 g, and 0.4512 g of YPTQ, respectively. The Loratadine group received 3 mL of PBS containing 0.3 mg of loratadine via gavage. All SD rats were sacrificed on day 35. (**B**) Allergy scores of all groups on Day 21 (n = 10). (**C**) Allergy scores of all groups on Day 28 (n = 10). (**D**) Number of nasal rubbings in all groups on day 35 (n = 10). (**E**) Number of sneezing in all groups on day 35 (n = 10). (**F**) Rhinorrhea score in all groups on day 35 (n = 10). (**G**) Allergy scores of all groups on day 35 (n = 10). (**H**–**M**) IL-4, IL-5, IL-13, IL-33, Total IgE, and OVA-Specific IgE levels in the NALF were quantified by ELISA (n = 5). Data are expressed as mean ± SD. *P < 0.05, **P < 0.01 and ***P < 0.001, significantly different from the ANOVA group.

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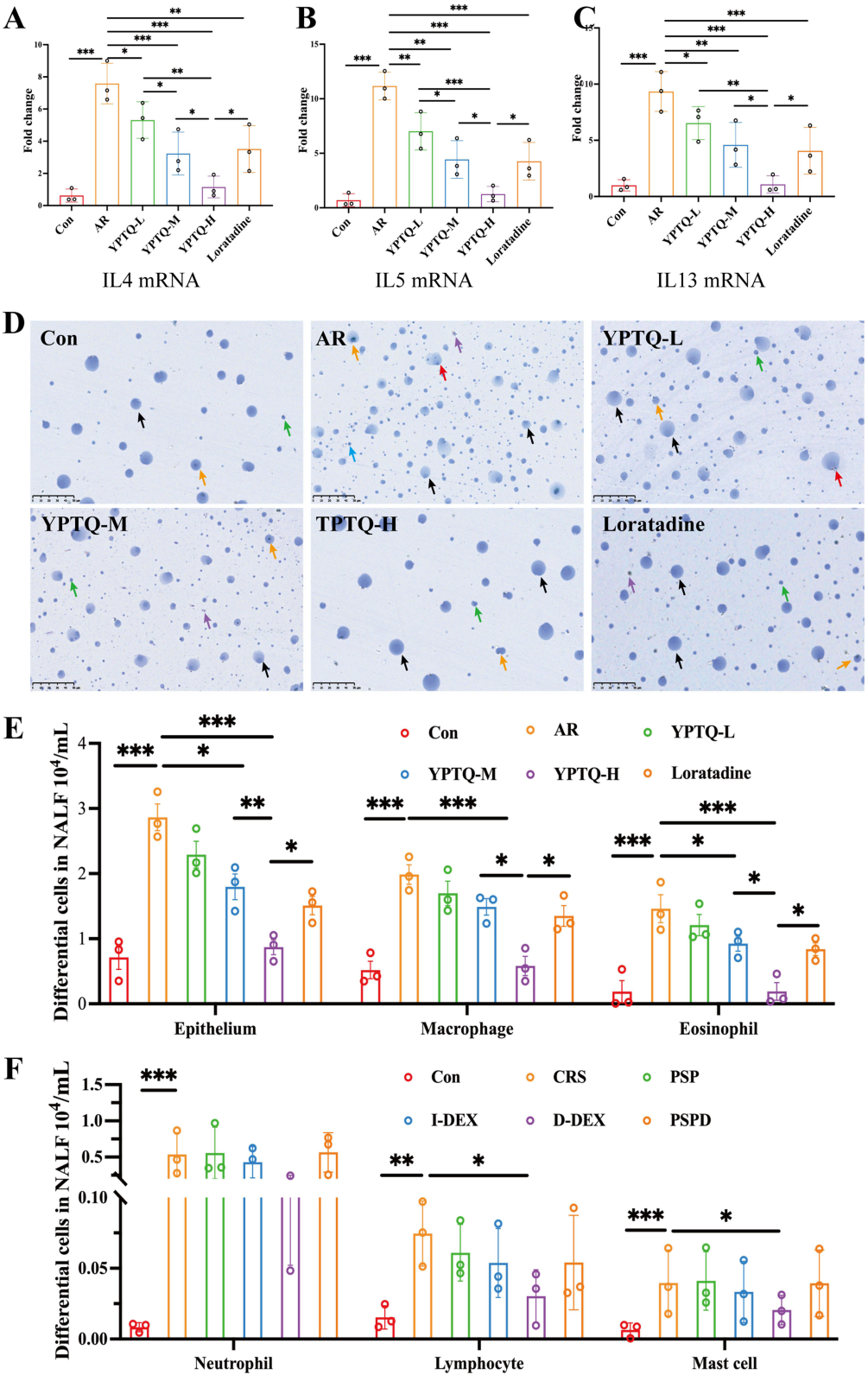

Figure 3 YPTQ reduces the expression of T_H2-type cytokines in the nasal mucosa and inhibits differentiated inflammatory cells in NALF. (**A–C**) The mRNA expression of IL-4, IL-5, and IL-13 in the nasal mucosa was determined by RT-qPCR (n = 3). (**D**) Representative Diff quick stained images of the NALF. The colored arrows denote the following cell types: black, epithelial cells; red, macrophages; yellow, eosinophils; green, neutrophils; blue, lymphocytes; and purple, mast cells. Scale bars = 100 μm. (**E** and **F**) Statistics of epithelial cells, macrophages, eosinophils, neutrophils, lymphocytes, and plasma cells in NALF from all groups (n = 3). Scale bar = 100 μm. Data are expressed as mean ± SD. *P < 0.05, **P < 0.01 and ***P < 0.001, significantly different from the ANOVA group.

Additionally, Diff-Quik staining revealed the differentiation of immune cells in NALF (Figure 3D). Compared to the Con group, the AR group showed increased numbers of epithelial cells, macrophages, eosinophils, neutrophils, lymphocytes, and mast cells (Figure 3E and F). Treatment with both YPTQ and loratadine reduced the numbers of epithelial cells, macrophages, and eosinophils (Figure 3E and F). However, the increased numbers of lymphocytes and mast cells observed in the AR group were only significantly reduced in the YPTQ-H group (Figure 3E). Notably, none of the treatments suppressed the elevated number of neutrophils induced by OVA in the nasal lavage fluid (Figure 3F).

YPTQ Effectively Reduces Inflammatory Cell Infiltration in Nasal Mucosa

The infiltration of eosinophils into the mucosal layer is an important pathological feature of allergic rhinitis.[17] This infiltration, in coordination with mast cells releasing histamine and goblet cells secreting mucus, exacerbates the local allergic reaction in the nasal cavity. We monitored the infiltration of eosinophils, mast cells, and goblet cells in the nasal mucosa of rats using HE staining, Toluidine Blue staining, and PAS staining, respectively. The results showed that as the dose of YPTQ increased, the extent of inflammatory cell infiltration in the nasal mucosa of the AR group decreased sequentially. Notably, the therapeutic effect of the YPTQ-H group was comparable to that of the Con group (Figure 4A–C, Figures S2–S4). Furthermore, loratadine demonstrated a superior ability to reduce inflammatory cell infiltration compared to the YPTQ-L group, though its efficacy was surpassed by the YPTQ-H group (Figure 4A–C).

YPTQ Reversed the Expression of MUC2 and Claudin1 in Nasal Mucosa Induced by OVA

The expression of MUC2 increased significantly, leading to excessive mucus secretion, which is a primary factor causing rhinorrhea in AR.[18] After OVA stimulation, the expression level of MUC2 in the AR group increased sharply. Additionally, the suppressive effects of low-dose YPTQ and loratadine on MUC2 expression were relatively limited, whereas the suppressive effects of mid-dose and high-dose YPTQ were more significant (Figure 5A and Figure S5). This dose-dependent suppression suggests that YPTQ may modulate MUC2 expression to reduce mucus secretion and alleviate runny nose symptoms.

Claudin1, a tight junction protein, plays a crucial role in maintaining epithelial barrier function.[19] However, the expression of Claudin1 was significantly reduced in the AR group, which may impair barrier function and exacerbate allergic reactions. Following treatment with loratadine, Claudin1 expression slightly increased, but this change was relatively moderate. In contrast, under high-dose YPTQ treatment, Claudin1 expression increased significantly (Figure 5B and Figure S6). This result indicates that YPTQ not only effectively inhibits allergic reactions but also enhances epithelial barrier function, providing multiple mechanisms of action for treating allergic rhinitis.

YPTQ Restored the Imbalanced T_{FR} Cells in Nasal Mucosa, Promoted the Expression of CTLA4

TFR cells can inhibit the ability of TFH cells to synthesize IgE antibodies and trigger allergic reactions.[7] To investigate whether YPTQ exerts immunotherapeutic effects in allergic rhinitis by regulating TFR cells, we used flow cytometry to detect TFR cells in the nasal mucosa. The results showed that compared with the Con group, the proportion of TFR cells in the AR group was significantly reduced. After 2 weeks of treatment with different doses of YPTQ, the imbalanced TFR cells showed varying degrees of increase, with the most significant increase in the YPTQ-H group (Figure 6A and Figure S7).

CTLA4 (Cytotoxic T lymphocyte-associated protein 4) is an important inhibitory receptor, and TFR cells can promote the expression of CTLA4 to inhibit the activation and proliferation of T cells.[8] To further understand the restoration of TFR cell function by YPTQ, we detected the expression of CTLA4 in the nasal mucosa using immunofluorescence. As shown in Figure 6B and Figure S8, YPTQ not only increased the proportion of TFR cells but also dose-dependently promoted the expression of CTLA4.

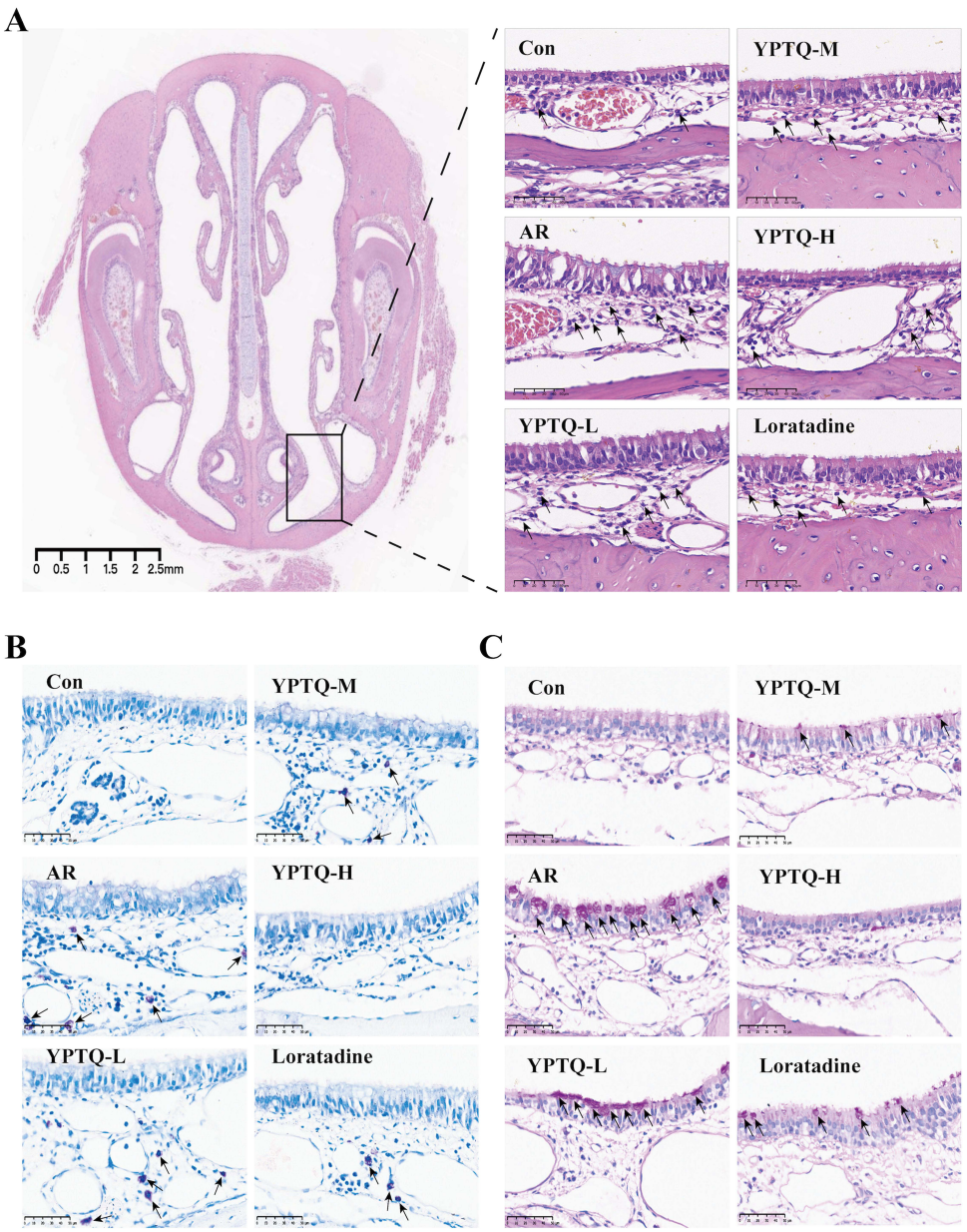

Figure 4 Effects of YPTQ on inflammatory cell infiltration in the nasal mucosa. (**A**) Representative HE-stained images of eosinophils. Arrows point to eosinophils. (**B**) Representative TB-stained images of mast cells. Arrows point to mast cells stained purple. (**C**) Representative PAS-stained images of goblet cells. Arrows point to goblet cells stained purple. Scale bars = 2.5 mm on the left side of (**A**); Scale bars = 50 μm on the right side of (**A**–**C**).

The Systemic Application of YPTQ Exhibits Superior Safety

During systemic application, improper use of traditional Chinese medicine can lead to many severe complications. To investigate the safety impact of prolonged oral administration of YPTQ on rats, we recorded the body weight of rats in each group weekly and performed blood serum biochemical tests and HE staining on major organs. As shown in Figure 7A–I, the levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatininen (Cr), direct bilirubin (DBIT), total bilirubin (TBIT), albumin (ALB), alkaline phosphatase (ALP), urea (Ur), and uric acid (UA) showed no statistical differences among the groups. This indicates that even high-dose YPTQ does not cause harm to liver or kidney function. Additionally, the body weight of rats in each group gradually increased (Figure S9), and the structures of major organs were clear and intact (Figure 7J). No toxic side effects were observed in any dose group of YPTQ.

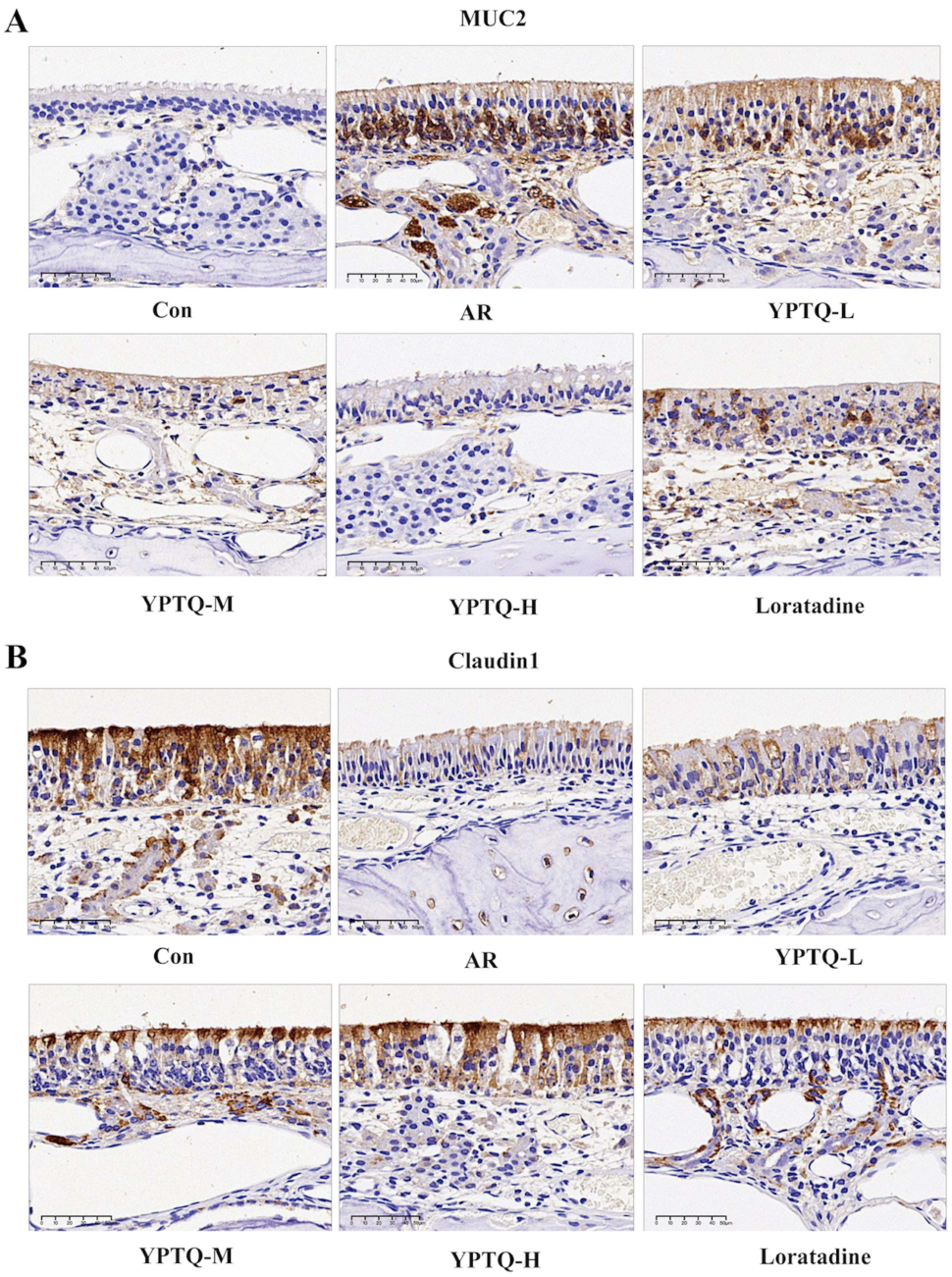

Figure 5 YPTQ attenuated OVA-induced alterations in MUC2 and Claudin1 expression within the nasal mucosa. (**A**) Representative IHC images of the MUC2$^+$ cells. (**B**) Representative IHC images of the Claudin1$^+$ cells. Scale bars = 50 μm on the left.

Discussion

Allergic rhinitis (AR) is a prevalent chronic inflammatory condition of the nasal mucosa, characterized by symptoms such as nasal congestion, sneezing, rhinorrhea, and itching.[20] It is primarily mediated by immunoglobulin E (IgE)-dependent mechanisms and involves complex immune responses, including the activation of T_H2 cells, mast cells, eosinophils, and goblet cells.[21] While conventional treatments like antihistamines (eg, Loratadine) provide symptomatic relief, their limited efficacy in addressing the underlying immunological dysregulation has spurred interest in alternative therapies.[22] Traditional Chinese medicine (TCM) formulations, such as YPTQ, offer a promising approach by targeting multiple pathological pathways.[23] This study systematically evaluated the therapeutic efficacy, mechanisms, and safety of YPTQ in an OVA-induced AR rat model, revealing its potential as a multi-target treatment for AR.

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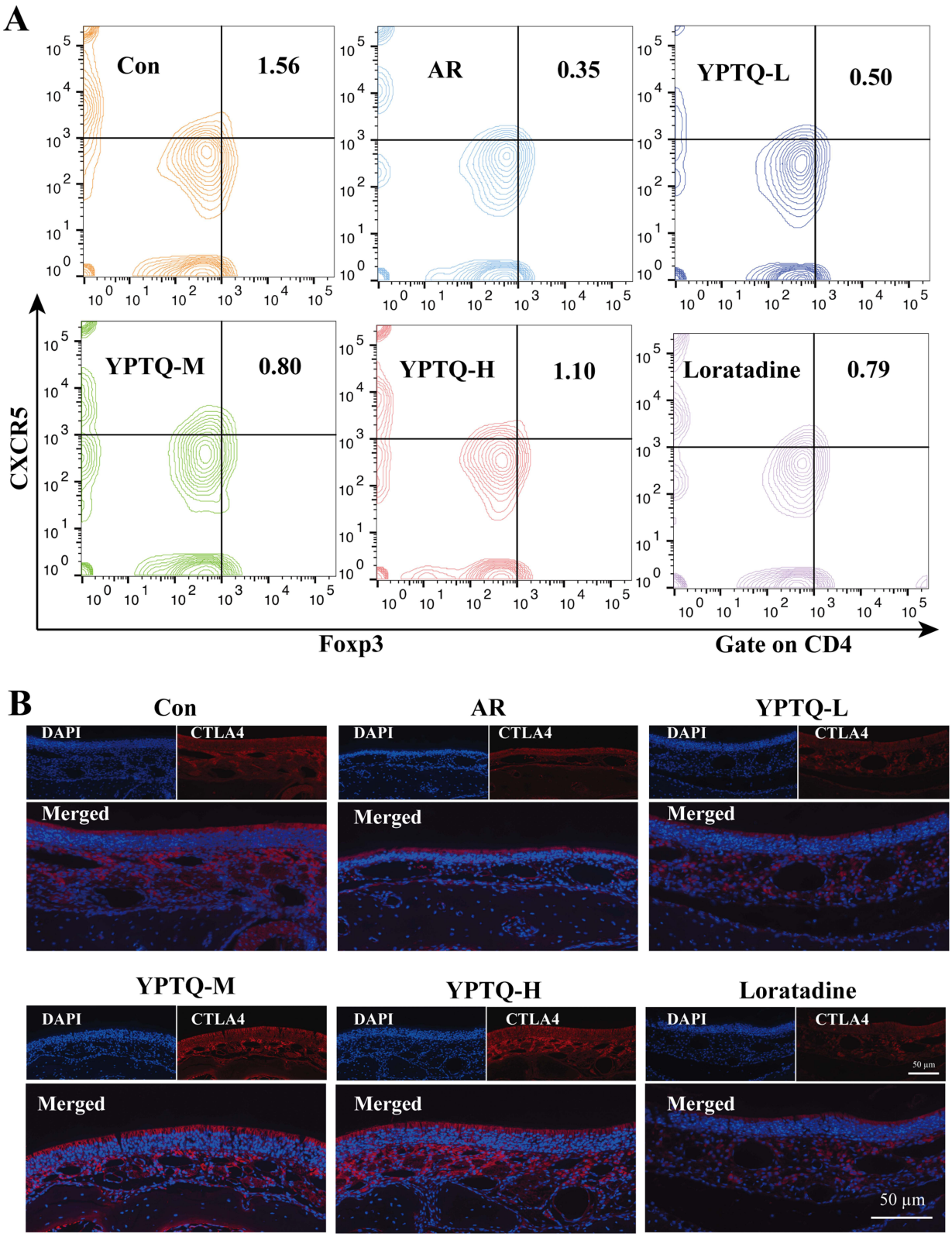

Figure 6 YPTQ regulates imbalanced T_{FR} cells and promotes CTLA4 expression. (**A**) Representative flow charts of $CD4^+$ $CXCR5^+$ $Foxp3^+$ T_{FR} cell subsets in the nasal mucosa (n = 3). (**B**) Representative IF images of the CTLA4. Scale bars = 50 μm on the right.

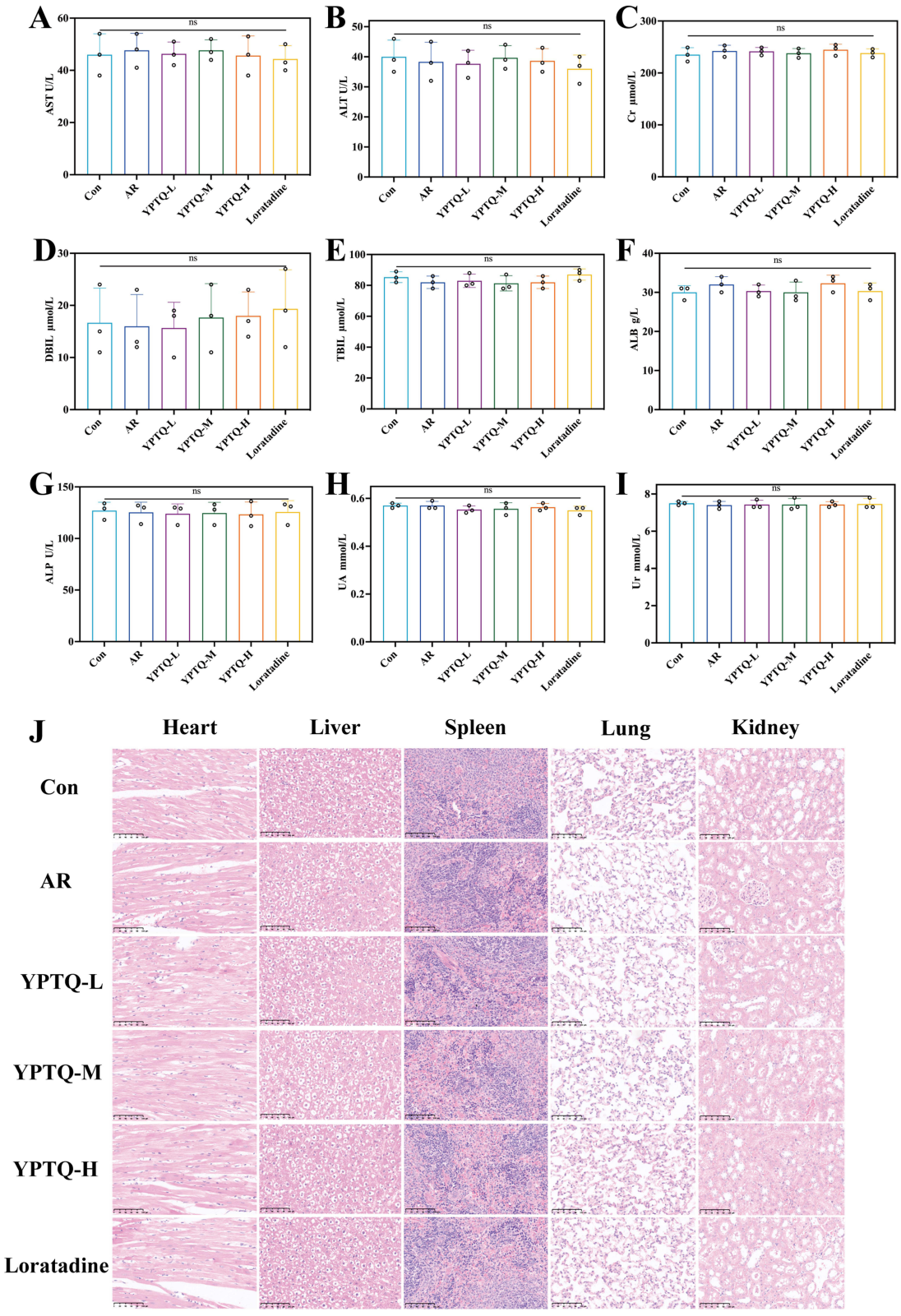

Figure 7 Biological safety of the YPTQ. (**A–I**) Levels of ALT, AST, Cr, DBIT, TBIT, ALB, ALP, Ur, and UA in the serum of rats from each group after 2 weeks of treatment (n = 3). (**J**) HE staining Photographs of major organs after 2 weeks of treatment (n = 3); Scale bars = 50 μm on the left side of (**J**). Data are expressed as mean ± SD. The abbreviation "ns" denotes no significant difference from the ANOVA group.

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The metabolomic analysis identified 8614 metabolites in YPTQ, with 2930 compounds successfully annotated. Lipids (25.57%) and terpenoids (10.14%) were the most abundant classes, highlighting their potential roles in YPTQ's bioactivity. Lipids, known for their anti-inflammatory properties, may contribute to modulating immune responses and reducing inflammation in AR.[24] Terpenoids, widely recognized for their antioxidant and immunomodulatory effects, likely play a critical role in mitigating oxidative stress and regulating immune cell activity.[25] Pathway enrichment analysis revealed that YPTQ metabolites primarily exert their effects through pathways such as the biosynthesis of secondary metabolites, amino acid metabolism, and xenobiotics biodegradation. These pathways are essential for maintaining cellular homeostasis and modulating immune responses, suggesting that YPTQ's therapeutic effects may stem from its ability to influence multiple biological processes.[26]

YPTQ treatment significantly alleviated allergic symptoms in a dose-dependent manner, with the high-dose YPTQ (YPTQ-H) group outperforming Loratadine. This superior efficacy suggests that YPTQ not only targets histamine-mediated pathways but also addresses broader immunological dysregulation. Inflammatory cytokines, particularly T_H2-type cytokines (IL-4, IL-5, and IL-13), play a central role in AR pathogenesis by promoting IgE production, eosinophil recruitment, and mucus hypersecretion.[27–29] In the AR group, these cytokines were markedly elevated, along with total IgE and OVA-specific IgE levels. YPTQ treatment suppressed these inflammatory mediators in a dose-dependent manner, with YPTQ-H showing the strongest inhibitory effects. The reduction in cytokine levels was further corroborated by RT-qPCR analysis, which revealed downregulation of IL-4, IL-5, and IL-13 mRNA transcription, indicating that YPTQ directly modulates T_H2 cell activity at the transcriptional level. IL-33, a key alarmin involved in amplifying T_H2 responses, was also significantly inhibited by YPTQ, particularly in the YPTQ-H group. This highlights YPTQ's ability to intervene early in the inflammatory cascade, dampening the initiation and propagation of allergic responses.

The significant inhibition of IL-33 by YPTQ, as previously mentioned, highlights its potential to intervene in non-IgE -mediated pathways, thereby introducing the concept of divergent AR endotypes. Beyond the well-established IgE-mediated mechanism, a non-IgE-mediated endotype driven by alarmins (eg, IL-33, TSLP) and innate lymphoid cells (ILC2s) is increasingly recognized.[30,31] Additionally, epithelial barrier dysfunction caused by oxidative stress triggers the release of alarmins amplify allergic sensitization.[32] The multi-target efficacy of YPTQ, capable of simultaneously suppressing both the IgE/Th2 axis and the alarmin/ILC2 axis, positions it as a comprehensive therapy that can address this pathological diversity. This capacity to modulate multiple endotypes underpins its superior effect and suggests its particular utility in complex or refractory AR cases where conventional, mono-targeted therapies often fall short.

Histological analyses demonstrated substantial infiltration of eosinophils, mast cells, and goblet cells in the nasal mucosa of AR rats, contributing to tissue damage, mucus hypersecretion, and exacerbation of symptoms. YPTQ treatment reduced the infiltration of these inflammatory cells in a dose-dependent manner, with YPTQ-H achieving effects comparable to the control group and surpassing Loratadine. This reduction in cellular infiltration underscores YPTQ's anti-inflammatory properties and its potential to restore nasal mucosal integrity. MUC2, a mucin protein, is a key contributor to mucus hypersecretion in AR.[18] The sharp increase in MUC2 expression observed in the AR group was significantly suppressed by mid- and high-dose YPTQ, indicating its role in alleviating rhinorrhea. Furthermore, Claudin1, a tight junction protein essential for maintaining epithelial barrier integrity,[19,33] was markedly reduced in the AR group, potentially exacerbating allergen penetration and immune activation. YPTQ-H treatment restored Claudin1 expression, suggesting that YPTQ not only reduces inflammation but also enhances epithelial barrier function, providing dual benefits in AR management.

T follicular regulatory (TFR) cells are critical for maintaining immune tolerance by suppressing T follicular helper (TFH) cell activity and IgE production.[34–36] The AR group exhibited a significant reduction in TFR cell proportions, which was reversed by YPTQ treatment in a dose-dependent manner. YPTQ-H not only restored the balance of TFR cells but also promoted the expression of CTLA4, an inhibitory receptor that regulates T cell activation and proliferation. These findings suggest that YPTQ exerts immunotherapeutic effects by enhancing TFR cell function and restoring immune homeostasis, thereby reducing IgE-mediated allergic responses. Safety is a critical consideration in the systemic application of TCM formulations. Prolonged oral administration of YPTQ did not cause any adverse effects on liver or kidney function, as evidenced by stable levels of ALT, AST, and other biochemical markers. Histological examination confirmed the integrity of major organs, and body weight measurements indicated normal growth patterns in all groups. These results demonstrate that YPTQ is safe for long-term use, even at high doses.

The promising efficacy and safety profile of YPTQ underscore its potential not only as a multi-target therapy but also as an ideal candidate for the application of precision medicine in allergic rhinitis management. The heterogeneity of AR, evidenced by the coexistence of IgE-mediated and non-IgE-mediated endotypes, implies that conventional treatment approach is often inadequate. Precision medicine aims to address this by tailoring therapeutic strategies to individual patient characteristics, particularly their dominant underlying endotype. The multi-target nature of YPTQ, capable of simultaneously modulating IgE, T_H2 cytokines, alarmins, and epithelial barrier function, positions it uniquely to treat patients with mixed or complex endotypes that are refractory to mono-targeted therapies. Future research should focus on developing biomarkers—such as specific cytokine profiles, IgE levels, or genetic markers—to identify these distinct endotypes. This will enable the strategic deployment of YPTQ for the right patient subgroups, thereby maximizing therapeutic outcomes and advancing the era of personalized medicine in allergology.

The promising results of this study suggest that YPTQ could serve as a safe, effective, and multi-target treatment for AR, particularly for patients unresponsive to conventional therapies. Future research should prioritize clinical trials to validate these findings in human populations and evaluate the long-term effects of YPTQ. Exploring the mechanisms of individual metabolites within YPTQ could further elucidate its therapeutic potential. Additionally, comparative studies assessing the cost-effectiveness of YPTQ versus existing pharmaceutical interventions would enhance its value in clinical practice. Given its potential to address complex pathological pathways, YPTQ may also find application in other allergic conditions requiring immune modulation.

Conclusion

In conclusion, YPTQ represents a safe, effective, and multi-target therapeutic option for AR management. Its ability to modulate immune responses, reduce inflammatory cell infiltration, and restore epithelial barrier function highlights its potential as a novel treatment paradigm. By addressing the limitations of conventional therapies, YPTQ offers a promising alternative for improving the quality of life in AR patients and advancing the field of allergy research.

Abbreviations

AR, Allergic rhinitis; YPTQ, YuPingTongQiao; TCM, Traditional Chinese Medicine; CRS, Chronic rhinosinusitis; ECRS, Eosinophilic chronic rhinosinusitis; NECRS, Non-eosinophilic chronic rhinosinusitis; T_H, T helper; T_{FH}, follicular helper T cells; T_{FR}, follicular regulatory T cells; AIT, allergen-specific immunotherapy; OVA, Ovalbumin; SEB, Staphylococcal enterotoxin B; RT-qPCR, Reverse transcription quantitative real-time polymerase chain reaction; ELISA, Enzyme-linked immunosorbent assay; HE, Hematoxylin and eosin; PAS, Periodic acid-Schiff; TB, Toluidine blue; FC, Flow cytometry; NALF, Nasal lavage fluid; BPC, Base peak chromatogram; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; Cr, Creatininen; DBIT, Direct bilirubin; TBIT, Total bilirubin; ALB, Albumin; ALP, Alkaline phosphatase; Ur, Urea; UA, Uric acid; DC, Dendritic cells; GC, Goblet cells.

Ethics Approval and Consent to Participate

This research followed the ARRIVE guidelines and all animal experiments were approved by the Animal Ethics Committee of Ren Ji hospital.

Data Sharing Statement

All data generated and analyzed during this research are available from the corresponding author on reasonable request.

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Yongquan Jiang, Hao Chen, and Yanan Guo are first co-authors. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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