DOI: 10.26599/FSHW.2025.9250879

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Exploring association of tea consumption with food allergy: findings and validation based on a prospective cohort study

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ABSTRACT: Food allergies (FA) are characterized by Th2-dominant immune reactions and intestinal barrier dysfunction with increased incidence worldwide. Tea intake can significantly affect biological activities and health-related allergic diseases. However, the correlation between tea intake and the risk of FA or the underlying mechanism have not been well explained. This study aimed to unveil the correlation between tea intake and the risk of FA, as well as the underlying mechanisms involving gut microbiota and allergenic factors. A prospective cohort study was conducted on the connection between tea intake and the risk of FA based on the UK Biobank. A two-sample Mendelian randomization (MR) study was conducted to further analyse the causal genetic association. A murine model (BALB/c WT mice) of ovalbumin (OVA)-induced FA was utilized for experimental validation. The tea polyphenol epigallocatechin gallate (EGCG) was assessed for its effects on allergic symptoms, serum levels, Th1/Th2 cytokine balance, and gut microbiota, to elucidate the underlying mechanisms. The population study including 411,584 UK Biobank participants revealed a lowered risk of FA upon tea intake. Further analysis of MR showed no genetic association with FA incidence. The experimental analysis verified that the tea polyphenol EGCG significantly alleviated allergic symptoms, reduced OVA-specific IgE and histamine levels, and shifted the Th1/Th2 balance toward Th1 dominance. EGCG improved intestinal barrier integrity by upregulating tight junction proteins and restored the Firmicutes/Bacteroidetes ratio in the gut microbiota. Mechanistically, EGCG downregulated the TLR4/MyD88/NF-κB signalling pathway, reducing inflammation associated with allergic sensitization. A significant correlation between tea intake and FA was identified, with emphasis on EGCG-mediated intervention by mitigating symptoms, restoring immune balance, and enhancing gut health. This study provides evidence supporting the reduced risk of FA upon tea intake and unveils the mechanisms underlying tea polyphenolic EGCG-mediated underpinnings.

Keywords: *Cohort study; Tea intake; food allergy; EGCG; gut microbiota*

1. Introduction

The prevalence of food allergy (FA) has increased worldwide significantly in recent decades, affecting up to 8% of children and 3% of adults worldwide[1, 2]. FA is defined as immunoglobulin E (IgE)-mediated allergic reactions, with the underpinning of T cell-dependent activation of B cells to produce allergen-specific IgE[3]. Upon re-exposure, allergen-specific IgE binds to FcεRI on mast cells and basophils to release mediators

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Received 16 June 2025
Received in revised from 26 July 2025
Accepted 1 September 2025

such as histamine, which ultimately cause acute symptoms[4, 5]. Currently, there is no cure for FA, and strict avoidance of food allergens is the primary choice for sensitive individuals[6, 7]. Alternatively, natural products or food nutrients are increasingly observed to interact with the immune system, potentially modulating immune responses, restoring immune tolerance, and reducing the severity of allergic reactions[8, 9].

As a widely consumed beverage, tea has been recognized to improve or restore health because of its biological effects, including anti-oxidative, anti-inflammatory, and immunomodulatory properties[10]. Numerous studies have reported the health-beneficial effects of tea on the risk of osteoporosis, type II diabetes, and cardiovascular disease[11-13]. Limited observational studies have identified the correlation between tea consumption and allergic reactions such as asthma and dermatitis, supporting the conclusion that increased tea intake may reduce the risk of atopic dermatitis and allergic asthma[14]. However, the association between tea consumption and FA remains inconclusive, and detailed investigation should be conducted to elucidate the intervention and mechanism of tea on FA. Tea is rich in a variety of polyphenols (such as epigallocatechin gallate (EGCG), theanine, theaflavins, etc.), which may biologically contribute to the alleviative effect on allergic reactions by modulating immune or intestinal barrier function. EGCG is the dominant polyphenolic component in green tea (50%-80% of total catechins), and has been verified with significant anti-inflammatory and immunomodulatory properties[15, 16]. Specifically, EGCG has been shown to suppress Th2-related cytokines, such as IL-4 and IL-13, while promoting Th1-related cytokines, including interferon-gamma (IFN-γ), to help restore immune equilibrium[17], which could serve as the underlying mechanism for the alleviative effect of tea on FA. However, synergistic or additive effects of other compounds (e.g., theanine's mast cell stabilization) warrant further investigation. A prospective cohort-based study on the correlation between tea consumption and the risk of FA could facilitate and address the proposal of a dietary-based intervention strategy.

In this study, we investigated the association between tea intake and FA risk through a cohort study. The COX proportional hazards model was utilized to analyze the risk relationship between tea intake and FA. Then, genome-wide association was investigated to potentially correlate the genetic connection of FA with tea consumption through Mendelian randomization (MR) analysis. The detailed mechanism of tea consumption-mediated alleviation of FA was unveiled using an FA murine model to indicate the mediated effect of EGCG on FA-related implications, including serum IgE, Th1/Th2 balance, and gut microbiota. This study seeks to provide new insights into the correlation between tea intake and FA and offer scientific evidence supporting nutritional strategies for food-related allergic disease intervention.

2. Materials and methods

2.1 Materials

EGCG with a purity higher than 98% was obtained from Shanghai Macklin Biochemical Co., Ltd (Shanghai, China). Ovalbumin (OVA) and complete and incomplete adjuvants were purchased from Sigma Aldrich (St. Louis, MO, USA). The reagents used in this study were of analytical grade unless otherwise stated.

2.2 Cohort study on the association of tea intake and risk of FA based on UK Biobank

The UK Biobank study was approved by the Northwest Multi-Centre Research Ethics Committee, and the current study was conducted under the UK Biobank application number 90831. UK Biobank was used as a data source (application number: 670065). UK Biobank (https://www.ukbiobank.ac.uk/) is a large population-based prospective study that recruited approximately 500,000 participants aged 40-69 years from the United Kingdom between 2006 and 2010[18, 19]. All participants in the UK Biobank completed questionnaires, underwent physical measurements, and provided blood, urine, and saliva samples for the generation of genetic, proteomic, and metabolomic data. All participants provided informed written consent for the use of their data in the study[20]. Participants with baseline allergies and those with missing data on tea intake, sex, age, race, body mass index (BMI), smoking status, or drinking status were excluded from the analysis. In our study, data from 411,584 individuals were available for analysis.

In the baseline questionnaire, information on habitual tea intake was assessed (UKB Data-Field: 1488), and participants were asked, "How many cups of tea do you have per day (including black and green tea)?" For this question, participants were asked to choose the number of cups per day ("less than one", "Do not know", "Prefer not to answer", or they indicated the number of cups). For our analyses, participants who responded "Do not know" or "Prefer not to answer" were removed, and the category of less than one cup per day was indicated as 0.5 cups per day for statistical analysis.

FA events were recorded by the International Classification of Disease (ICD-10) coding system: Allergy status, other than to drugs and biological substances (ICD codes: Z91.0). Incident death events were identified by death registry records. Follow-up began at recruitment and lasted until one of these events: allergy was diagnosed, death, loss to follow-up, or the end of study in March 2022.

In the present study, we considered the following potential covariates: age, sex, race (White, Asian or Asian British, Black or Black British, and other ethnic group), smoking status (never, previous, and current), drinking status (never, previous, and current), BMI (< 25, 25 to < 30, 30 to < 35, and ≥ 35 kg/m^2), education level (college degree and above, the rest of the population), income (less than £18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, and greater than 100,000), and Townsend deprivation index (<0 and ≥0). All measurements were obtained using the baseline questionnaire.

The baseline characteristics of the tea intake sample were summarized as mean and percentage; continuous variables were compared using ANOVA or Mann–Whitney U test, and categorical variables were compared using the chi-squared test. Restricted cubic spline models were used to assess potential nonlinear associations between tea intake per day and the risk of incident FA. Cox proportional hazards regression models were also used to study the relationship between tea intake and the risk of FA. Tea intake was divided into 0, 0.5-1, 2-3, and ≥4 cups per day. All models were adjusted for age, sex, race, BMI, smoking status, drinking status, education level, income, and the Townsend deprivation index.

2.3 Tea intake and FA: a Mendelian randomization (MR) study

In the large UK Biobank-based prospective cohort study, tea intake significantly reduced the risk of FA. We conducted a two-sample MR study to evaluate the role of tea intake in the progression of FA using open genome-wide association study (GWAS) data to assess the causal relationship between tea intake and the risk of allergic diseases. The MR approach is based on three assumptions: (1) that genetic variants used as instrumental variables (IVs) are significantly associated with exposure; (2) the genetic variation is not associated with any confounding variables; and (3) there is no direct relationship between genetic variation and outcomes, except through exposure[21, 22].

GWAS data for tea intake phenotypes were obtained from the UK Biobank and can be retrieved from the IEU Open GWAS website (https://gwas.mrcieu.ac.uk/) with GWAS ID (ukb-b-6066)[23]. GWAS data for FA (ebi-a-GCST90038662) were obtained from the GWAS Catalog (https://www.ebi.ac.uk/gwas/). To avoid bias in MR estimates due to sample overlap, the outcome phenotype included in this study did not include participants from the UK Biobank. In addition, we further analysed the genetic relationship between two representative teas, herbal tea (ukb-b-13344) and green tea intake (ukb-b-4078), and FA.

Single nucleotide polymorphisms (SNPs) associated with tea intake at genome-wide significance thresholds $P < 5E{-}08$ were selected. Independence between these selected SNPs was assessed on the basis of pairwise linkage disequilibrium (LD). LDs for these SNPs were calculated using 10,000 genomic LD clusters ($r^2 < 0.001$)[24]. We filtered the outcome data for SNPs that were significantly associated with exposure ($P < 5E{-}05$). To determine the intensity of IVs, the F-statistic (β^2/SE^2) was utilized. An IV with an F-statistic < 10 was considered a weak instrument[14].

For the primary MR analysis, the random effects inverse variance weighted (IVW) method was performed. For significant associations, we further verified the results using three additional MR methods: MR Egger regression, weighted median, and weighted mode. To identify and exclude potential pleiotropic instruments, we performed the MR pleiotropy residual sum and outlier test (MR-PRESSO). Outlier instrumental variables identified by the MR-PRESSO analysis were removed incrementally to reduce the effect of horizontal pleiotropy. Cochran's Q test was executed to check heterogeneity across the individual causal effects. MR-Egger regression was performed to evaluate the pleiotropy of instrumental variables[25].

2.4 Animals

Thirty-two healthy female pathogen-free BALB/c mice were acquired from Beijing Vital River Laboratory Animal Technology Co. Ltd (Beijing, China) and housed in the Nankai University Laboratory Animal Center. All experimental protocols were approved by the Institutional Animal Care and Use Committee of Nankai University (protocol code SYXK-2019-0001). The mice had a libitum access to food and water and were acclimatized for one week prior to the commencement of the experiments.

2.5 Sensitization and Allergic Challenge of Mice

The mice were randomly assigned to four groups (n=8 for each group): a control group (CON), an OVA sensitization model group (OVA), a low-dose EGCG intervention group (LEO), and a high-dose EGCG intervention group (HEO). The establishment of the FA model comprised two sequential steps: sensitization

and provocation. In brief, mice in the OVA, LEO, and HEO groups were sensitized through intraperitoneal injection of 200 μL of OVA on days 0, 7, and 14, with a concentration of 0.5 mg/mL. Mice in the CON group received an equivalent volume of normal saline. From days 15 to 35, mice in the LEO and HEO groups were administered 25 mg/kg and 50 mg/kg of EGCG, respectively, while mice in the CON and OVA groups received intragastric saline daily, with a fixed administration volume of 200 μL.

On day 32, mice in the OVA, LEO, and HEO groups were subjected to the initial immunological challenge with 200 μL of 0.25 mg/mL OVA. On day 36, the mice received a second intraperitoneal injection of 200 μL of 2.5 mg/mL OVA. The CON group was administered an equivalent volume of normal saline. One hour post-challenge, the allergic manifestations in the mice were evaluated and scored as detailed in Tables S6 and S7[26, 27]. Following the experimental procedures, the mice were subjected to a 12-hour fasting period and then anesthetized using isoflurane prior to euthanasia. The spleen index was calculated (mg/g×10 body weight). Additionally, serum, spleen, and colon samples were collected for subsequent analysis.

2.6 Serum biochemical analysis

The levels of OVA-specific IgE (OVA-sIgE), histamine concentration (HIS), and mast cell protease-1 (MCPT-1) in serum samples were determined via ELISA (Nanjing Jiancheng Institute of Bioengineering, Nanjing, China). IgG1 and IgG2 were determined using ELISA kit according to the manufacturer's instructions (Enzyme-linked Biotechnology Co., Ltd, Shanghai, China).

2.7 Histological Analysis of Intestinal Tissue Sections

The colon tissue was fixed in 4% paraformaldehyde for a duration of 24 to 48 hours, subsequently embedded in paraffin, and sectioned into 5 μm thick slices. These sections were stained with haematoxylin-eosin (H&E) to evaluate tissue morphology. Goblet cells were identified in the paraffin sections following staining with periodic acid-Schiff (PAS). The intestinal tissues were scored based on criteria established in the literature, as detailed in Table S8[28]. The sections were incubated with anti-ZO-1 (21773-1-AP, Proteintech, Wuhan, China) or anti-Occludin (27260-1-AP, Proteintech, Wuhan, China) monoclonal antibodies, followed by incubation with a secondary antibody. DAB reagent was applied for the chromogenic reaction, and haematoxylin was added for nuclear counterstaining.

2.8 Intestinal flora analysis

Faecal microbial DNA (n=4 mice per group) was extracted from mouse faecal samples and subjected to 16S rRNA sequencing. Operational taxonomic units (OTUs) were clustered at a 97% similarity threshold, and taxonomic assignment was performed using the SILVA database. Alpha diversity indices, including observed species and the Chao1 index, were calculated to evaluate microbial diversity within samples. Beta diversity was analysed based on the unweighted UniFrac distance and visualized using orthogonal partial least squares discriminant analysis (OPLS-DA). Differentially abundant taxa were identified using linear discriminant analysis effect size (LEfSe) with a threshold LDA score >2.0. Spearman's correlation analysis was performed to explore the relationship between gut microbiota composition and relevant metabolic parameters. All

analyses were conducted using the Novogene Cloud platform and statistical tools integrated into the pipeline[29].

2.9 Quantitative Real-Time PCR analysis (qRT-PCR)

The expression levels of Th1, Th2, and Treg-related cytokines, along with key transcription factors (IL-2, IL-12, IFN-γ, IL-4, IL-13, T-bet, GATA-3, IL-10, TGF-β, Foxp3), were quantified using a reverse transcription quantitative polymerase chain reaction (RT-qPCR) system. Additionally, the mRNA expression levels of tight junction (TJ) proteins (ZO-1, Occludin, Claudin) were assessed. Results were normalized to β-actin, which served as an internal control. The primer sequences used in qRT-PCR are detailed in Table S9.

2.10 Western bolt analysis

Proteins were extracted from colon tissue using RIPA lysis buffer and then used for protein analysis. The membrane was incubated with specific antibodies against TLR4 (1:1000, Invitrogen, Cat# 482300), MyD88 (1:1000, Cell Signaling Technology, Cat# 4283S), NF-κB p65 (1:1000, Cell Signaling Technology, Cat# 8242S), Phospho-NF-κB P65 (1:1000, Cell Signaling Technology, Cat# 3033T), GAPDH (1:1000, Servicebio, Cat# GB11001), followed by an enzyme-conjugated secondary antibody. Finally, an ECL assay kit was used to visualize the protein bands, GAPDH served as the internal loading control for corresponding densitometric analysis, which was subsequently quantified using ImageJ software.

2.11 Statistical analysis

For cohort analysis and MR analysis of tea intake and FA, analyses were performed using R software (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria). All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant. For the animal experiments, data analysis was carried out using GraphPad Prism 8.0 (GraphPad Software Inc., San Diego, CA, USA). Results were expressed as mean ± Standard Error of Mean (SEM). Statistical analyses for each group were performed using one-way analysis of variance (ANOVA), followed by Dunnett's multiple comparison test and the Kruskal–Wallis test. The cut-off value for statistical significance was $P < 0.05$.

3. Results

3.1 Significant correlation of tea intake with incidence of FA

3.1.1 Nonlinear Association between tea intake and FA

A total of 411,584 participants were included in the final analysis from 501,495 baseline participants. Among them, 350,966 (85.3%) participants reported tea intake, with 13.7% consuming 0.5-1 cup/day, 34.5% consuming 2-3 cups/day, and 51.8% consuming ≥4 cups/day. During the follow-up period, 9,050 participants (2.2%) developed FA. The baseline characteristics are summarized in Table S1.

Restricted cubic spline models were used to evaluate the relationship between tea intake and allergies. The association between tea intake and risk of allergy was nonlinear (p for nonlinear <0.001) and was illustrated in unadjusted (Fig. 1A) and multiple-adjusted models (Fig. 1B), indicating a lower risk of FA with 2-3 cups of tea intake per day.

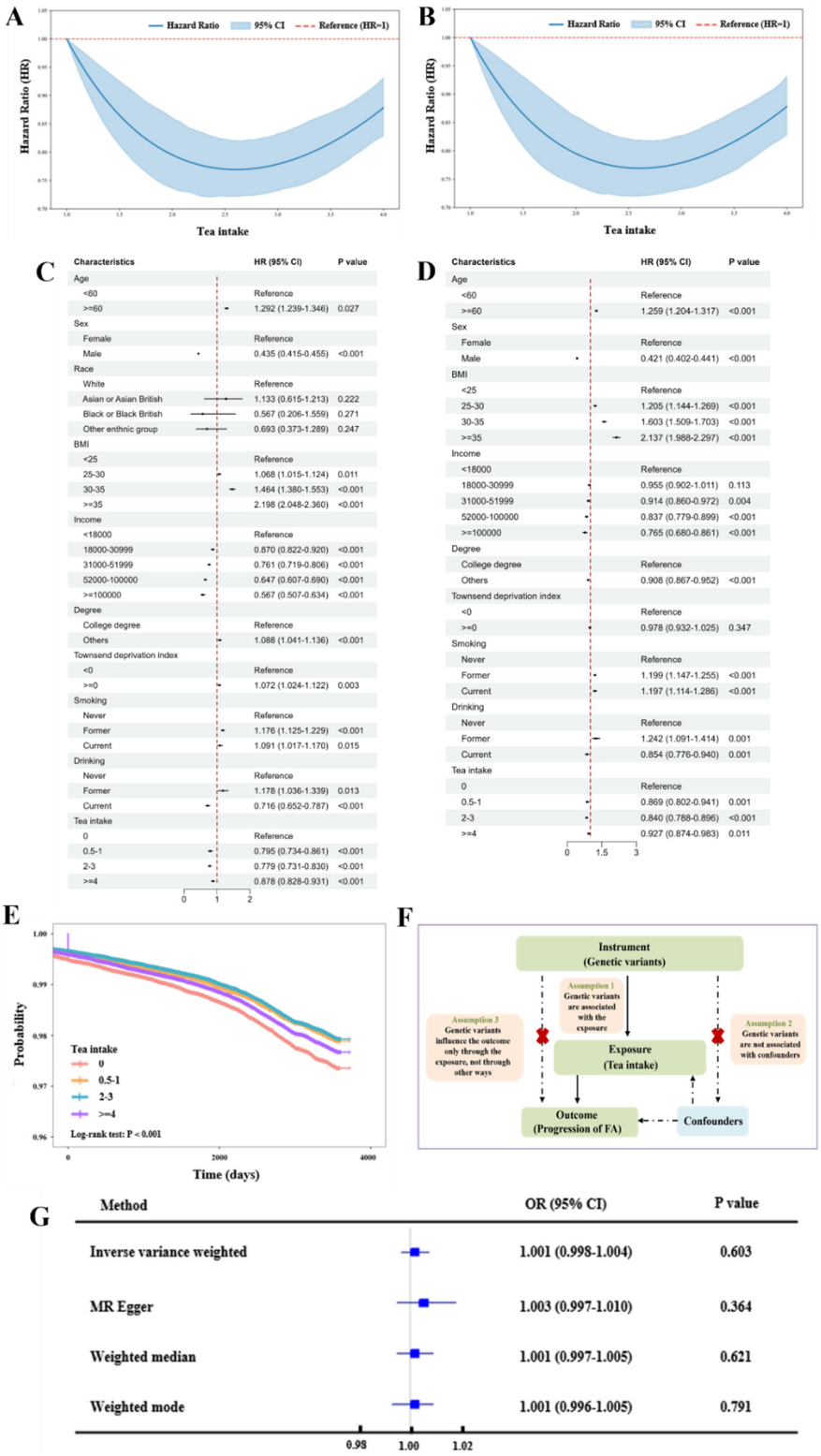


Fig. 1. The association between tea intake and FA based on cohort analysis and MR. Restricted cubic spline models for the relationship between tea intake and FA. (A) The restricted cubic spline model was unadjusted: tea intake and FA. (B) Restricted cubic spline model was adjusted by age, sex, race, BMI, smoking status, drinking status, education, income, and Townsend Index: tea intake and FA. The 95% CIs of the adjusted HRs were represented by the shaded area. CI, confidence interval. (C) Tea intake and each subgroup were related to FA in the unadjusted cox model. (D) Multivariable model was adjusted for sex, age, BMI (<25, 25 to <30, 30 to <35, and ≥35 kg/m^2), smoking status (never, previous, and current), drinking status (never, previous, and current), an education level (College degree and above, the rest of the population), income (less than £18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, and greater than 100,000), townsend deprivation index (<0 and ≥0). Hatched vertical line indicates the null reference value of "1". (E) Analysis of the survival curve of allergic reactions upon tea intake. (F) Overview of the study design. Broken lines represent potential pleiotropic or direct causal effects between variables that would violate MR assumptions. (G) Forest plot showed MR analysis results to evaluate the causal association between tea intake and progression to FA using four methods.

3.1.2 Tea intake reduced the risk of FA

To investigate the association between tea intake and FA, tea consumption was categorized into four groups: 0, 0.5-1, 2-3, and ≥ 4 cups/day. Tea intake was associated with a lower risk of FA in the unadjusted Cox proportional hazards regression models (Fig. 1C). After multivariate adjustment, tea intake was still associated with a reduced risk of FA. Compared to non-tea drinkers, hazard ratios (HRs) (95% CI) for tea intake of 0.5 to 1, 2 to 3, and ≥ 4 cups/day were 0.869 (95% CI, 0.802 to 0.941; P = 0.001), 0.84 (95% CI, 0.788 to 0.896; $P < 0.001$), and 0.927 (95% CI, 0.874 to 0.983; P = 0.011), respectively (Fig. 1D). These results demonstrate a clear dose-dependent relationship between tea consumption and reduced FA risk, with optimal protection observed at 2-3 cups/day (HR=0.84). The persistent association after multivariate adjustment suggests tea's protective effects are independent of common lifestyle confounders. Notably, the attenuated benefit at ≥4 cups/day may indicate a ceiling effect or potential trade-offs with excessive intake, warranting further investigation into optimal dosing thresholds for allergy prevention. In conclusion, tea intake can reduce the risk of FA as illustrated by the survival curve (Fig. 1E).

3.2 Genetic analysis on the FA risk and tea intake

Our MR framework design was depicted in Fig. 1F. IVs for MR analysis of tea intake and FA are detailed in Table S2. In general, 39 independent SNPs were selected for correlation analysis with tea intake. The F-statistic exceeded the conventional threshold of 10 for all SNPs. MR analysis showed no significant causal relationship between genetically predicted tea intake and FA (Odds ratio (OR) = 1.001, 95% CI = 0.998-1.004, p = 0.603), this suggests that there is no genetic factor between tea intake and allergy risk. The same results were obtained using the other three MR methods (Fig. 1G). The scatter plot illustrates the estimated effect size of FA for SNPs associated with tea intake (Fig. S1A). The funnel plot shows that the selected IVs were evenly distributed without bias (Fig. S1B).

Next, we performed a sensitivity analysis to examine the causal relationship between tea intake and FA progression. No heterogeneity of effects was detected by Cochran's Q test, and no significant horizontal pleiotropy was observed, as the intercept of the MR-Egger did not deviate significantly from zero. The MR-PRESSO analysis detected no potential instrument outliers at a nominal significance level of 0.05 (Table S5). The results of the leave-one-out method showed that causal effects were not driven by a single instrumental variable (Fig. S1C). Similarly, herbal and green tea intake yielded the same results, with no genetic link to FA (Tables S3-5, and Fig. S1D-K).

3.3 Tea polyphenolic component of EGCG alleviated OVA induced FA in mice

A prospective cohort analysis based on comprehensive data from the UK Biobank confirmed a potential association between tea intake and the incidence of FA, but further MR analysis showed no genetic association between the two. We believe that tea drinking is a protective factor for FA and hypothesize that the key polyphenolic compound EGCG in tea may serve as the mediator to elucidate the mechanism of tea intake-related alleviation of FA. Although tea contains a variety of biologically active polyphenolic compounds, such as L-theanine, catechins, etc., EGCG was selected as the main experimental subject of this

study due to its prominent role in alleviating allergic reactions, especially in regulating Th1/Th2 balance and enhancing intestinal barrier function. To validate this hypothesis, an OVA-induced BALB/c mouse model was established to mimic allergic reactions and the intervention upon EGCG ingestion (Fig. 2A). As illustrated in Fig. 2B and 2C, comparative analyses revealed that mice in the OVA-sensitized group exhibited notable weight gain relative to controls, a trend that reversed upon EGCG treatment.

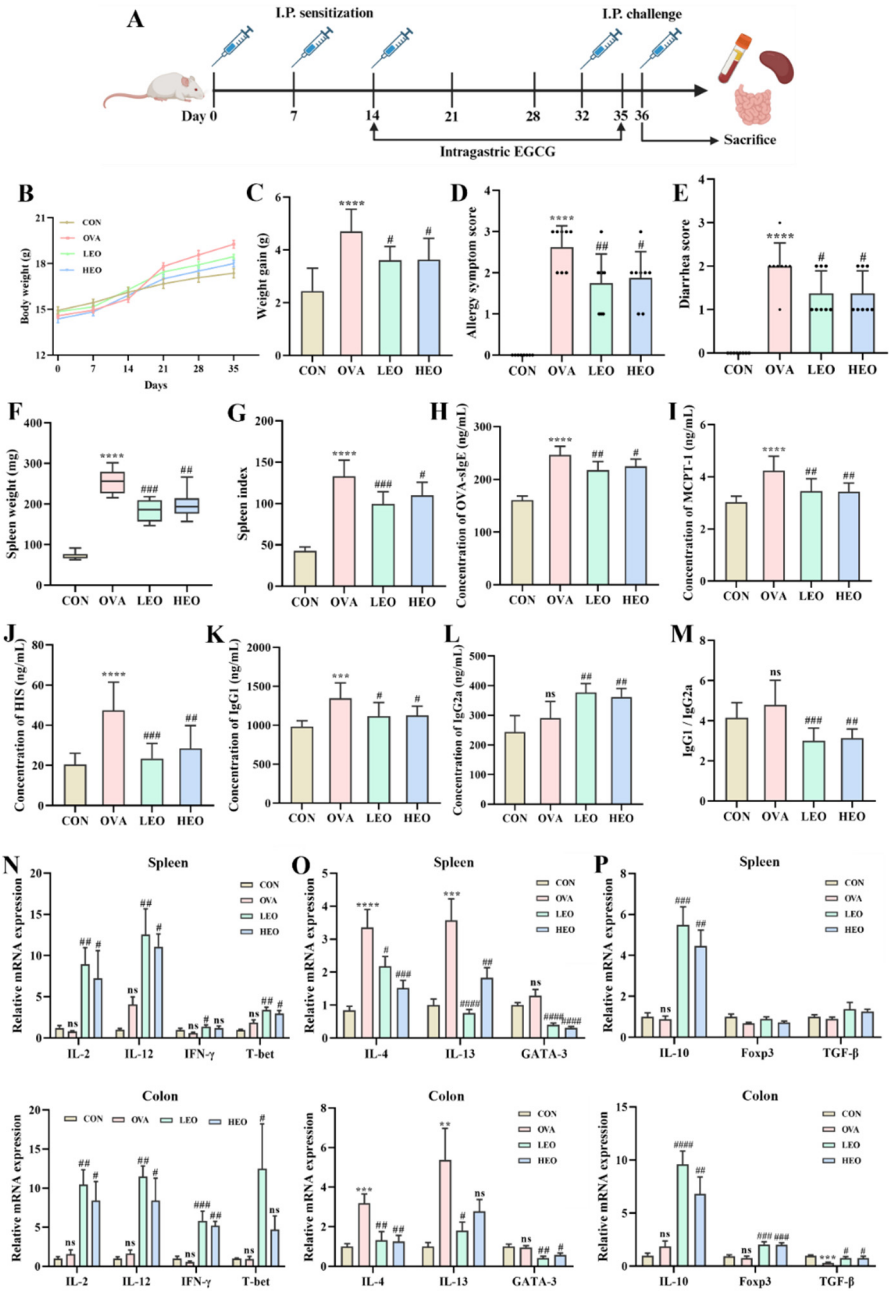


Fig. 2. EGCG intervention mitigated OVA-induced FA related symptoms and regulates Th1, Th2, and Treg cell responses. (A) Schematic diagram of the establishment of an OVA-sensitive mouse model and the strategy for EGCG intervention. (B) Body weight. (C) Weight gain at the end of the experiment. (D) Effect of EGCG intervention on allergy and (E) diarrhea scores in OVA-sensitive mice. (F) Spleen weight. (G) Spleen index. The levels of (H) OVA-specific IgE, (I) mast cell protease-1 (MCPT-1), (J) histamine (HIS), (K) IgG1, (L) IgG2a, (M) IgG1/IgG2a ratio in the serum were measured. (N) Relative mRNA expression of key transcription factors and related cytokines of Th1 cells in the spleen and colon. (O) Relative mRNA expression of key transcription factors and related cytokines of Th2 cells in the spleen and colon. (P) Relative mRNA expression of related cytokines of Treg cells in the spleen and colon. Data were shown as the mean ± SEM. Compared to CON, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, or ****: $P < 0.0001$; compared to OVA, $^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$, or $^{\#\#\#\#}$: $P < 0.0001$. CON: control; OVA: OVA-sensitized mice; LEO: OVA-sensitized mice treated with 25 mg/kg EGCG; HEO: OVA-sensitized mice treated with 50 mg/kg EGCG.

Compared with the CON group, mice in the OVA group showed significantly higher allergy and diarrhoea scores. The OVA group exhibited erect fur and varying degrees of irritability, including behaviours such as scratching of the nose and head, as well as swelling and congestion in the eyes, and severe diarrhoea was noted. These results confirm that OVA sensitization induced classic allergic and gastrointestinal responses, mediated by mast cell-derived mediators and intestinal inflammation.[30] However, the corresponding symptoms showed significant improvement in mice with EGCG intervention (Fig. 2D and 2E).

It was observed that the spleen of mice enlarged with an increase in spleen index, potentially indicating an activated immune response upon OVA stimulation. However, after EGCG intervention, both the spleen size and spleen index decreased (Fig. S2). Notably, the improvement observed in the low concentration group was more pronounced than that in the high concentration group (Fig. 2F and 2G). Splenomegaly in OVA-sensitized mice indicates systemic immune activation, while EGCG's reversal of this effect suggests its broad immunosuppressive properties, potentially via Th2 inhibition.

3.4 EGCG regulated serum Igs of allergic mice

IgE levels were significantly elevated in the OVA group compared to the CON group. However, these levels were notably decreased following intervention with EGCG (Fig. 2H). These results demonstrate that EGCG effectively suppresses IgE production, a key driver of mast cell activation and allergic inflammation, suggesting its potential to disrupt the allergic cascade at the initial sensitization phase. In addition, MCPT-1 and HIS, which are key mediators of mast cell degranulation and allergy symptom elicitation, were measured to assess potential anti-allergic activity. The OVA antigen triggered an increase in MCPT-1 and HIS levels, which was significantly reduced after EGCG intervention (Fig. 2I and 2J). As shown in Fig. 2K-M, IgG1 levels were reduced and IgG2a levels were increased in the EGCG-treated group compared to the OVA group. The shift from IgG1 to IgG2a suggests EGCG promotes an immune rebalancing from allergic toward protective responses, potentially enhancing allergen tolerance. These results suggest that EGCG can decrease IgE levels and ameliorate mast cell-mediated allergic diseases, potentially through modulating Th1/Th2 imbalance.

3.5 EGCG regulated Th1 and Th2 cell responses in mice

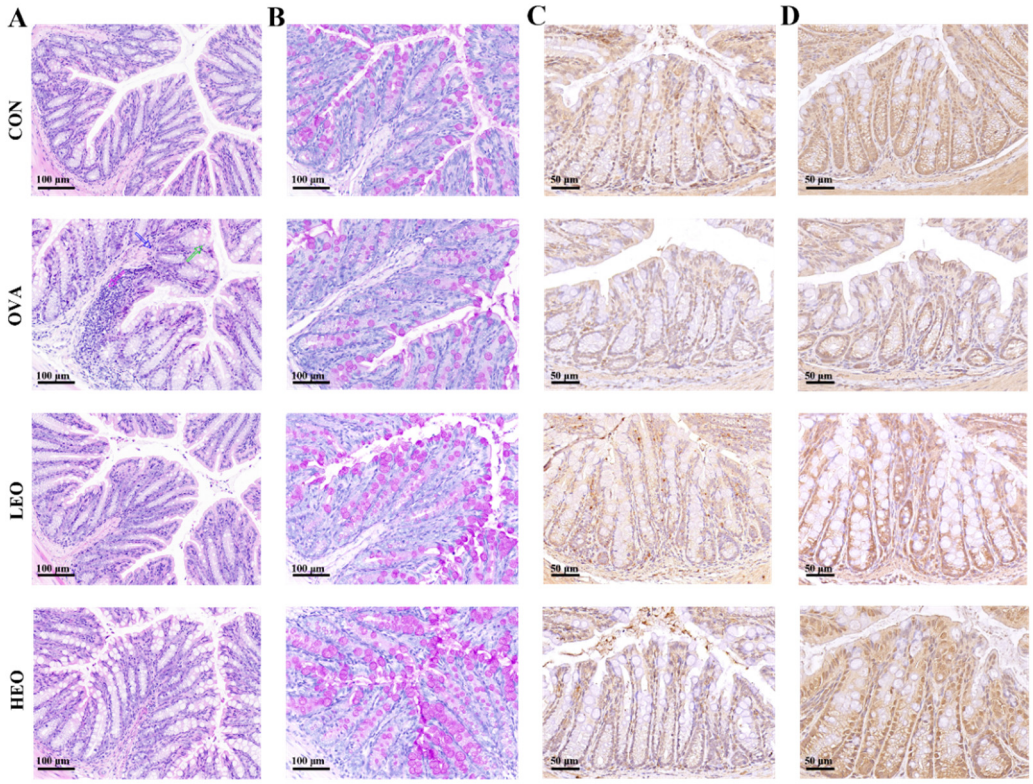
As shown in Fig. 2N and 2O, significant increases in IL-4 and IL-13 were observed in sensitized mice, and the levels of IL-4 and IL-13, including the key transcription factor GATA-3, were significantly reduced after EGCG intervention. EGCG prevented the reduction in the levels of Th1-related cytokines (IL-2, IL-12, IFN-γ) and the key transcription factor T-bet. This dual regulatory effect further suggests EGCG's potential to restore immune homeostasis by shifting the immune response from a Th2-dominant allergic profile toward a more balanced Th1/Th2 ratio.

In this context, the potential of EGCG to influence the differentiation of $CD4^+$ T cells into Treg cells was examined. The findings indicated that the transcriptional levels of key regulatory molecules, including Foxp3, IL-10, and TGF-β, were significantly elevated in the colon of the EGCG-treated groups. These factors are critical for the regulation of Treg cell function and homeostasis, but no significant effect was found in the

spleen (Fig. 2P). Collectively, these results suggested that EGCG mitigates OVA-induced FA by promoting Treg cell differentiation, thereby modulating the Th1/Th2 imbalance.

3.6 EGCG safeguarded the intestinal barrier against FA related damage

As shown in Fig. 3A, the H&E staining results indicated that mice with OVA-induced food allergies exhibited reduced intestinal crypt depth (blue arrow), abnormal epithelial morphology (green arrow), and extensive inflammatory infiltrates (pink arrow) compared with the CON group. PAS staining indicated goblet cells secreting Mucin-2 protein, which gave the mucus protein in goblet cells a purplish-red colour (Fig. 3B). In the OVA group, there was significant intestinal damage, and the intestinal tissue damage was reduced after EGCG treatment, but it was not statistically significant (Fig. S3A). The relative expression of the antimicrobial peptide RegIII-γ mRNA secreted by epithelial cells increased. The increased expression of RegIII-γ suggests enhanced epithelial defense mechanisms following EGCG treatment, potentially contributing to improved gut barrier function and microbiota homeostasis in FA. The number of goblet cells increased (Fig. S3B), and the expression of Mucin-2 was significantly upregulated, which maintained the formation of the mucin layer. TJ proteins are critical for preserving the integrity of the intestinal barrier, and enhancement of this barrier function may mitigate the severity of FA[31]. Following intervention with EGCG, it was observed that the mRNA level of Claudin (Fig. 3E) and protein expressions of intestinal epithelial TJ proteins Occludin (Fig. 3C) and ZO-1 (Fig. 3D) were upregulated. These results suggest that EGCG may inhibit the osmotic effect of OVA and other allergens in FA by increasing the level of TJ proteins. Furthermore, the levels of colonic inflammatory cytokines IL-1β (Fig. 3F), TNF-α (Fig. 3G), and IL-22 (Fig. 3H) in mice were quantified, revealing that EGCG effectively attenuated low-grade colonic inflammation in a model of FA.



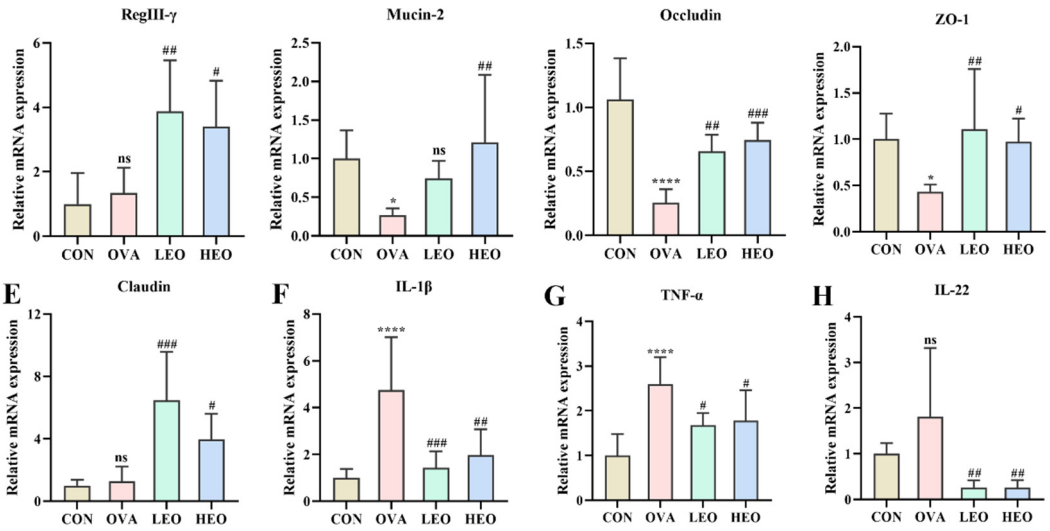


Fig. 3. **EGCG intervention alleviated OVA-induced FA related gut barrier impairment**. (A) Representative histologic images of hematoxylin and eosin (H&E) staining of colon sections. The histogram shown the relative mRNA expression of RegIII-γ. (B) Representative histologic images of periodic acid-Schiff (PAS) staining of colon sections. The histogram shown the relative mRNA expression of Mucin-2. (C) Representative histological images of Occludin IHC staining of colon sections and relative expression of mRNA. (D) Representative histological images of ZO-1 IHC staining of colon sections and relative expression of mRNA. (E) Relative mRNA expression of Claudin. (F) Relative mRNA expression of IL-1β. (G) Relative mRNA expression of TNF-α. (H) Relative mRNA expression of IL-22. Data were shown as the mean ± SEM. Compared to CON, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, or ****: $P < 0.0001$; compared to OVA, $^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$, or $^{\#\#\#\#}$: $P < 0.0001$. CON: control; OVA: OVA-sensitized mice; LEO: OVA-sensitized mice treated with 25 mg/kg EGCG; HEO: OVA-sensitized mice treated with 50 mg/kg EGCG.

3.7 EGCG restored the homeostasis of intestinal microbiota

The gut microbiota plays a critical role in modulating the allergic response to dietary antigens[32]. Consequently, we investigated the impact of EGCG on the homeostasis of gut microbiota by analyzing its composition. Venn diagrams revealed common and specific microbial communities in the gut of four groups of mice (Fig. 4A). An increase in both the Shannon and Chao1 indices indicates enhanced diversity and richness within the sample. As illustrated in Fig. 4B and 4C, the α-diversity of intestinal microbiota in OVA mice was significantly lower compared to that in CON mice. Notably, the α-diversity of the gut microbiota exhibited a marked increase following EGCG intervention. These findings demonstrate that EGCG intervention effectively restores gut microbial diversity that was diminished by OVA sensitization. The recovery of α-diversity (both richness and evenness) suggests EGCG may create a more balanced gut ecosystem. This microbial restoration likely contributes to EGCG's therapeutic effects by promoting colonization resistance against pathobionts and enhancing immune regulatory networks.

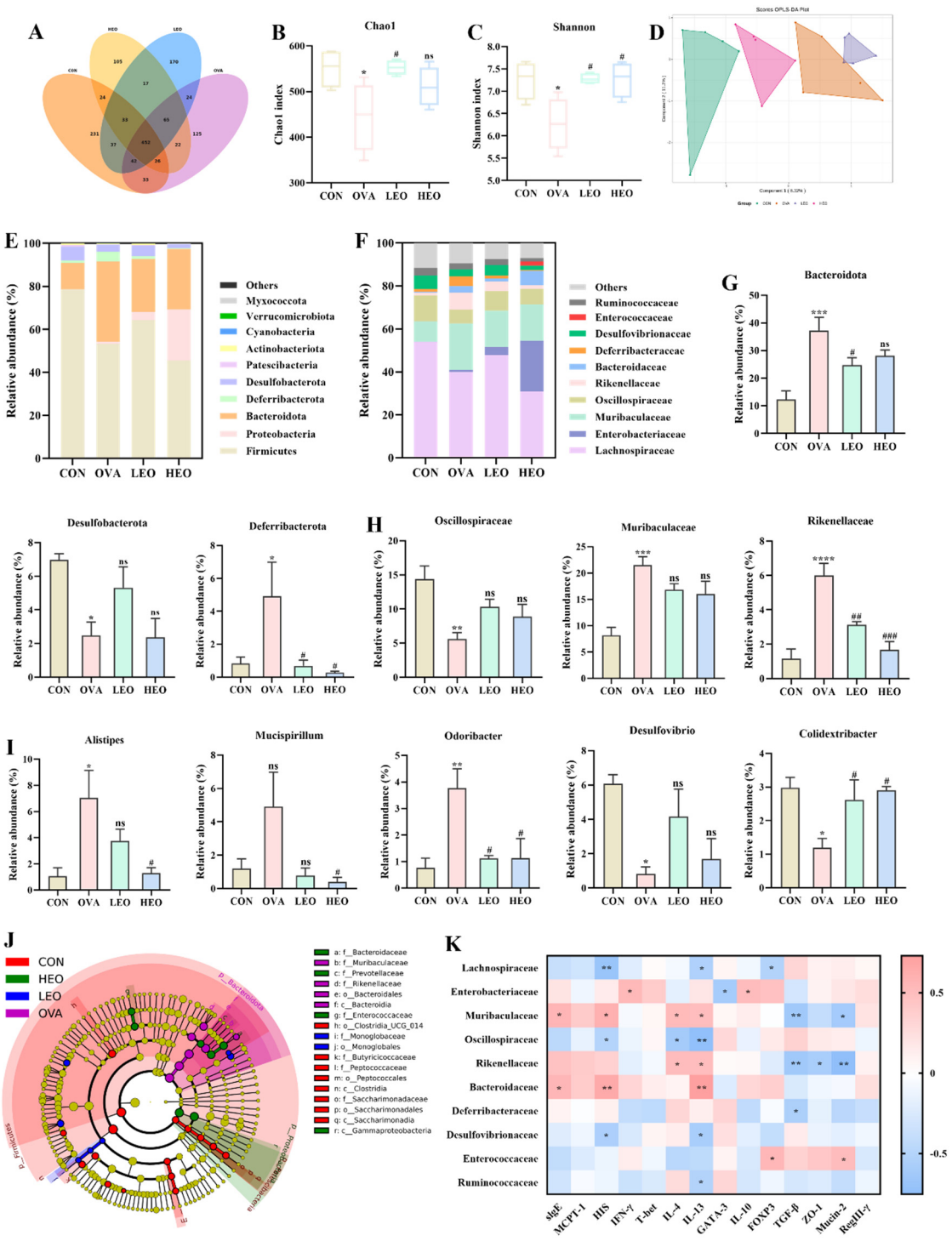


Fig. 4. **EGCG modulated OVA-induced gut microflora dysbiosis**. (A) Venn diagram of the different groups. (B) Chao1 index. (C) Shannon index. (D) Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA). (E) Bacterial composition of mouse gut at the phylum. (F) Bacterial composition of mouse gut at the family. (G) Bacterial abundance at the phylum level. (H) Bacterial abundance at the family level. (I) Relative abundance of the significantly differential flora at the genus level. (J) Branch diagram depicting the output of the LEfSe analysis. (K) Correlation analysis between intestinal microbiota at the family level and allergy-related index. Data were shown as the mean ± SEM. Compared to CON, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, or ****: $P < 0.0001$; compared to OVA, $^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$, or $^{\#\#\#\#}$: $P < 0.0001$. CON: control; OVA: OVA-sensitized mice; LEO: OVA-sensitized mice treated with 25 mg/kg EGCG; HEO: OVA-sensitized mice treated with 50 mg/kg EGCG.

As shown in Fig. 4D, the gut microbial structure was altered among the CON, OVA, and EGCG intervention groups. The differences in colony composition among the various groups were further

investigated. Fig. 4E and 4F present the relative abundance histograms of the top 10 annotated species at the phylum and family levels, respectively. At the phylum level, *Firmicutes* and *Bacteroidetes* were dominant in all groups. The proportion of *Firmicutes* in the OVA sensitization group decreased, and the abundance of *Bacteroidetes* increased significantly, disrupting the ratio of *Firmicutes* and *Bacteroidetes* and affecting intestinal homeostasis, After EGCG intervention, this balance was effectively restored. The restoration of the Firmicutes/Bacteroidetes (F/B) ratio by EGCG is particularly noteworthy, as an imbalanced F/B ratio has been linked to increased gut permeability and Th2-skewed immune responses in FA.[33] This suggests EGCG may ameliorate allergic inflammation by correcting dysbiosis-induced barrier dysfunction. In addition, *Deferribacterota* and *Desulfobacterota* abundance were significantly changed, with *Deferribacterota* abundance being restored after EGCG intervention (Fig. 4G), *Desulfobacterota* are known sulfate-reducing bacteria associated with hydrogen sulfide production in the gut.[34] At the family level, after EGCG intervention, the changes in abundance of *Oscillospiraceae*, *Muribaculaceae*, and *Rikenellaceae* because of OVA sensitization were either inconspicuous or significantly restored (Fig. 4H). Further, we analysed the differences at the bacterial genus level: *Alistipes*, *Mucispirillum*, *Odoribacter*, *Desulfovibrio*, and *Colidextribacter*, all of which were improved after EGCG intervention (Fig. 4I). These results suggest that EGCG shifts the gut microbiota to an immunotolerant state. The LEfSe analysis showing the gut microbial biomarkers in each group is presented in Fig. 4J.

To clarify the correlation between the gut microbiota and OVA-induced allergy-related indices, and to explore the possible specific strains affected by EGCG in alleviating allergies, Spearman correlation analysis was used to analyse the correlation between intestinal microbiota and allergy-related indices at the family level. As shown in Fig. 4K, *Muribaculaceae* had a positive correlation with the levels of sIgE, HIS, IL-4, and IL-13, but a negative correlation with the levels of TGF-β and Mucin-2. *Oscillospiraceae* had a negative correlation with the levels of HIS, IL-4, and IL-13. *Rikenellaceae* had a positive correlation with the levels of IL-4 and IL-13, but a negative correlation with the levels of TGF-β, ZO-1, and Mucin-2. *Bacteroidaceae* had a positive correlation with the levels of sIgE, HIS, and IL-13.

3.8 EGCG regulated the signalling of TLR4/MyD88/NF-κB

Based on the MR analyses, there may be no genetic association between tea intake and FA. Given the crucial role of TLR4 in pathogen recognition and innate immune activation, the transcription levels were determined. The results revealed that the TLR4 levels in the OVA group were significantly elevated compared to the CON group. Following EGCG intervention, TLR4 levels in the LEO and HEO groups decreased by 56.6% and 50.9%, respectively (Fig. 5A), and MyD88 transcription levels also significantly decreased (Fig. 5B). These findings notably inspired the detailed investigation of the role of the NF-κB signalling pathway in the immunoregulatory effects of EGCG against FA.

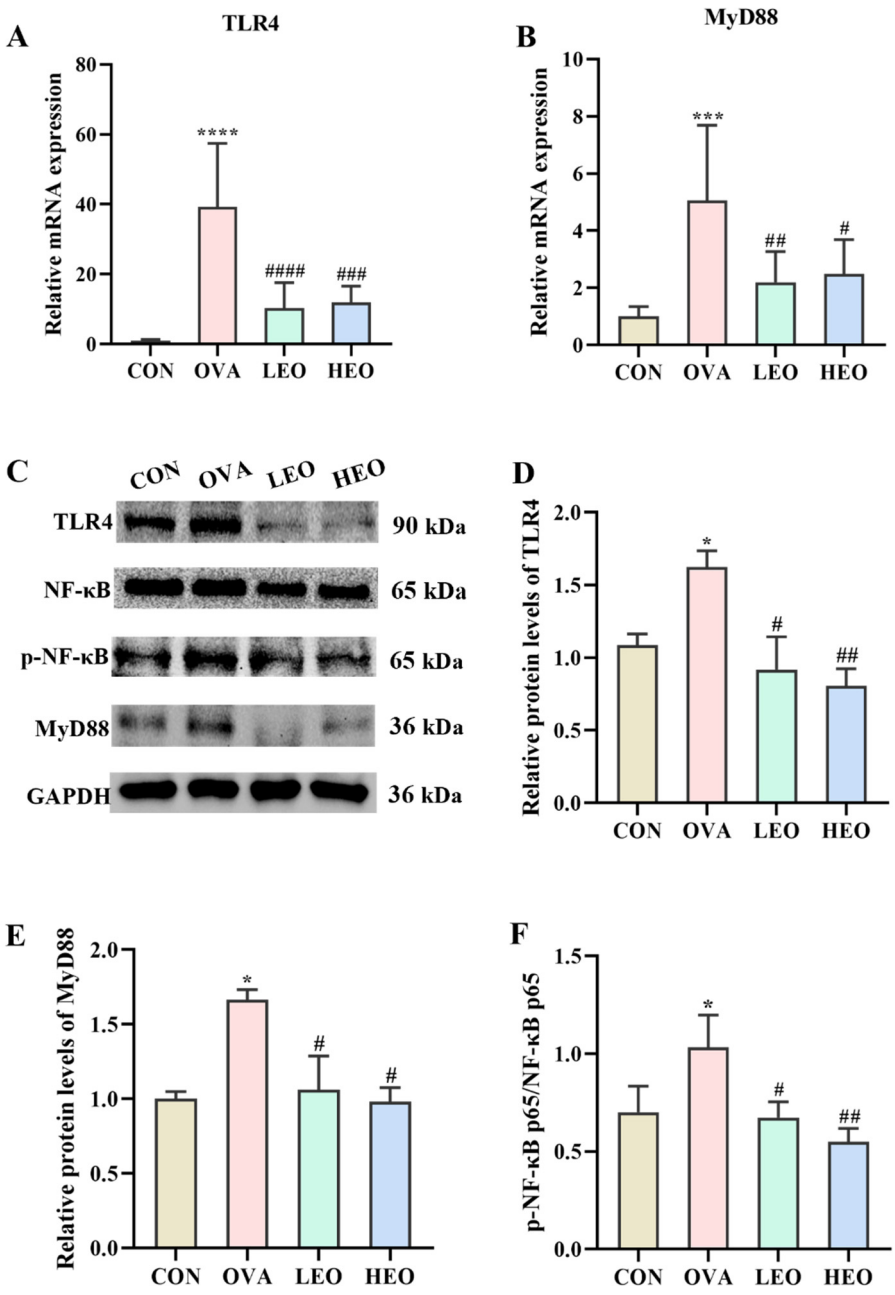


Fig. 5. EGCG alleviated OVA-induced FA through TLR4 and downstream MyD88/NF-κB signaling pathway. (A) Relative mRNA expression of TLR4. (B) Relative mRNA expression of MyD88. (C) Western blot results of TLR4, NF-κB p65, p-NF-κB p65, MyD88 and GAPDH. (D) Protein levels of TLR4. (E) Protein levels of MyD88. (F) Gray-value histogram of p-NF-κB p65/ NF-κB p65. Data were shown as the mean ± SEM. Compared to CON, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, or ****: $P < 0.0001$; compared to OVA, $^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$, or $^{\#\#\#\#}$: $P < 0.0001$. CON: control; OVA: OVA-sensitized mice; LEO: OVA-sensitized mice treated with 25 mg/kg EGCG; HEO: OVA-sensitized mice treated with 50 mg/kg EGCG.

The transcriptional and translational level analysis of related signaling molecules confirmed that OVA sensitization resulted in increased levels of TLR4 and MyD88, which subsequently activated NF-κB p65. This activation upregulated the levels of phosphorylated NF-κB p65 (p-NF-κB p65), contributing to the production of inflammatory factors involved in the onset and progression of allergies (Fig. 5C-F). However, treatment with EGCG significantly downregulated the expression of pro-inflammatory factors, indicating that EGCG modulates the TLR4/MyD88/NF-κB signalling pathway to alleviate allergic responses.

4. Discussion

As a popular beverage, tea has attracted significant attention for its role in the intervention and modulation of internal disorders. In this prospective cohort study based on the UK Biobank, we found a non-linear association between tea drinking and FA. Using a Cox proportional hazards regression model, we demonstrated that daily tea consumption can reduce the risk of developing FA. However, in a subsequent two-sample MR analysis, there was no causal genetic association between tea intake and FA. This may be owing to the MR analysis evaluating overall tea intake without distinguishing between different tea types, potentially leading to a compensatory effect among various tea components and contributing to the observed null association. Nevertheless, considering the broader body of evidence, tea consumption appears to play a protective role against FA, highlighting its potential as a beneficial dietary factor in immune regulation.

As the primary polyphenolic active compound in green tea, EGCG has been widely recognized for its broad biological activities, particularly its anti-inflammatory, antioxidative, and immunomodulatory properties[35]. Growing evidence supports the modulatory effect of EGCG on FA, suggesting it may underlie the association between tea consumption and reduced FA risk[36]. In *vivo* analysis demonstrated that EGCG mitigates allergic symptoms by targeting multiple facets of the immune system, including Th1/Th2 balance, mast cell stabilization, and intestinal barrier integrity, potentially elucidating the mechanism underlying the reduced FA risk associated with tea intake.

In the experimental section, results showed that OVA induced an increase in thymus and spleen indices in allergic mice, accompanied by observable behavioral symptoms. These symptoms were alleviated following EGCG intervention. In addition, IgE is a key mediator of allergic sensitization and subsequent mast cell activation[37]. Allergen-specific IgE, His, and MCPT-1 levels were reduced after EGCG treatment. Interestingly, the low-dose EGCG intervention had a more pronounced effect than the high-dose intervention. The reduction in these biomarkers supports the suppression of allergic responses and suggests that EGCG may protect against both early- and late-phase allergic reactions. This dual-phase inhibition is critical for effective allergy management, and may alleviate persistent immune dysregulation caused by chronic allergy.

Beyond IgE modulation, the regulation of Th1 and Th2 cytokines by EGCG further underscores its therapeutic potential. FA is characterized by a skewed Th2 response, wherein IL-4 stimulates B cell differentiation and IgE production and induces mast cell degranulation, aggravating allergic reactions[38]. Chen *et al*.[39] found that barley bran extract could reduce OVA-mediated allergic reactions by balancing Th1/Th2 immune responses. Similarly, EGCG reduced Th2 cytokines while promoting Th1-associated cytokines, such as IL-2 and IFN-γ, indicating a rebalancing of the immune response toward a more tolerogenic state. The upregulation of T-bet, a transcription factor essential for Th1 differentiation, highlights EGCG's capacity to restore Th1/Th2 balance, which may be decisive in mitigating chronic allergic conditions.

The role of Treg cells in modulating allergic responses has gained significant attention. In this study, findings further support the hypothesis that EGCG enhances Treg function. By increasing the expression of

Foxp3 and TGF-β, EGCG appears to promote Treg expansion, which is essential for maintaining immune homeostasis and preventing overactive immune responses[40].

Intestinal barrier integrity is another critical factor in the pathogenesis of FA. Disruption of tight junctions between epithelial cells permits allergen translocation across the gut lining, triggering systemic immune activation[41]. This study demonstrated that EGCG enhances the expression of TJ proteins such as ZO-1 and Occludin, thereby strengthening the intestinal barrier. This effect not only limits allergen penetration but also reduces the inflammatory burden on the gut-associated immune system. By preserving gut integrity, EGCG contributes to a more effective first line of defence against dietary antigens, potentially lowering the incidence and severity of allergic reactions over time.

Beyond its direct effects on immune cells and barrier function, EGCG's impact on gut microbiota composition adds another dimension to its therapeutic potential. Gut dysbiosis is closely associated with allergic diseases, as microbial imbalances can enhance immune reactivity. Results showed that EGCG restored microbial homeostasis, notably by correcting the *Firmicutes*-to-*Bacteroidetes* ratio—a key indicator of gut health[42]. The increased abundance of beneficial microbial families such as *Oscillospiraceae*, along with the reduced presence of pro-inflammatory taxa such as *Desulfovibrio* and *Alistipes*, underscores EGCG's ability to modulate the gut–immune axis. This suggests that EGCG's anti-allergic effects may, in part, be mediated through reshaping the gut microbiome to favour immune tolerance.

The link between gut microbiota and systemic immune responses is increasingly recognized, particularly in allergic diseases[43]. By promoting the growth of beneficial microbes, EGCG may support not only intestinal health but also systemic immunomodulation. The correlation analysis between gut microbiota composition and allergy-related biomarkers further emphasizes this connection. For example, the positive correlation between *Muribaculaceae* and allergy biomarkers such as sIgE and IL-4 suggests that microbial composition influences immune sensitivity. EGCG's ability to reduce the abundance of these pro-allergic taxa may contribute to its overall anti-allergic effect.

Finally, the study identified the TLR4/MyD88/NF-κB signalling pathway as a key mechanism mediating EGCG's alleviative effect on FA. TLR4 activation is a known trigger for inflammation and allergic responses, leading to the production of pro-inflammatory cytokines such as IL-1β and TNF-α[44-46]. EGCG downregulated TLR4 expression and inhibited the downstream activation of MyD88 and NF-κB, thereby dampening the inflammatory cascade. This mechanistic insight is significant, as it shows that EGCG not only addresses allergic symptoms but also intervenes at the molecular level to prevent the amplification of inflammatory signals. The reduced phosphorylation of NF-κB p65, a marker of its activation, further confirms that EGCG suppresses pro-inflammatory gene expression, with potential implications for treating other inflammatory diseases beyond FA. Overall, these findings reveal the correlation between tea intake and FA risk and identify a mechanism mediated by tea polyphenolic components. These results provide a strong foundation for further research on dietary-based interventions for allergic diseases. Although EGCG is selected as the dominant component in this study, other tea polyphenols such as theanine may also contribute

to the antiallergic process through independent or synergistic pathways. For example, theanine inhibits histamine release by blocking mast cell FcεRI receptors, while theaflavins in black tea downregulate IL-6 and TNF-α[47]. It is worth noting that Xu *et al.*[27] found that theanine combined with EGCG could alleviate allergic symptoms better than a single ingredient, suggesting that the synergistic effect of polyphenols in actual tea consumption may be the key to its protective effect. Future studies should be proposed to verify this hypothesis through component combination experiments.

5. Conclusion

This study provides substantial evidence that tea intake may significantly reduce the risk of FA, with the tea-derived polyphenolic compound EGCG serving as one of key mediators of tea's protective effects by modulating immunological pathways and restoring gut microbiota balance. The detailed results demonstrated that EGCG reduced allergen-specific IgE levels, rebalanced Th1/Th2 cytokine responses, and reinforced the intestinal barrier by upregulating TJ proteins. Furthermore, its modulation of beneficial microbial families underscores EGCG's potential as a gut microbiota regulator. By addressing both immunological and microbial factors involved in allergic responses, the mechanism underlying tea's protective effect on FA was elucidated, with EGCG playing a central role. Further research is warranted to validate these findings in clinical settings and to better understand the role of tea intake in FA intervention.

Compliance with Ethics Requirements

The study was conducted following the Declaration of Helsinki. The UK Biobank has research tissue bank approval from the North West Multi-Center Research Ethics Committee. Written informed consent was obtained from all participants. The present study was approved by UK Biobank under application number 90831. All GWAS data used in this study are available in the IEU open GWAS project (https://gwas.mrcieu.ac.uk/), therefore exempt from the approval of the ethics review body as the data used are public, anonymous, and de-identified. All Institutional and National Guidelines for the care and use of animals (fisheries) were followed.

Competing interests declaration

The authors declare no competing financial interest.

Acknowledgments

This work was financially supported by National Natural Science Foundation of China (No. 32272403) and the Natural Science Foundation of Tianjin city (grant number 23JCQNJC02040). We would like to acknowledge the IEU Open GWAS database for providing the data. We also want to thank investigators and participants in the UK Biobank study. Additional data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online.

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