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Tannic acid mitigates salmonella-induced lung injury via gut-lung axis in broilers

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ABSTRACT

Tannic acid (**TA**), a polyphenolic compound derived from plants, exhibits anti-inflammatory, antibacterial, antiviral, and antioxidant biological activities. *Salmonella*, a prevalent foodborne pathogen, poses a significant threat to poultry, resulting in considerable economic losses for the animal husbandry industry. In this study, we investigated the protective effects of TA against lung and intestinal injuries induced by a transient *Salmonella* infection in broilers. After a ten-day infection period, although *Salmonella* was not detected in the intestinal content of broilers, the infected broilers exhibited reduced body weight and compromised intestinal barrier function. *Salmonella* infection facilitated the growth of detrimental bacteria in the lungs and ileums, triggering an inflammatory response. TA inhibited the pathogen's colonization in the lungs and reduced serum levels of lipopolysaccharide (**LPS**) as well as lung levels of myeloperoxidase (**MPO**). Moreover, TA down-regulated the expression of pro-inflammatory cytokines and hindered the polarization of M1 macrophages in the lungs.

In summary, TA mitigates *Salmonella*-induced lung inflammation and immune imbalance by its anti-inflammatory, antioxidant and antibacterial properties in broilers.

Introduction

In the process of broiler breeding, chicks exhibit a high susceptibility to bacterial and other pathogens due to the underdevelopment of their immune system and gut microbiota (Crhanova *et al.*, 2011). *Salmonella*, recognized as one of the most significant foodborne pathogens, poses a high risk of infection in chicks (Dar *et al.*, 2019). *Salmonella* is transferred from the environment to chicks, where it is widely distributed and colonizes the chicken's intestinal tract, is more common in the initial stages of a chicken's life, and usually diminishes in the later stages. Although the mortality rate of *Salmonella*-infected broilers is low, *Salmonella* infections cause growth retardation in broilers and lead to economic losses for the poultry industry, posing a serious food safety hazard. In addition, the continued colonization of broilers in the intestinal tract leads to environmental contamination and poses one of the most serious threats to food safety and public health. In addition to causing intestinal infections in broilers through contaminated feed and water, *Salmonella* can also disseminate via aerosols, facilitating cross-infection within poultry flocks. Consequently, the lungs serve as a pivotal site where *Salmonella* infection can trigger systemic inflammatory responses, leading to significant economic losses in the poultry industry (El-Sharkawy *et al.*, 2017; Mshelbwala *et al.*, 2019; Nazir *et al.*, 2025). *Salmonella* invades the host's intestinal epithelial cells and disseminates throughout the body via the bloodstream, leading to infection. In recent years, the gut-lung axis has emerged as a prominent area of research for examining the interrelationship between the gut and the lungs. The epithelium of both the gut and lungs constitutes the first line of defense for the human body and regulates local and systemic immune responses through stable symbiotic bacteria residing in the gut and respiratory tract. When their barrier function is compromised, epithelial and immune cells are activated to produce a substantial quantity of inflammatory mediators, which can trigger immune responses at distant sites via blood and lymph circulation (Budden *et al.*, 2017; Dang and Marsland, 2019). Although the location and functions performed by the

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gut and the lungs in the body are very different, some studies have shown that there is a connection between these two organs in inflammatory bowel disease and chronic inflammation of the lungs. Gut microbiota and their metabolites can be transferred to the lungs via circulation, playing a significant role in host susceptibility to bacterial pneumonia. Existing evidence shows that intestinal infections can impact the immune response in the lungs, thereby increasing the risk of secondary lung inflammation (Trivedi *et al.*, 2021). Consequently, *Salmonella* infections not only compromise intestinal health but may also adversely affect the respiratory system, leading to chronic inflammation.

Tannic acid (**TA**) is a polyphenolic compound of natural plant origin with biological activities including antibacterial, antiviral, antiparasitic, and antioxidant (Khanbabaee and van Ree, 2001). In recent decades, many studies have reported that appropriate amounts of tannic acid can effectively improve the feed utilization and performance of livestock and poultry, promote intestinal health, and improve the quality of animal products, which has an up-and-coming application prospect. Previous evidence showed that plant tannins can regulate intestinal barrier function and gut microbiota, promoting intestinal health (Li *et al.*, 2022), and adding tannins to the feed can increase the final body weight of broilers, improve growth performance, and enhance the immunity of broilers (Niu *et al.*, 2022) However, the relationship between *Salmonella*-induced intestinal inflammation and chronic lung injury remains unclear, as does the potential protective role of TA in mitigating lung injury. This study aims to clarify the key role of the gut-lung axis in *Salmonella*-induced lung injury in broilers, and explore the innovative application value of TA.

Materials and methods

Tannic acid and reagents

The primary reagents and antibodies used are listed in Table S1.

Experimental design and animal treatment

The study was conducted in accordance with the Animal Welfare and Use Guidelines of China and received approval from the Animal Welfare Committee of Hunan Agricultural University (Approval number: 2024102). Two hundred fifty 1-day-old white-feathered broilers were randomly assigned to groups, each comprising five replicates, as illustrated in Fig. 1A: (1) CON: a basal diet; (2) SE: orally administered *Salmonella* at a dose of 3×10^8 CFU on days 10 and 11 of age; (3) SE+TA (L): a basal diet supplemented with 200 mg/kg tannic acid, along with oral administration of *Salmonella* as in SE group; (4) SE+TA(H): a basal diet supplemented with 400 mg/kg tannic acid, along with oral administration of *Salmonella* as in SE group; (5) TA(H): 400 mg/kg tannic acid added to the basal diet. During the 3-week trial period, the broilers were provided with unrestricted access to feed and water. The experimental diets were formulated in accordance with the Chinese broiler feeding standard (NY/T 33-2004). The Formulations of the basal diets and the nutritional levels for broilers throughout all phases of the experiment are detailed in Table S2.

Salmonella challenge test

The *Salmonella* strain *CICC 21510* was obtained from the China Center for Industrial Culture Collection. The strain was inoculated into an LB liquid medium and incubated at 37°C with shaking for 16-18 hours. To determine the concentration of *Salmonella* in the bacterial suspension, the cultured broth was diluted with sterile phosphate buffered saline (**PBS**) and subsequently spread onto an LB solid medium. The plates were then incubated at 37°C for 24 hours. After incubation, the colonies were counted and diluted to a final concentration of 3×10^8 CFU/mL using sterile PBS. On the 10th and 11th days of age, the SE, SE+TA(L), and SE+TA(H) groups were orally administered 1 mL of the *Salmonella* suspension at a concentration of 3×10^8 CFU, while the CON

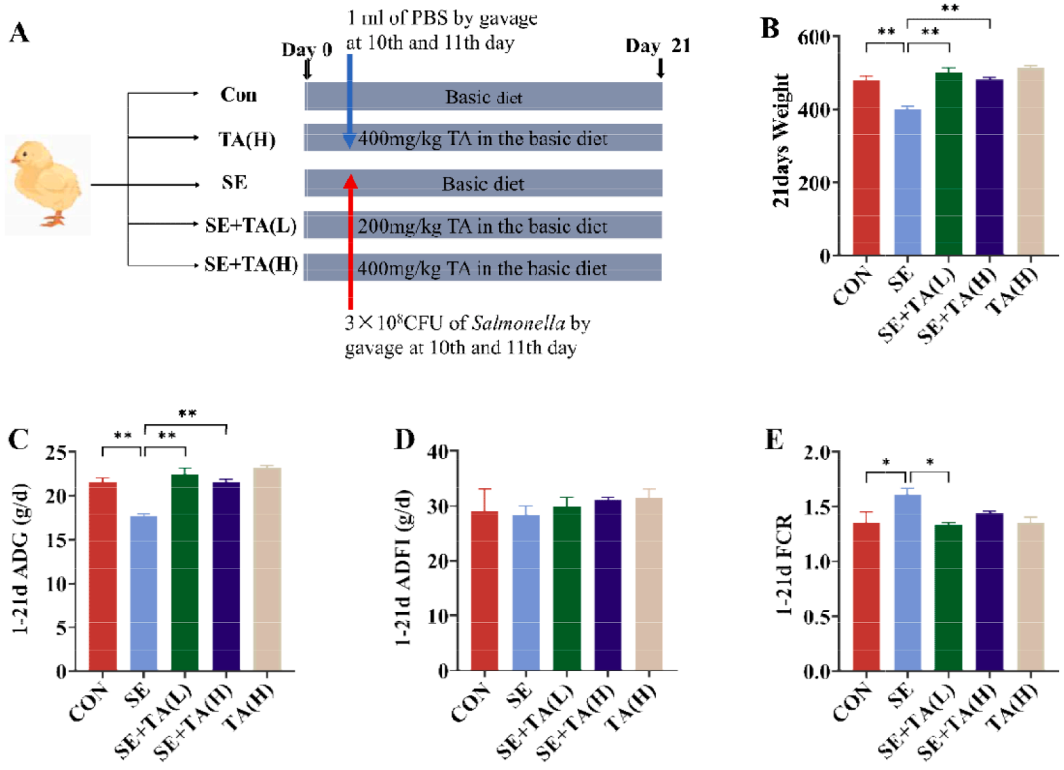

Fig. 1. TA improved the growth performance of *Salmonella*-infected broilers. (A) Animal grouping and experimental design. (B) 21-day body weight. (C) The average daily gain(ADG). (D) Average daily feed intake(ADFI). (E) Feed conversion ratio(FCR). CON: Control; TA: Group with tannic acid supplemented in feed, SE: The *Salmonella*-challenged, SE+TA(L): SE + 200 mg/kg TA, SE+TA(H): SE + 400 mg/kg TA, TA(H): 400 mg/kg TA. Significant differences: $^*P < 0.05$, $^{**}P < 0.01$.

and TA(H) groups were orally administered 1 mL of sterile PBS on the same day.

Sample collection

Broilers were weighed to determine body weight and their feed intake was recorded at 1, 7, 14, and 21 days of age. The average daily gain (**ADG**), average daily feed intake (**ADFI**), and feed conversion ratio (**FCR**) were calculated for each stage and for the entire experimental cycle. At the end of the experiment, 15 broilers were randomly selected from each treatment group and euthanized by the cervical dislocation method after collecting blood from the sub-wing veins.

Histological analysis

Fresh ileum and lung tissues were fixed in a 4 % paraformaldehyde solution and subjected to gradient ethanol dehydration the following day. The hematoxylin-eosin (H&E) staining and immunofluorescence staining of the ileum and lungs was analyzed as described in our previous study (Wang *et al.*, 2023; Zhang *et al.*, 2023). Information regarding the antibodies used is provided in Table S1.

Enzyme-linked immunosorbent assay (ELISA) test

According to the manufacturer's instructions, the levels of lipopolysaccharide (LPS, Shanghai Enzyme-linked Biotechnology Co., Ltd) in serum and myeloperoxidase (MPO, Lun Chang Shuo Biotech) in lung tissue were measured.

Quantitative real-time polymerase chain reaction(qPCR)

The relative expression of mRNAs in the lung and ileum was analyzed by qPCR, following the methodology outlined in our previous study (Yan *et al.*, 2022). The synthetic primers utilized in this study (Sangon, Shanghai, China) are detailed in Table S3.

16S rRNA sequencing and data processing

Ileal contents and lung tissues that were preserved in liquid nitrogen were taken for genome extraction as described previously (Zhang *et al.*, 2022).

Oxidative-antioxidative assay

The antioxidant capacity of lung tissue was determined using a kit from Nanjing Jiancheng Biotech Co., Ltd. according to the manufacturer's instructions, and the data were subjected to rigorous analysis.

Statistical analyses

Using SPSS 25 software, data conforming to a normal distribution were subjected to a test for homogeneity of variances and one-way ANOVA. Results were expressed as the mean ± standard error (**$\bar{X}$ ± SEM**), with $P < 0.05$ (*) considered significant and $P < 0.01$ (**) considered highly significant. In the analysis of microbial diversity, the Wilcoxon rank sum test was used to assess differences between groups for alpha diversity. The bray was utilized for the distance algorithm in both principal coordinates analysis (**PCoA**) analysis. For multiple comparisons in species difference analysis, the Kruskal-Wallis rank sum test was applied.

Results

TA improved the growth performance of salmonella-infected broilers

At day 21, the body weight of the SE group was significantly lower than that of the CON group ($P < 0.05$). In contrast, the SE+TA(L) and SE+TA(H) groups exhibited a significant increase in body weight compared to the SE group (Fig. 1B). ADG was significantly reduced in *Salmonella*-infected broilers compared to the CON group ($P < 0.05$), while ADFI showed no significant difference, as depicted in Fig. 1C and D. Notably, the addition of TA to the diet significantly increased ADG and, specifically, the SE+TA(L) group reduced the FCR ($P < 0.05$; Fig. 1E). These results indicated that dietary TA might ameliorate the growth performance decline in broilers induced by *Salmonella*.

Effects of TA on the morphological structure of the ileum and lung in salmonella-infected broilers

We assessed the effect of TA on *Salmonella*-induced intestinal and lung pathology in broilers using H&E staining. As shown in Fig. 2A, the ileum of the SE group exhibited pronounced hemorrhagic spots, and the intestinal villi were disrupted with an irregular arrangement. The inclusion of TA in the feed significantly alleviated these lesions ($P < 0.05$) compared to the SE group. At day 21, the crypt depth in the ileum of the SE group broilers was significantly greater than that in the CON group, while both the SE+TA(L) and SE+TA(H) significantly reduced crypt depth ($P < 0.05$), as illustrated in Fig. 2C-E. Additionally, Comparison with the CON group, the SE group exhibited alveolar collapse, interstitial thickening, and substantial infiltration of inflammatory cells. However, the inclusion of TA in the diet significantly improved the morphological structure of the lungs (Fig. 2B). Additionally, we assessed MPO content in lung tissue and serum LPS levels using ELISA (Fig. 2F-G). Both MPO and LPS levels were significantly elevated in the SE group ($P < 0.05$). Notably, the SE+TA(L) group significantly reduced both MPO and LPS levels, while the SE+TA(H) group significantly lowered LPS levels ($P < 0.05$).

TA ameliorated the intestinal barrier dysfunction induced by salmonella in broilers

We analyzed the expression levels of Claudin-1 and Mucin-2 (**MUC-2**) in the ileum of broilers using immunofluorescence, as illustrated in Fig. 3A-C. Supplementation of the diet with 200 mg/kg of TA significantly up-regulated the expression of Claudin-1 and MUC-2, which were down-regulated due to *Salmonella* infection ($P < 0.05$), This finding was further corroborated by qPCR results (Fig. 3D-H). In the SE group, the mRNA expression levels of *Claudin-1, Occludin, Zonula occludens-1* (***ZO-1***), *MUC-2*, and *secretory immunoglobulin A* (***SIgA***) were significantly lower in the ileal tissues compared to the CON group ($P < 0.05$). TA treatment significantly up-regulated the mRNA expression of *Claudin-1, Occludin, MUC-2*, and *SIgA*, however, it did not significantly affect the mRNA expression level of *ZO-1*.

TA alleviated the Ileal inflammation induced by salmonella in broilers

We assessed *Salmonella* infection-induced intestinal inflammation by measuring the expression levels of interleukin-1β (**IL-1β**) and tumor necrosis factor (**TNF-α**) in ileal tissues using immunofluorescence (Fig. 4A-C). The infection resulted in increased expression of these pro-inflammatory cytokines, while treatment with TA significantly down-regulated their expression ($P < 0.05$). This finding was further corroborated by qPCR analysis (Fig. 4D-E). Additionally, we examined the mRNA expression levels of *interleukin-6* (***IL-6***), *interferon-γ* (***IFN-γ***) and *interleukin-4* (***IL-4***) in the ileum (Fig. 4F-H). The mRNA expression levels of *IL-6, IFN-γ* and *IL-4* were significantly higher in the SE group compared to the CON group ($P < 0.01$). In contrast, in the SE+TA(L) group, the mRNA expression levels of *IL-4 IL-6* and *IFN-γ* were significantly down-regulated ($P < 0.01$).

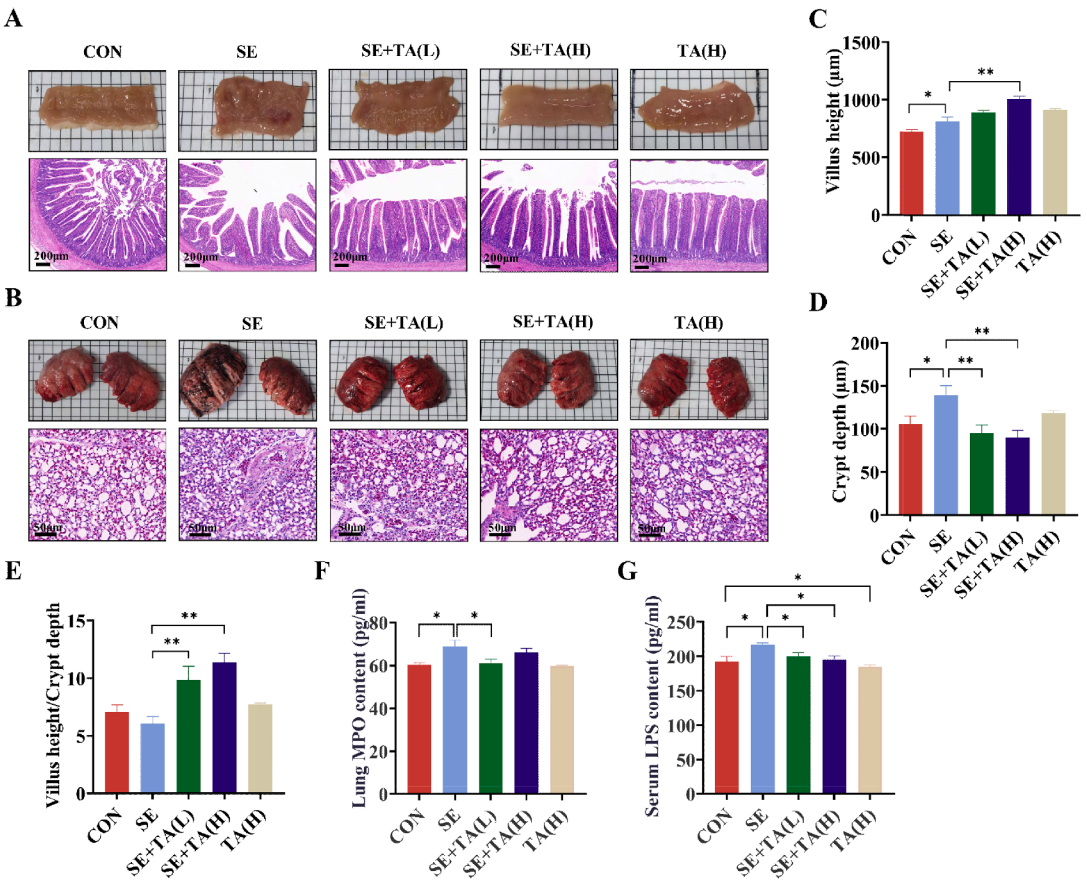

Fig. 2. Effects of TA on the morphological structure of the ileum in *Salmonella*-infected broilers. (A) Gross appearance and H&E staining of pathological sections of the ileum (original magnification × 50). (B) Gross appearance and H&E staining of pathological sections of the lung (original magnification × 300). (C) Villus height (**VH**,μm). (D) Crypt depth (**CD**,μm). (E) VH:CD. (F) MPO content of the lung. (G) LPS content in serum. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

Effects of TA on the Ileal microbiota in salmonella-infected broilers

To accurately assess the impact of TA on gut microbiota composition following *Salmonella* infection, ileal contents from the CON, SE, and SE+TA(L) groups were selected for 16S rRNA gene sequencing. 220 operational taxonomic units (**OTUs**) common to all three (Fig. 5A). The diversity and abundance of the ileal microbiota were evaluated using the Shannon and Simpson indices for an alpha diversity assessment (Fig. 5B-C). Interestingly, both indices were significantly higher in the SE+TA(L) group compared to the SE group ($P < 0.05$). As illustrated in Fig. 5D-E, both the SE group and the addition of tannins significantly altered the composition of broiler ileal microorganisms compared to the CON group. At the phylum level (Fig. 5F), the dominant phyla across all groups were *Firmicutes, Bacteroidota*, and *Proteobacteria*, with the SE group exhibiting a decreased abundance of *Firmicutes* and an increased abundance of *Proteobacteria*. Notably, the relative abundance of *Desulfobacterota* in the SE group was significantly higher than that in the other two groups ($P < 0.05$; Fig. 5G). Additionally, *Salmonella* infection led to an increase in the relative abundance of *Burkholderiales* in the ileum of broiler chickens, whereas the inclusion of tannins reduced the colonization of *Burkholderiales* in the ileum (Fig. 5H). The relative abundance of *Desulfovibrionales* was significantly higher in the SE group ($P < 0.05$; Fig. 5I). The SE group exhibited a relative decrease in *Ruminococcus_torques_group*, alongside an increase in *Pelomonas, Escherichia-Shigella*, and *Ralstonia*. Notably, TA treatment led to a reduction in the abundance of *Pelomonas, Escherichia-Shigella*, and *Ralstonia* (Fig. 5J). The relative abundance of *Lactobacillus* was significantly lower in both the SE and SE+TA(L) groups compared to the CON group ($P < 0.05$). The histogram of LDA revealed an enrichment of *Lactobacillaceae* in the CON group. Additionally, The abundance of *Acetitomaculum, Desulfovibrionales* and *Psychrobacter* significantly increased in the SE treatment, while an enrichment of *Bacteroides_fragilis* was observed in the SE+TA(L) group (Fig. 5L).

Effects of TA on the lung microbiota in salmonella-infected broilers

The lungs serve as the primary site for gas exchange between the organism and the environment, and the composition of their microbiota is closely related to the health of the respiratory system. We analyzed the lung microbiota of three groups: CON, SE, and SE+TA(L), using 16S rRNA gene sequencing. As shown in Fig. 6A, 185 OTUs shared among the three groups. Treatment with TA significantly increased the Shannon index of the lung microbiota in *Salmonella*-infected broilers (Fig. 6B-C). The beta diversity of the lung microbiota was analyzed, with both PCoA and PLS-DA indicated that neither *Salmonella* infection nor the addition of tannic acid significantly affected the lung microbial composition (Fig. 6D-E). At the phylum level, the SE group exhibited a increase in the abundance of *Proteobacteria* and a decrease in the relative abundance of *Bacteroidota*. Additionally, the microbial composition of the SE+TA(L) group was found to be more similar to that of the CON group. Notably, the relative abundance of *Planctomycetota* in the SE+TA(L) group was significantly higher than that in the other two groups ($P < 0.05$; Fig. 6G). At the order level, significant differences in *Chitinophagales, Cytophagales, Tepidisphaerales, Myxococcales*, and *Polyangiales* observed among the CON, SE, and SE+TA(L) groups, as determined by the Kruskal-Wallis rank sum test ($P < 0.05$; Fig. 6I). At the genus level, the relative abundance of *Enterococcus, Acinetobacter, Escherichia-Shigella*, and *Salmonella* increased in the SE group compared to the other two groups (Fig. 6J).

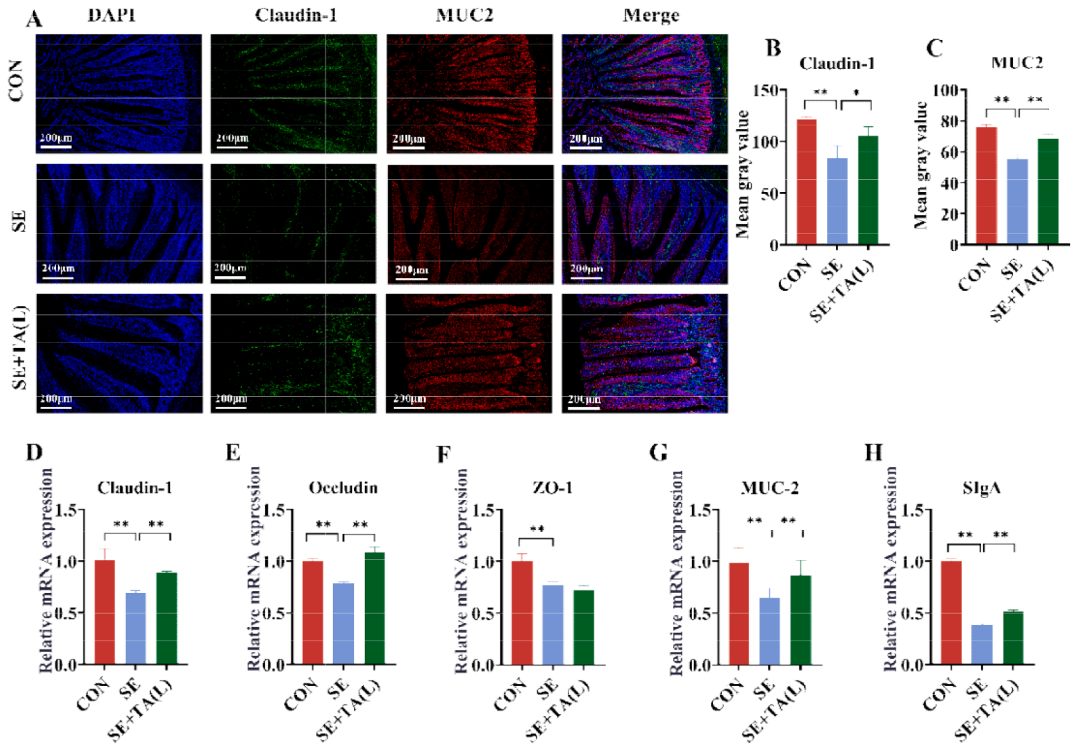

Fig. 3. TA ameliorated the intestinal barrier dysfunction induced by *Salmonella* in broilers. (A) Immunofluorescence double staining of Claudin-1 and MUC-2 (original magnification × 100). (B-C) Fluorescence intensity statistics of Claudin-1 and MUC-2. (D-H) Relative mRNA expressions of *Claudin-1, Occludin, ZO-1, MUC-2* and *SIgA* in ileal tissue. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

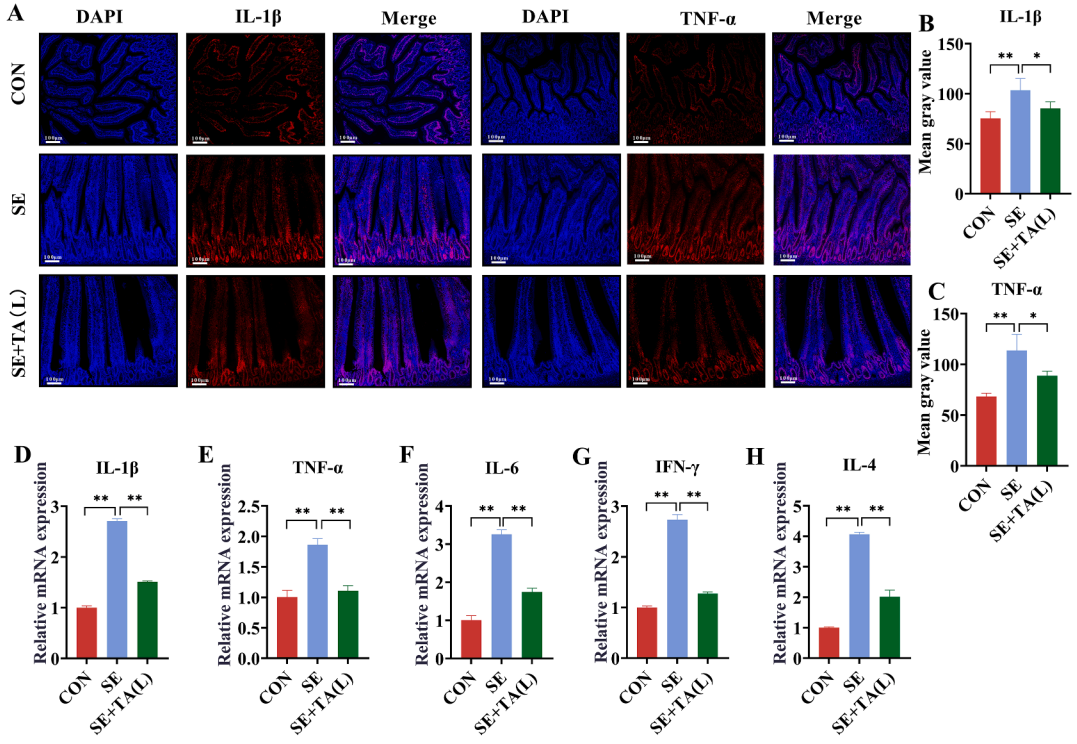

Fig. 4. TA alleviated the ileal inflammation induced by *Salmonella* in broilers. (A) Immunofluorescence of IL-1β and TNF-α in the ileal tissue of broilers (original magnification × 100). (B-C) Fluorescence intensity statistics of IL-1β and TNF-α. (D-H) Relative mRNA expressions of *IL-1β, TNF-α, IL-6, IFN-γ* and *IL-4*. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

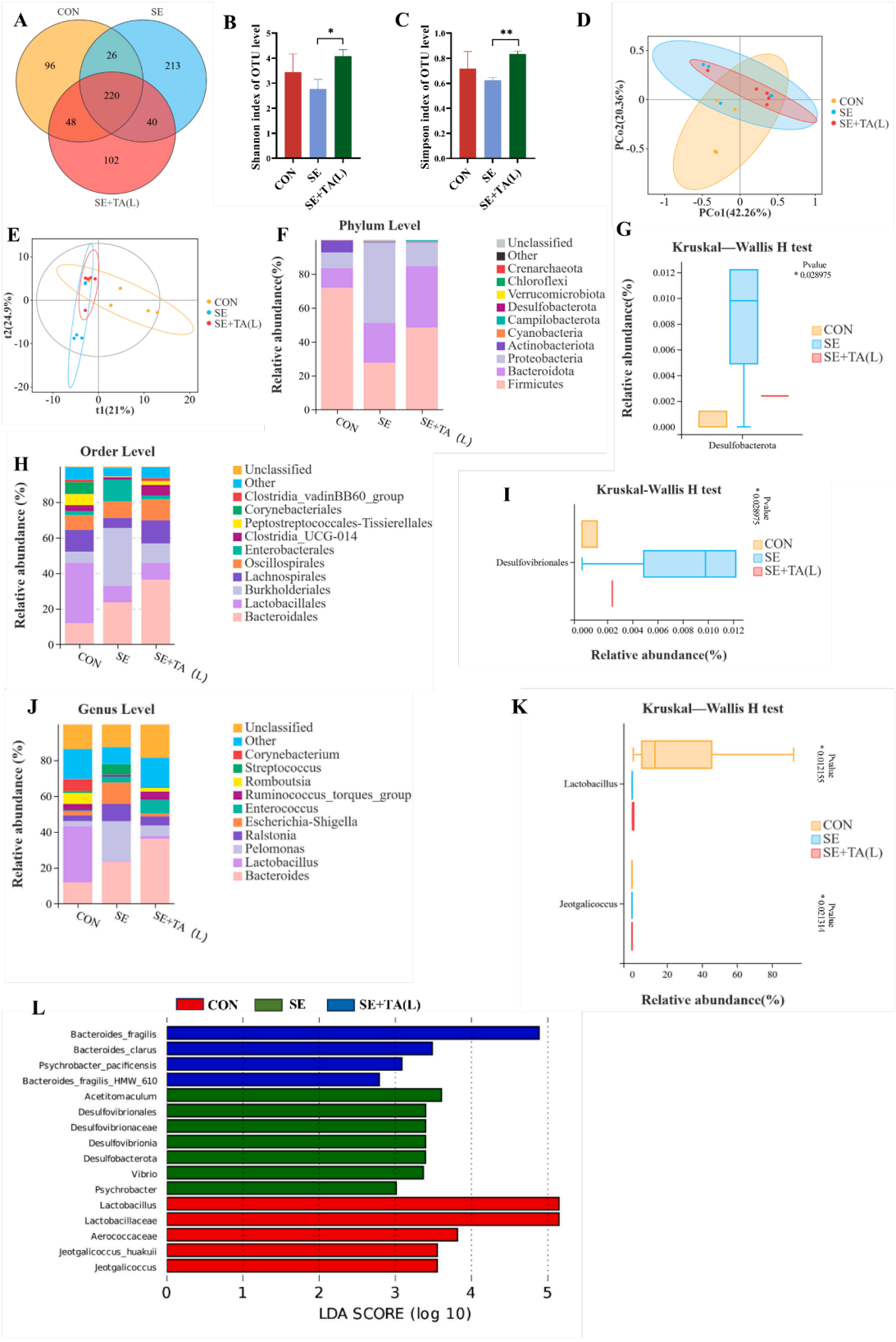

Fig. 5. Effects of TA on the ileal microbiota in *Salmonella*-infected broilers. (A) Venn diagram of intestinal microorganisms in each treatment group. (B-C) α-Diversity of Shannon, Simpson. (D) Calculation of PCoA of samples for β-diversity analysis. (E) Calculation of PLS-DA of samples for β-diversity analysis. Microbiota compositions at phylum (F), order (H) and genus (J) levels. (G) Comparison of dominant phylum in the CON, SE, and SE+TA(L) groups. (I) Comparison of dominant order in the CON, SE, and SE+TA(L) groups. (K) Comparison of dominant genus in the CON, SE, and SE+TA(L) groups. (L) Histogram of LDA displayed the most enriched bacterial taxa in each group. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

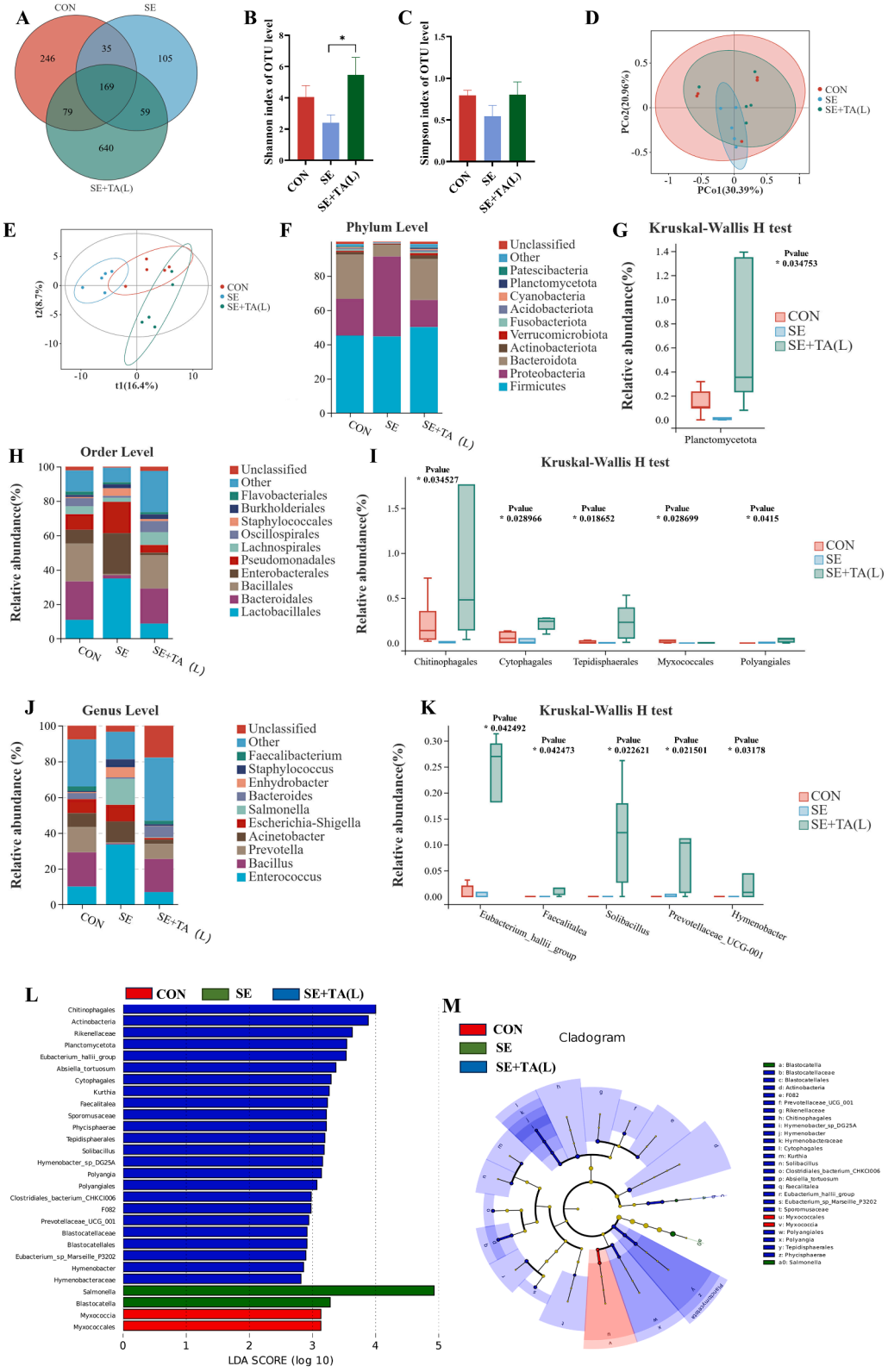

Fig. 6. Effects of TA on the lung microbiota in *Salmonella*-infected broilers. (A) Venn diagram of lung microorganisms in each treatment group. (B-C) α-Diversity of Shannon, Simpson. (D) Calculation of PCoA of samples for β-diversity analysis. (E) Calculation of PLS-DA of samples for β-diversity analysis. (F) Microbiota compositions at phylum level. (G) Comparison of dominant phylum in the CON, SE and SE+TA(L) groups. (H) Microbiota compositions at order level. (I) Comparison of dominant order in the CON, SE and SE+TA(L) groups. (J) Microbiota compositions at genus level. (K) Comparison of dominant genus in the CON, SE and SE+TA(L) groups. (L) Histogram of LDA displayed the most enriched bacterial taxa in each group (LDA score threshold > 2). (M) Taxonomic cladogram obtained from LEfSe analysis illustrated highly abundant taxa among groups. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

LEfSe employd linear discriminant analysis (**LDA**) to estimate the magnitude of the impact of species abundance on the differential effect and to identify the differential bacteria. As illustrated in Fig. 6L-M, the LEfSe taxonomic cladogram and histogram of LDA indicated an enrichment of *Myxococcia* in the CON group. Notably, the abundance of *Salmonella* was significantly elevated exclusively in the SE treatment. Furthermore, enrichment of *Chitinophagales, Actinobacteria, Rikenellaceae* and *Planctomycetota* was observed in the SE+TA(L) group.

Effects of TA on lung inflammation induced by salmonella infection

We concentrated on the Nuclear factor kappa-B (**NF-κB**) inflammatory signaling pathway. As illustrated in Fig. 7, our results demonstrated that the NF-κB pathway was activated by *Salmonella* infection, as

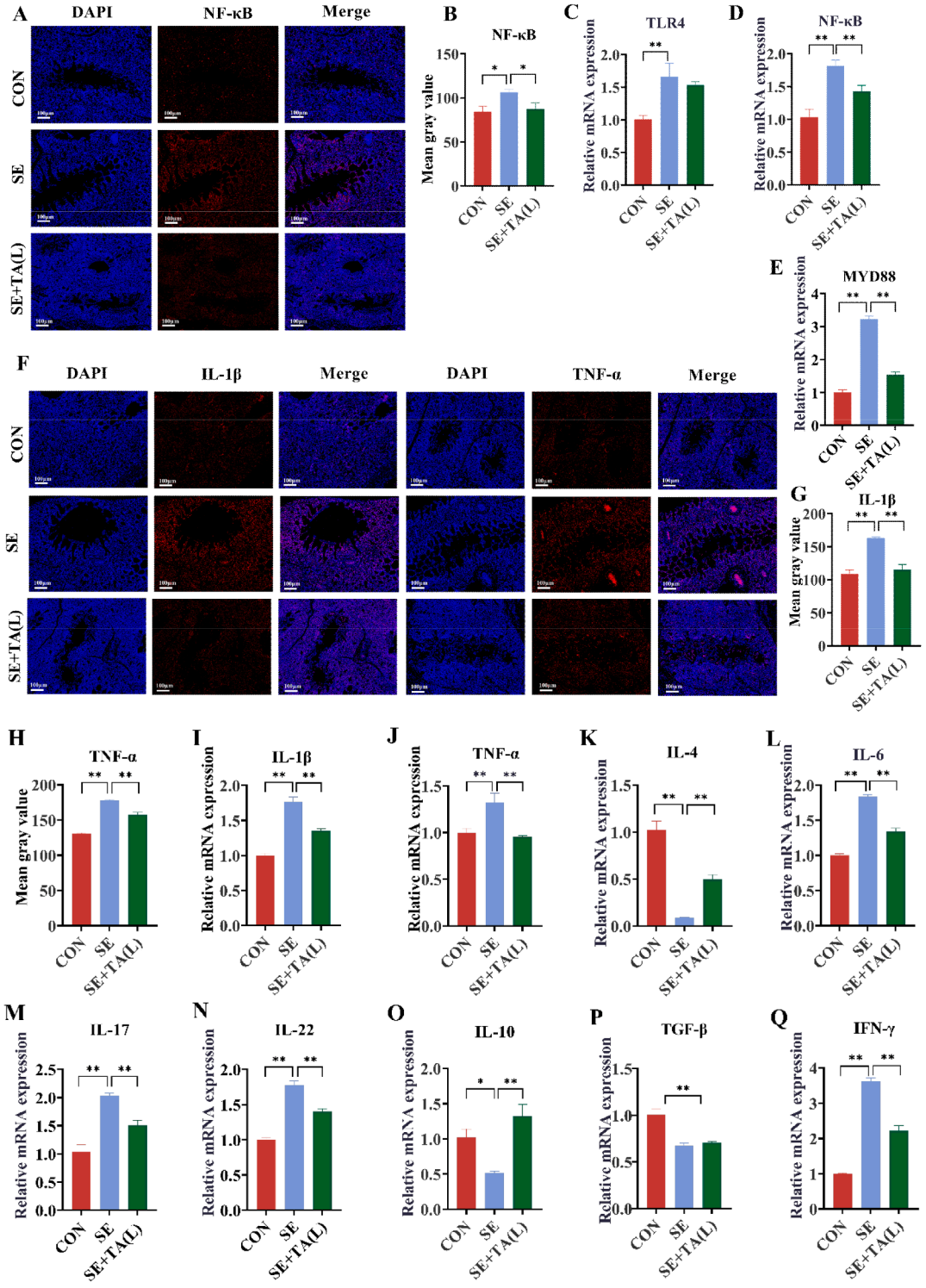

Fig. 7. Effects of TA on lung inflammation induced by *Salmonella* infection. (A) Immunofluorescence detection of NF-κB in the lung (original magnification × 100). (B) Fluorescence intensity statistics of NF-κB. (C-E) Relative mRNA expressions of *TLR4, NF-κB and MYD88*. (F) Immunofluorescence detection of IL-1β and TNF-α in the lung (original magnification × 100). (G-H) Fluorescence intensity statistics of IL-1β and TNF-α. (I-Q) Relative mRNA expressions of *IL-1β, TNF-α, IL-4, IL-6, IL-17, IL-22, IL-10, TGF-β* and *IFN-γ*. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

indicated by an increase in the average fluorescence intensity of NF-κB and a significant upregulation in the mRNA expression levels of *Toll-like receptor 4* (***TLR4***), *myeloiddifferentiationfactor88* (***MYD88***), and *NF-κB* ($P < 0.01$). The introduction of tannic acid into the system resulted in a decrease in the mean fluorescence intensity of NF-κB and a downregulation of the mRNA expression of *MYD88* and *NF-κB* ($P < 0.01$). To evaluate the protective effects of TA against *Salmonella*-induced lung injury, we examined the expression levels of inflammatory factors in lung tissues. The results indicated that, compared to the CON, there was a significant increase in the fluorescence intensity of IL-1β and TNF-α in the lungs of the SE. In contrast, the SE+TA(L) significantly reduced the fluorescence intensity of IL-1β and TNF-α compared to the SE group (Fig. 7F). *Salmonella* infection induced a significant upregulation of pro-inflammatory cytokines, including *IL-1β, TNF-α, IL-6, IL-17, IL-22*, and *IFN-γ*, while simultaneously causing a significant downregulation of the mRNA levels of anti-inflammatory cytokines, such as *IL-4* and *transforming growth factor-β* (***TGF-β***) ($P < 0.01$; Fig. 7I-Q). Treatment with TA notably reversed these alterations.

Effect of TA on salmonella-induced polarization of lung macrophages

Macrophages are essential immune cells that are extensively distributed across various organs and play a critical role in lung injury responses. The mean fluorescence intensity of CD11c, indicative of the M1 phenotype of lung macrophages, was significantly higher in the SE group compared to the CON group($P < 0.01$). The SE+TA(L) significantly reduced the mean fluorescence intensity of CD11c relative to the SE group, while concurrently increasing the mean fluorescence intensity of CD206 ($P < 0.01$), a marker for the M2 phenotype (Fig. 8A-C). The mRNA expression level of *inducible nitric oxide synthase* (***INOS***), a marker for M1-type macrophages, was significantly upregulated in the SE group compared to the other groups ($P < 0.01$; Fig. 8D). Notably, the SE+TA (L) group exhibited a further increase in the mRNA expression of the M2 macrophage marker *Arginase 1* (***AGR1***). ($P < 0.01$; Fig. 8E).

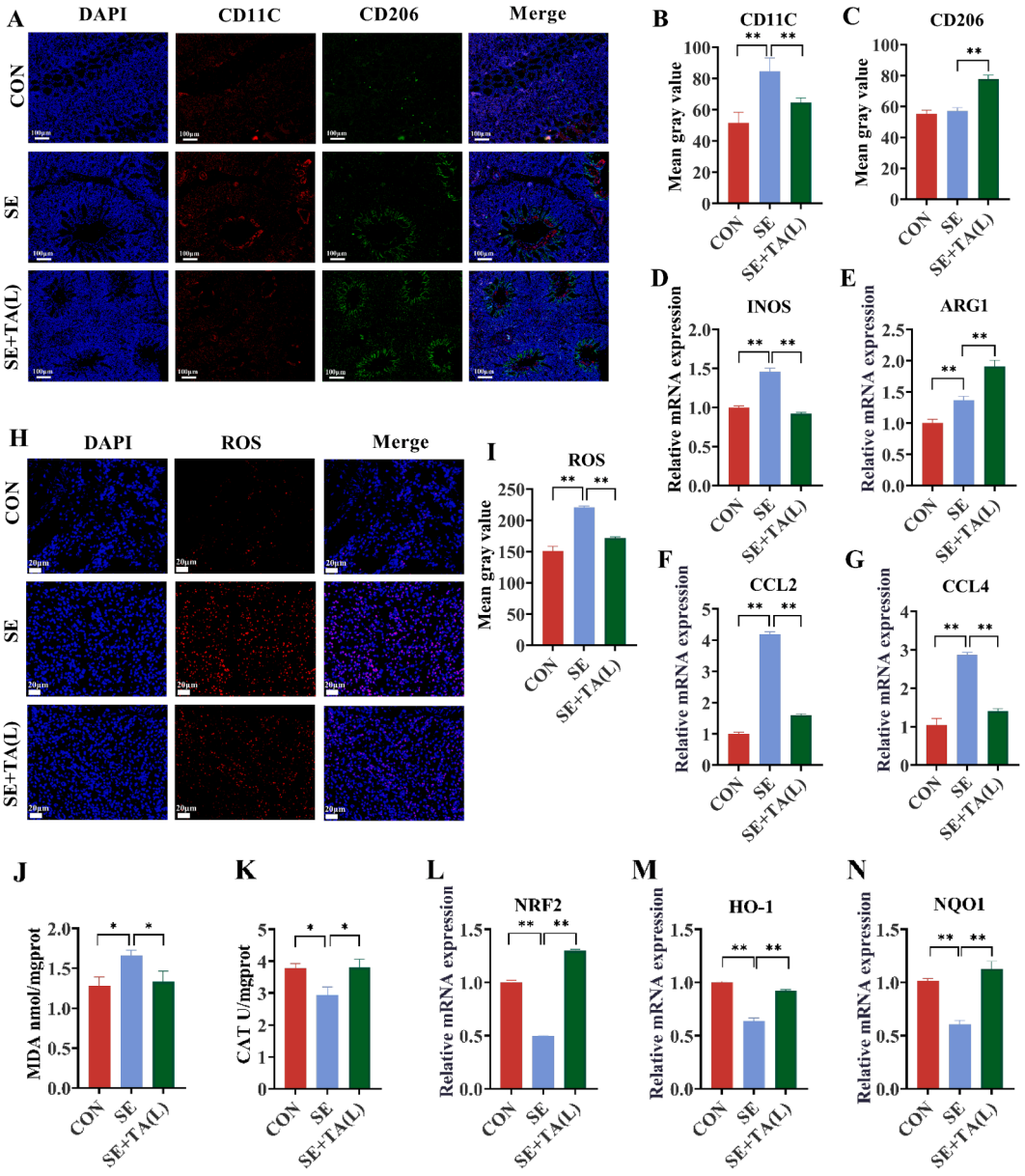

Fig. 8. Effect of TA on *Salmonella*-induced oxidative lung injury and macrophage polarization. (A) Immunofluorescence double staining of CD11C and CD206 (original magnification × 100). (B-C) Fluorescence intensity statistics of CD11C and CD206. (D-G) Relative mRNA expressions of *INOS, ARG1, CCL2*, and *CCL4*. (H) Immunofluorescence detection of ROS in the lung (original magnification × 400). (I) Fluorescence intensity statistics of ROS. (J) MDA content of the lung. (K) CAT content of the lung. (L-N) Relative mRNA expressions of *NRF2, HO-1*, and *NQO1*. Significant differences: $^{*}P < 0.05$, $^{**}P < 0.01$.

Additionally, the mRNA expression of *chemokines C-C chemokine ligand 2* (***CCL2***) and *chemokine C-C motif ligands 4* (***CCL4***) was significantly elevated in the SE group; however, treatment with tannic acid notably reversed these alterations ($P < 0.01$; Fig. 8F-G).

Effect of TA on the antioxidant capacity of salmonella-infected broilers

ROS staining indicated that *Salmonella* infection resulted in elevated ROS levels in the lungs (Fig. 8H). Consistently, MDA content in the lungs also increased significantly ($P < 0.05$) (Fig. 8J). However, treatment with TA reduced both ROS accumulation and MDA content. Compared to the CON, the SE group showed a significant decrease in CAT content, while the SE+TA(L) group exhibited a significant increase ($P < 0.05$; Fig. 8K). Furthermore, we determined the mRNA expression levels of the Nrf2/HO-1 signaling pathway in the lungs. The mRNA expression of the *nuclear factor erythroid-2 related factor 2* (***Nrf2***), *heme oxygenase-1* (***HO-1***), and *NAD(P)H quinone dehydrogenase 1* (***NQO1***) was significantly downregulated in the SE group ($P < 0.05$; Fig. 8L-N). In contrast, the inclusion of TA in the feed upregulated the mRNA expression of these genes ($P < 0.05$). These findings suggest that TA has the potential to mitigate oxidative damage induced by *Salmonella* in broiler lungs.

Discussion

Tannic acid ameliorates salmonella-induced decreased growth performance in broilers

Broilers are highly susceptible to *Salmonella* at the chick stage, and *Salmonella* colonization causes a number of clinical symptoms or asymptomatic persistent infections. *Salmonella* infections in broilers usually lead to malabsorption, anemia, decreased growth rate, and inefficient feed utilization (Kogut and Arsenault, 2017; Yan *et al.*, 2011). TA is a plant extract from a wide range of sources with a variety of biological activities. The polyphenolic structure of tannins gives them good antioxidant, anti-inflammatory, antibacterial and antiviral effects, and more and more domestic and international studies point to the fact that tannins can be used as potential feed additives. In this study, the 21-day-old body weight and average daily weight gain of broilers in SE+TA(L) and SE+TA(H) groups increased, and the feed-to-meat ratio of broilers in SE+TA(L) group decreased (Fig. 1). Thus, the addition of either 200 mg/kg or 400 mg/kg of TA to the ration improved *Salmonella*-induced reduction in broiler growth performance.

Tannic acid ameliorates salmonella-induced intestinal damage and subsequent lung injury in broilers

In recent years, the emerging intestinal-lung axis theory has revealed the close connection between the intestine and the lungs, and that the intestinal and lung mucosal sites are important barriers for body's direct defense against the external environment, which are associated with innate and adaptive immunity (Enaud *et al.*, 2020; Melo-González *et al.*, 2022). For example, several studies have shown that patients with inflammatory bowel disease (**IBD**) and animal models exhibit manifestations of lung pathology (Herrlinger *et al.*, 2002; Zhang *et al.*, 2022). Conversely, patients with different lung diseases such as asthma, chronic obstructive pulmonary disease (**COPD**), and 2019 coronavirus disease (**COVID-19**) also experience intestinal symptoms of malaise (Bhattacharya *et al.*, 2022; Chunxi *et al.*, 2020). Therefore, based on the research basis of the intestinal-lung axis, we next investigated the therapeutic role of TA in *Salmonella*-induced intestinal inflammation and lung injury. In this study, TA significantly ameliorated the pathological damage in the ileum and lungs compared to the SE group. Additionally, we examined serum LPS levels. Consistent with previous studies (Zhang *et al.*, 2020), we found significantly higher serum LPS levels in broilers in the SE group (Fig. 2G), indicating increased intestinal epithelial permeability. However, TA significantly reduced the levels of serum LPS. In addition, we found that TA reduced the amount of neutrophil-derived MPO in lung tissues. MPO activity is a sensitive and specific marker of lung injury and is used to assess quantitatively the accumulation of neutrophils in tissues (Chen *et al.*, 2017). The above results demonstrated that TA attenuates *Salmonella*-induced intestinal injury and secondary lung injury. In this experiment, both 200 mg/kg and 400 mg/kg of TA were found to significantly ameliorate *Salmonella*-induced damage, and both doses of TA significantly reduced the LPS content, while only the low dose of TA significantly reduced the MPO content, and in our experiment, the low dose of TA already showed a significant biological effect, and between the low-dose and high-dose groups did not show significant differences; therefore, in the subsequent assay, we chose only one dose of TA (200 mg/kg), i.e., for the CON group, the SE group, and the SE+TA(L) groups were tested.

Tannic acid ameliorates salmonella-induced intestinal barrier dysfunction in broilers

Intestinal barrier integrity is an important defense mechanism against pathogenic bacteria and their toxins in the intestines (Choi *et al.*, 2020). It has been reported that *Salmonella* infection leads to a reduction in intestinal tight junction proteins and disruption of barrier integrity increasing the risk of bacterial translocation in animals (He *et al.*, 2021; Wang *et al.*, 2018). Other studies on TA have reported that supplementation with TA enhances the integrity of the intestinal barrier in animals (Xu *et al.*, 2023; Yu *et al.*, 2020). Consistent with previous studies, TA treatment significantly reversed the *Salmonella* infection-induced reduction in *Claudin-1, Occludin, ZO-1, MUC-2*, and *SIgA* expression. These results indicate that TA effectively ameliorates *Salmonella*-induced intestinal barrier dysfunction.

Tannic acid alters salmonella-induced the gut and lung microbiota composition in broilers

Gut microbiota and the innate immune system play a vital role in resisting *Salmonella* colonization, which is essential for the host to avert interactions between *Salmonella* and the intestinal epithelium (He *et al.*, 2020). In our research, the addition of TA increased the Shannon and Simpson indices of gut bacteria. *Desulfobacterota*, a harmful pathogenic bacterium, has been reported to be positively associated with the production of inflammatory factors (Feng *et al.*, 2024; Wang *et al.*, 2022). *Salmonella* infection induced a state of dysbiosis within the gut microbiota, increasing the abundance of *Proteobacteria. Desulfobacterota* and *Desulfovibrionales* were significantly increased in SE groups ($P < 0.05$). At the genus level, *Salmonella* infection led to a decrease in the abundance of *Lactobacillus* and an increase in the abundance of pathogenic bacteria such as *Pelomonas, Escherichia-Shigella* and *Ralstonia* pathogens increased in abundance, but these changes were reversed by TA.

An imbalance within the lung microbiota can lead to respiratory diseases, notably asthma (Mathieu *et al.*, 2018). It was particularly interest that *Salmonella* was detected in the lungs of the SE group broilers. We hypothesized that *Salmonella* might be consumed in the intestinal tract, while some *Salmonella* colonizes the lungs by crossing the intestinal barrier and entering the bloodstream. Consistented with the gut microbiota results, *Escherichia-Shigella* colonization was also found in the lungs, and the addition of TA inhibited the presence of pathogenic bacteria such as *Enterococcus, Acinetobacter, Escherichia-Shigella*, and *Salmonella. Prevotella*, recognized as a beneficial bacterium in healthy lungs according to the previous study (Madapoosi *et al.*, 2022), in our study, the abundance of *Prevotella* was decreased in the lungs of the SE group, while TA increased the abundance of *Prevotella* in the lungs (Fig. 6).

Tannic acid ameliorates salmonella-induced lung injury in broilers by inhibiting the inflammatory response

When the epithelial barrier is impaired and tissue permeability is increased, LPS can promote the activation of inflammatory signaling in lung and intestinal tissues through the somatic circulation to amplify the immune response (Tang *et al.*, 2021). LPS can induce an inflammatory cascade by binding to TLR4 on the surface of cell membranes. In animal models, TLR4 plays a crucial role in regulating the upregulation of inflammation and the release of inflammatory cytokines (Deng *et al.*, 2017; Yao *et al.*, 2017). Notably, in our findings, the serum level of LPS was significantly increased in the SE group, and the *TLR4/MYD88/NF-κB* signaling pathway was activated in the lungs (Fig. 7). Inflammatory response plays an important role in the initiation and maintenance of lung injury (Brandenberger *et al.*, 2018). Pro-inflammatory cytokines such as *TNF-α* and *IL-1β* increase the permeability of lung epithelial cells, which further induces lung tissue damage and neutrophil accumulation (Zhao *et al.*, 2017). In our study, *Salmonella* infection resulted in significant upregulation of *IL-1β, TNF-α* and *IFN-γ* in the lungs, while the level of *IL-10* was significantly downregulated. In contrast, the addition of TA to the diet inhibited the *TLR4/MYD88/NF-κB* signaling pathway and significantly downregulated the expression levels of pro-inflammatory factors. The above results demonstrated that TA could inhibit the inflammatory response, thereby improving *Salmonella*-induced lung injury.

The protective effects of TA on lungs: modulation of macrophage function and antioxidant capacity

Macrophages are key effector cells of the pulmonary immune system (Stockis *et al.*, 2017). Macrophages produce a wide range of bioactive molecules that participate in both beneficial and detrimental outcomes of the inflammatory response. Thus, macrophages play an important role in the initiation, maintenance, and resolution of inflammation (Fujiwara and Kobayashi, 2005; Palmblad, 1984). Depending on the signals they encounter, macrophages form different phenotypes (Van Ginderachter *et al.*, 2006). Classically activated macrophages (pro-inflammatory M1), induced by inflammatory mediators such as LPS, IL-1β, and IFN-γ, produce pro-inflammatory cytokines (TNF-α, IFN-γ and IL-6,) and ROS (Anderson and Mosser, 2002). In contrast, M2 macrophages, activated by exposure to IL-4 and IL-10, generate more anti-inflammatory cytokines, such as IL-10 and TGF-β (Gordon, 2003). M2 macrophages are believed to be involved in dampening inflammatory responses, promoting tissue repair, and supporting type II immunity (Mosser, 2003). The results of this study show that, TA was able to inhibit M1 polarization of macrophages in the lungs while promoting M2 polarization, which may contribute to a reduction in pulmonary inflammation. Additionally, CCL2 and CCL4 are potent chemoattractants for macrophages and can significantly increase pulmonary inflammation (van Zoelen *et al.*, 2011). In our study, TA downregulated the mRNA expression of *CCL2* and *CCL4* in the lungs of *Salmonella*-infected broilers. In summary, these findings suggested that the protective effect of TA on the lungs is associated with the inhibition of M1 macrophage polarization and the promotion of M2 macrophage polarization.

Excessive inflammation triggers the production of various mediators, including cytokines, chemokines, and ROS (Park *et al.*, 2009; Kellner *et al.*, 2017). In our study, *Salmonella* infection led to an overproduction of ROS and a rise in MDA levels in the lungs of broilers. However, the addition of TA mitigated these effects by reducing ROS accumulation and MDA content. Furthermore, the synthesis of antioxidant enzymes is governed by the Nrf2/HO-1 signaling pathway (Wu *et al.*, 2021). In our research, TA activated the *Nrf2/HO-1* pathway and increased the mRNA expression of the downstream enzyme *NQO1*. This activation enhanced the antioxidant capacity of the broilers, thus alleviating the oxidative lung injury induced by *Salmonella*.

Conclusion

Dietary supplementation with TA has demonstrated significant improvements in the growth performance of broilers infected with *Salmonella*. This intervention modulates the composition of gut microbiota, enhances the integrity of the intestinal barrier, and inhibits the colonization of pathogenic bacteria in the lungs, as well as the polarization of M1 macrophages. Additionally, it mitigates lung inflammation and oxidative damage, thereby effectively alleviating *Salmonella*-induced lung injury.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIALS

Main reagents and antibodies (Table S1); feed formulations (Table S2); primer sequences used for RT-qPCR (Table S3).

Declaration of competing interest

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

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psj.2025.104973.

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