Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2025.302

RESEARCH ARTICLE

Effects of *Pasteurella Multocida* on the Apoptosis and Autophagy of Liver and Lung

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ARTICLE HISTORY (25-865)

Received: September 07, 2025
Revised: October 21, 2025
Accepted: October 23, 2025
Published online: November 25, 2025

Key words:
Apoptosis
Autophagy
Liver
Lung
Pasteurella multocida
Tibetan pigs

A B S T R A C T

Tibetan pigs are a vital source of income and meat for local residents. *P. multocida* is a main pathogen in pig respiratory diseases, seriously threatening Tibetan pig industry. However, few studies explored the pathogenicity of *P. multocida* isolated from Tibetan pigs. Thus, this study aims to investigate the pathogenicity *P. multocida* isolated from Tibetan pigs. Results indicated that *P. multocida* could cause organic damage, including the heart, spleen, liver, lungs, and kidneys. Furthermore, *P. multocida* dramatically increased the protein expression of IL-1β and IL-4, while decreasing the TNF-α level in the lungs. In the liver, the levels of IL-1β and IL-4 were dramatically increased during *P. multocida* infection. Importantly, we also found a significant increase in the expression of APAF1, Bax, and Cyt-c in the lungs, whereas the levels of Bcl2 and Caspase8 were dramatically decreased during *P. multocida* infection. Similarly, the levels of APAF1 and Caspase3 dramatically increased, whereas the Caspase9 was dramatically decreased in the liver during *P. multocida* infection. In the lungs, the levels of ATG5, mTOR, Beclin1, and LC3b increased significantly, while p62 showed an opposite trend. Likewise, *P. multocida* infection also decreased the levels of Beclin1 and p62 in the liver. In summary, this research investigated the effects of *P. multocida* on mice health. Results indicated that *P. multocida* infection can induce inflammatory responses and organic damage. In addition, excessive activation of apoptosis and autophagy may be one of the potential pathways for *P. multocida* to affect host health.

To Cite This Article: Wang Y, Huang Y, Yu X, Li Y, Li A and Tang Z, 2026. Effects of *Pasteurella multocida* on the apoptosis and autophagy of liver and lung. Pak Vet J, 46(1): 149-159. http://dx.doi.org/10.29261/pakvetj/2025.302

INTRODUCTION

Tibetan pigs are the important source of pork in the Qinghai-Tibet Plateau and possess many essential nutrients (Yang *et al*., 2024). Previous studies indicated that the intramuscular fat in Tibetan pigs is 3.5 to 4.2%, approximately 1.5 times that of common pigs (Zhu *et al*., 2022). Tibetan pigs are primarily free range and have a varied diet (Niu *et al*., 2022). This varied diet promoted the evolution of special nutritional metabolic pathways. For instance, the activity of the CYP450 enzyme family, which is involved in detoxification metabolism in their livers, has been significantly enhanced, contributing to the efficient conversion of plant secondary metabolites. Notably, Zhou *et al*. (2020) indicated that the abundances of cellulolytic bacteria (such as *Ruminococcus* and *Fibrobacter*) in the guts of Tibetan pigs is 2.3 times greater than that of common pigs. These microorganisms could secrete cellulolytic enzymes, which is beneficial to food digestion and absorption (Bian *et al*., 2025).

P. multocida is a prime zoonotic pathogen and may be separated into five serotypes: A, B, D, E, as well as F, depending on capsular antigen variations (Wu *et al*., 2025; Bitew *et al*., 2025). *P. multocida* can lead to numerous disorders in animals such as cholera fowl, swine pleuropneumonia, as well as bovine hemorrhagic septicemia and result in colossal economic losses (Yang *et al*., 2022; Kubatzky, 2022). Another synonym of swine plague is swine pasteurellosis while it is an acute, epidemic, sporadic, as well as secondary infectious condition owing to *P. multocida* (Cuevas *et al*., 2020; Piorunek *et al*., 2023). The disorder comprises acute septicemia (high temperature, skin congestion, as well as high mortality), fibrinous pleuropneumonia (respiration difficulties, abnormally functioning lung as well as liver), as well as chronic condition (abscesses as well as arthritis) (Yuan *et al*., 2024). Remarkably, this disorder is frequently accompanied with different parasites such as Mycoplasma hyopneumoniae so as to develop complicated as well as variable clinical symptoms (L).

Apoptosis and autophagy cross-talk in a complex manner and both contribute to host defense against infections (Wang *et al*., 2021; Song, 2024). Previously, research revealed that *P. multocida*'s pathogenicity was highly complicated with adhesion of bacteria, invasion, evasion of immunity, as well as destruction of host tissue (Soni *et al*., 2023). In addition, *P. multocida* infection can enormously impact apoptosis and autophagy (Cai *et al*., 2023). Specifically, apoptosis and autophagy balance is interrupted through numerous methods by type A as well as type B bacteria to result in pathological destruction. Investigating these mechanisms can be used to uncover *P. multocida*'s pathogenesis as well as design new therapy method. There are few research articles that investigated Tibetan pig-isolated *P. multocida*'s pathogenicity. Hence, this study aims to determine whether *P. multocida* that was isolated from Tibetan pig can drive organic damage in mice through apoptosis as well as autophagy mediation.

MATERIALS AND METHODS

Animal studies: *P. multocida* used herein was isolated from Tibetan pigs. To determine the sanitary hazards of *P. multocida*, we chose twenty Kunming mice as a model organism. The mice randomly joined two groups: control (CON) and experimental group (PM). In this study, we supplied adequate food and water for the control group as well as injected them with 0.1 mL normal saline. We inoculated the experimental group subcutaneously with 0.1 ml of *P. multocida* (1×10^8 CFU/mL) on the other hand to simulate bacterial infection. After completion of the experiment we harvested the organ and tissue for future study purposes.

Histopathological examination: Preparation of tissue sections and H&E staining was performed as detailed earlier (Cai *et al*., 2023). In brief, the fresh pieces of heart, liver, spleen, lung, and kidney were fixed with 4% paraformaldehyde overnight. The fixed tissue was then cleared and dehydrated through a series of ethanol and xylene gradients prior to paraffin embedding. The specimen's paraffin-embedded were cut to 4–5 µm sections and stained with H&E. The histological images were taken with a light microscope.

qRT-PCR: Total RNA was extracted, cDNA was reverse-transcribed, and qRT-PCR was performed as mentioned earlier (Cai *et al*., 2023; Li *et al*., 2025).

Western blotting: Western blotting analysis was prepared according to above studies (Zhu *et al*., 2020).

Immunohistochemistry (IHC) and Immunofluorescence (IF) staining: Specific procedures of IHC staining and IF staining were carried out according to the above-related research works (Guo *et al*., 2020; Zhu *et al*., 2020).

Data statistics and analysis: Statistics analysis was carried out with one-way ANOVA. In addition, gray scale analysis was conducted with software ImageJ and P-values <0.05 indicated significant differences.

RESULTS

Histopathological examination of spleen and heart in mice injected with *P. multocida* showed inappetence, increased eye discharge, and death within three days. Subsequently, hearts and spleens were performed for histopathological evaluation. Results indicated that the heart and spleen cells of the control mice had normal morphology, without inflammation or necrosis (Fig. 1A, C). In contrast, the hearts of the experimental mice displayed loss of myocardial cell nuclei, vacuolar degeneration, and disorder of myocardial structure (Fig. 1B). Additionally, red marrow hemorrhage, partial area of coagulative necrosis, decreased lymphocyte counts, and a small amount of neutrophil infiltration were found in the spleen (Fig. 1D).

Histopathological evaluation of liver, lung, and kidney: The results indicated that the liver, lung, and kidney tissues of the control mice were well-organized and exhibited no pathological changes. Conversely, the liver tissue of the experimental mice displayed indistinct hepatic cord boundaries, a proliferation of red blood cells between hepatocytes, hemorrhage and congestion within the blood vessels, fatty degeneration of hepatocytes, and infiltration of inflammatory cells in the hepatic lobules (Fig. 2A). The bronchiolar lumens of the lungs contained cellular exudates, while the alveolar cavities exhibited hemorrhage, cellular infiltration, and thickening of the alveolar septa (Fig. 2B). Additionally, neutrophil infiltration and a minor presence of proteinaceous exudate were noted in the lung tissue. The kidney tissue demonstrated significant hemorrhage, mild congestion in the corticomedullary tubules and interstitium, as well as slight swelling of the renal tubular epithelial cells characterized by loose and lightly stained cytoplasm (Fig. 2C).

Expression of genes and proteins of apoptosis-related factors in lung: To further investigate the negative effects of *P. multocida* infection on host health, we employed fluorogenic quantitative PCR and Western blot analyses to examine alterations in the gene and protein expression of apoptosis-related factors in the lungs. Results indicated that *P. multocida* infection significantly reduced the expression level of Caspase3 ($P<0.01$), while significantly increasing the expression level of APAF1 ($P<0.001$), with no observed effect on Bcl2 gene expression (Fig. 3A-C). Western blot analysis demonstrated that *P. multocida* infection significantly elevated the protein expression of Bax and Cyt-c, but did not affect the protein expression of APAF1, Bax, and p53 (Fig. 3D, E). Additionally, Bcl2 protein expression was dramatically lower that in the PM compared to the CON, whereas no significant difference was observed in the protein expression of Caspase3 and Caspase9 between both groups (Fig. 3F). These findings indicated that *P. multocida* may cause lung damage by regulating lung apoptosis.

Moreover, IHC and IF were used to further investigate the expression and distribution of apoptosis-related proteins in the lungs during *P. multocida* infection. IHC results indicated that *P. multocida* infection significantly increased APAF1 protein expression and decreased Caspase8 protein expression, while having no effect on

Caspase9, p53, or Bcl2 (Fig. 4A-E, G). IF analysis indicated that the expression of Bax protein was significantly higher in the PM compared to the CON (Fig. 4F, H).

Expression of genes and proteins of autophagy-related factors in lung: RT-qPCR analysis revealed that the gene expression of p62 in the PM were significantly lower than that in the CON ($P<0.01$), whereas the gene expression of LC3b was higher ($P<0.01$) (Fig. 5A, B). Furthermore, there was no significant difference in the gene expression of Beclin1 between the CON and PM (Fig. 5C). Western blot analysis demonstrated that *P. multocida* infection significantly reduced the expression level of p62 protein ($P<0.05$) while significantly increasing the expression level of mTOR protein ($P<0.01$) (Fig. 5E, F). Notably, *P. multocida* infection had no significant impact on the protein expression of ATG5, LC3b, and Beclin1 (Fig. 5D, G, H).

Additionally, IHC and IF were employed to analyze the localization and expression of autophagy-related proteins in the lungs during *P. multocida* infection. The results of IHC indicated that the protein expression levels of ATG5, Beclin1, and LC3b were significantly elevated in the experimental group compared to the CON ($P<0.05$, $P<0.01$, or $P<0.001$), whereas the expression level of p62 protein was significantly decreased ($P<0.001$) (Fig. 6A-F). IF results showed that *P. multocida* infection could lead to a significant increase in the expression level of mTOR protein ($P<0.01$) (Fig. 6G).

Expression of genes and proteins of apoptosis-related factors in liver: Results indicated that the gene expression levels of APAF1, Bax and p53 were significantly more preponderant in the experimental group than in the control group ($P<0.05$, or $P<0.0001$), whereas the gene expression levels Cyt-c was lower ($P<0.05$) (Fig. 7A, C, D, E). Furthermore, there were no significant differences in the gene expression of Bcl2 and Caspase3 between the CON and PM (Fig. 7B, F). We also observed that *P. multocida* infection resulted in a significant upregulation of APAF1 and Caspase-3 protein levels ($P<0.05$), while Caspase-9 protein levels were significantly downregulated ($P<0.05$) (Fig. 7G, H, J, K). Notably, *P. multocida* infection did not affect the expression levels of Bax, Cyt-c, and p53 proteins (Fig. 7G, I, J, L).

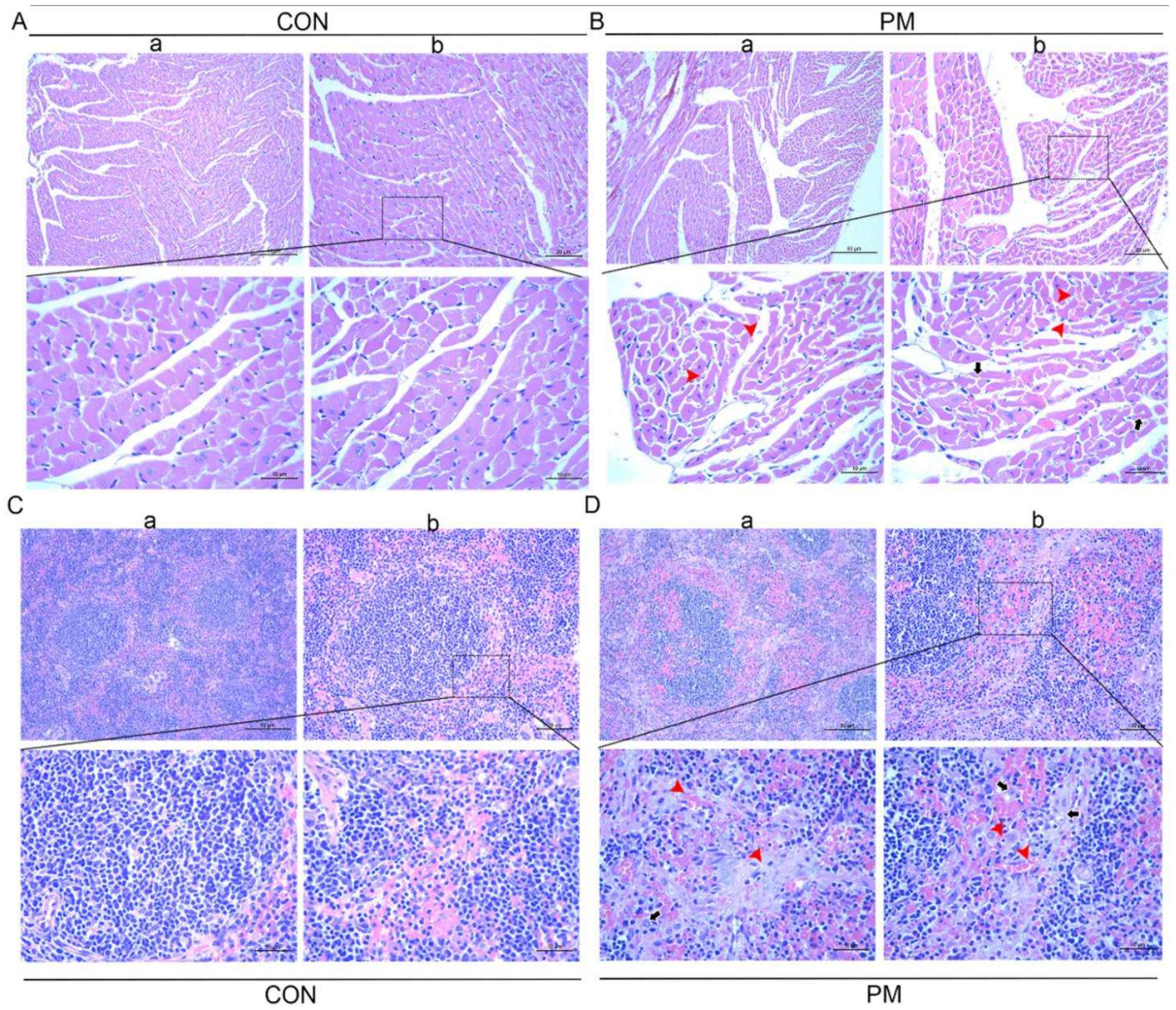

Fig. 1: Effects of *P. multocida* on the heart and spleen of mice. H&E staining results of hearts from the control (A) and experimental (B) mice. H&E staining results of spleens from the control (C) and experimental (D) mice. The red arrows indicate erythrocyte infiltration, and black arrows indicate vacuolated cells and abnormal cells. a: 10×, b: 20 ×.

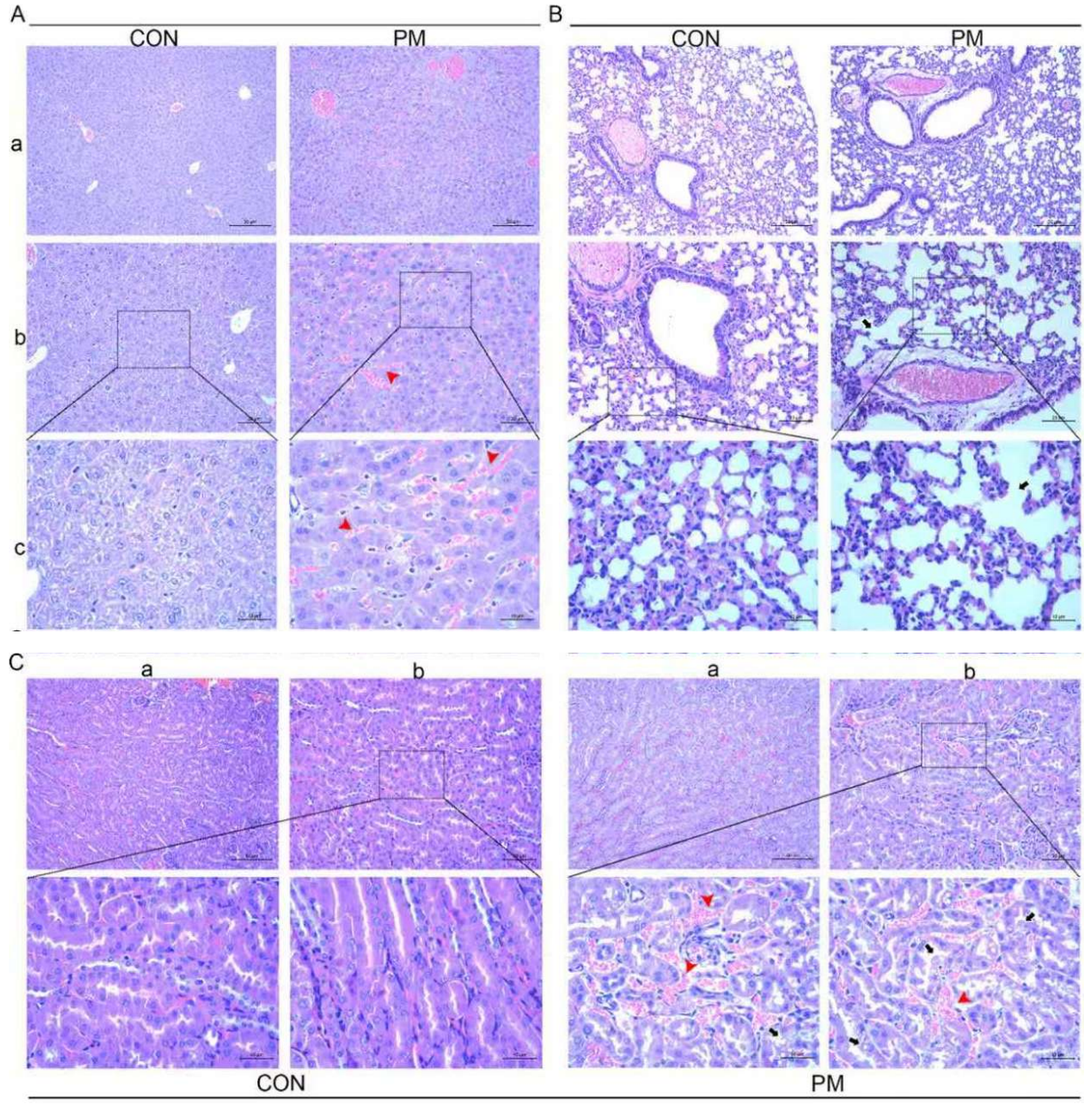

Fig. 2: Effects of *P. multocida* on the liver, lung, and kidney of mice. A: H&E staining results of liver. B: H&E staining results of lung. C: H&E staining results of kidney. The red arrows indicate red blood cell infiltration; black arrows indicate vacuolated cells and abnormal cells. a: 10×, b: 20 ×.

Expression of genes and proteins of autophagy-related factors in liver: The fluorescence quantitative PCR results indicated that *P. multocida* infection significantly increased the gene expression levels of the LC3b and mTOR ($P<0.05$ or $P<0.001$), while exhibiting no significant effect on the gene expression of the ATG5 (Fig. 8A-C). Additionally, Western blot analysis demonstrated that the protein expression levels of Beclin1 and p62 were markedly higher in the PM compared to the CON ($P<0.05$ or $P<0.001$), but no significant differences were observed in the protein expression levels of ATG5 and LC3b (Fig. 8D, E).

Effects of *P. multocida* infection on the expression of inflammation-related genes and proteins: Results indicated that *P. multocida* infection significantly increased the gene expression level of IL-1β in the lung and liver ($P<0.001$ or $P<0.0001$) (Fig. 9A, C). Furthermore, Western blot analysis revealed that *P. multocida* infection significantly downregulated TNF-α protein expression in the lung ($P<0.05$) and upregulated IL-1β protein expression in the liver ($P<0.001$) (Fig. 9B, D). However, no significant differences were observed in the IL-1β protein expression of lung and TNF-α protein expression in the liver between the CON and PM.

IF analysis demonstrated significantly elevated levels of IL-1β and IL-4 proteins in the lungs of the experimental group compared to the control group ($P<0.001$ or $P<0.0001$) (Fig. 10A, D). These findings were in line with IHC (Fig. 10B, C). Additionally, IHC indicated no significant difference in TNF-α protein expression in the lungs between both groups.

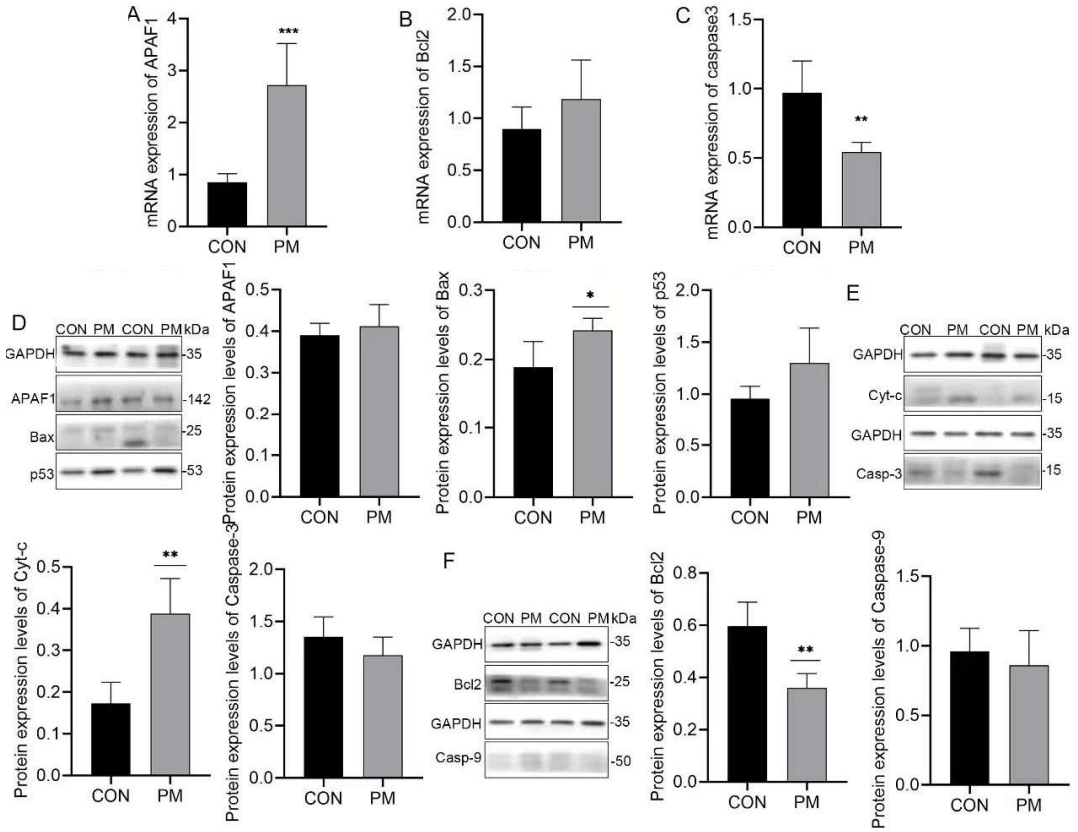

Fig. 3: *P. multocida* affected the lung apoptosis. A-C: The expression of apoptosis-related genes. D: The protein expression of APAF1, Bax, and p53. E: The protein expression of Cyt-c and Caspase3. F: The protein expression levels of Bcl2 and Caspase9.

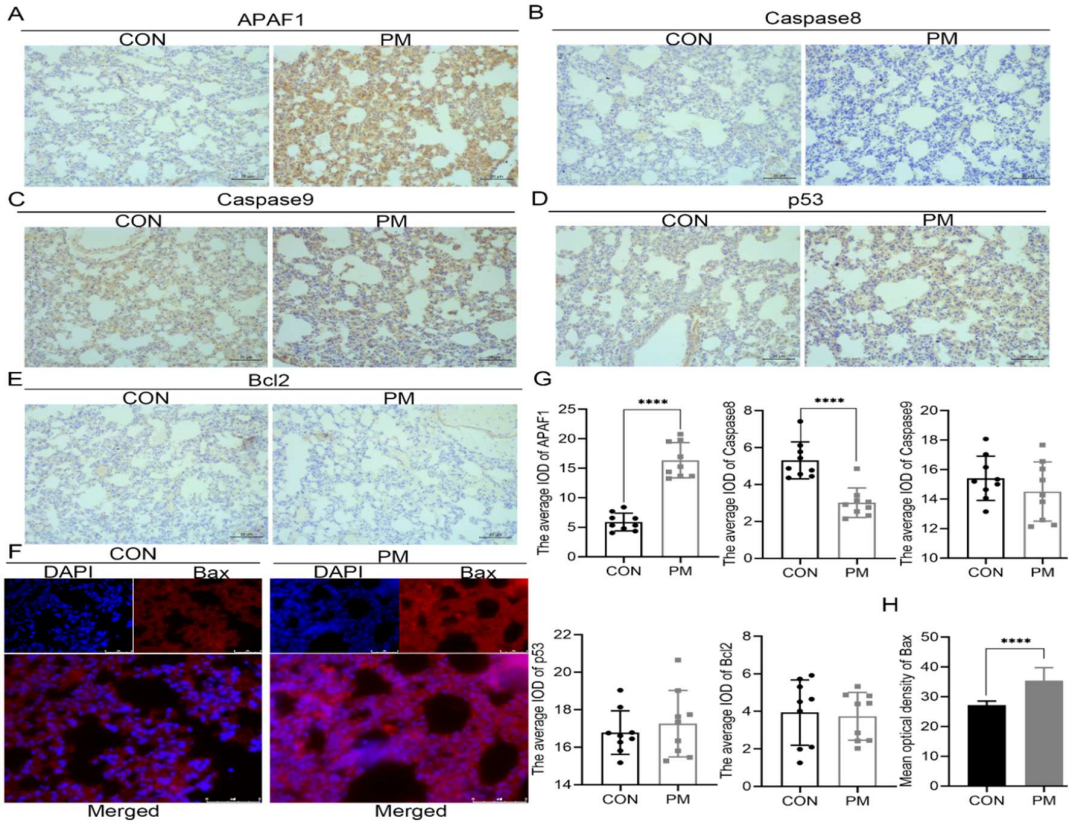

Fig. 4: Expression of proteins associated with lung apoptosis. A-G: The protein expression levels of APAF1, Caspase8, Caspase9, p53 and Bcl2. H: The mean fluorescence intensity of Bax.

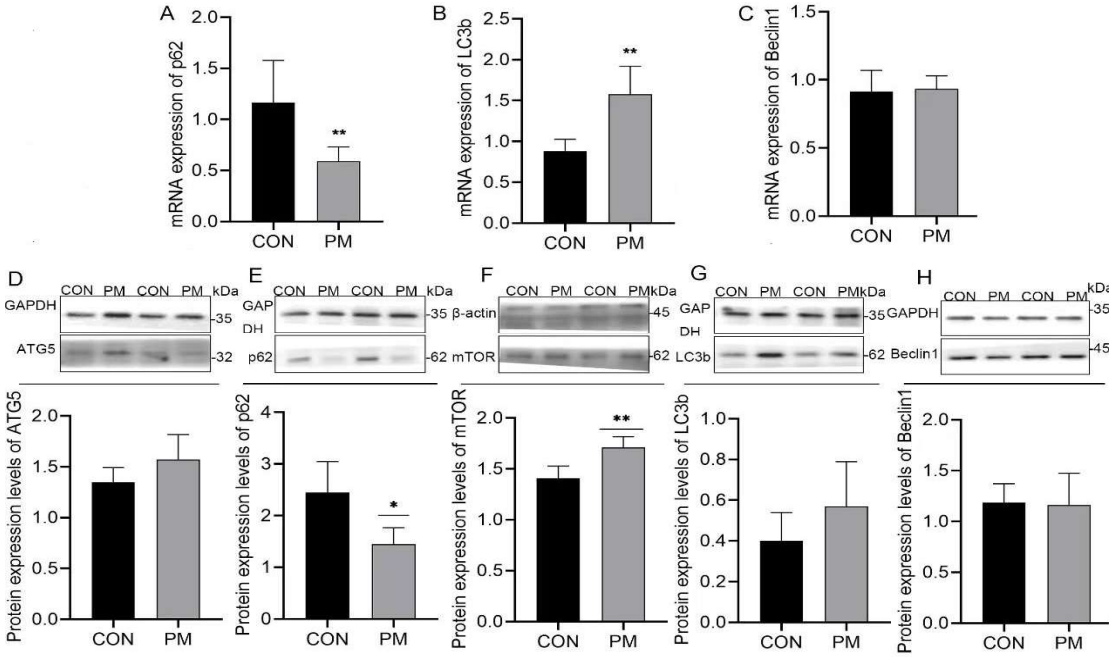

Fig. 5: *P. multocida* infection affected lung autophagy. A-C: Gene expression of ATG5, p62, mTOR, LC3b and Beclin1. D-H: Protein expression ATG5, p62, mTOR, LC3b and Beclin1.

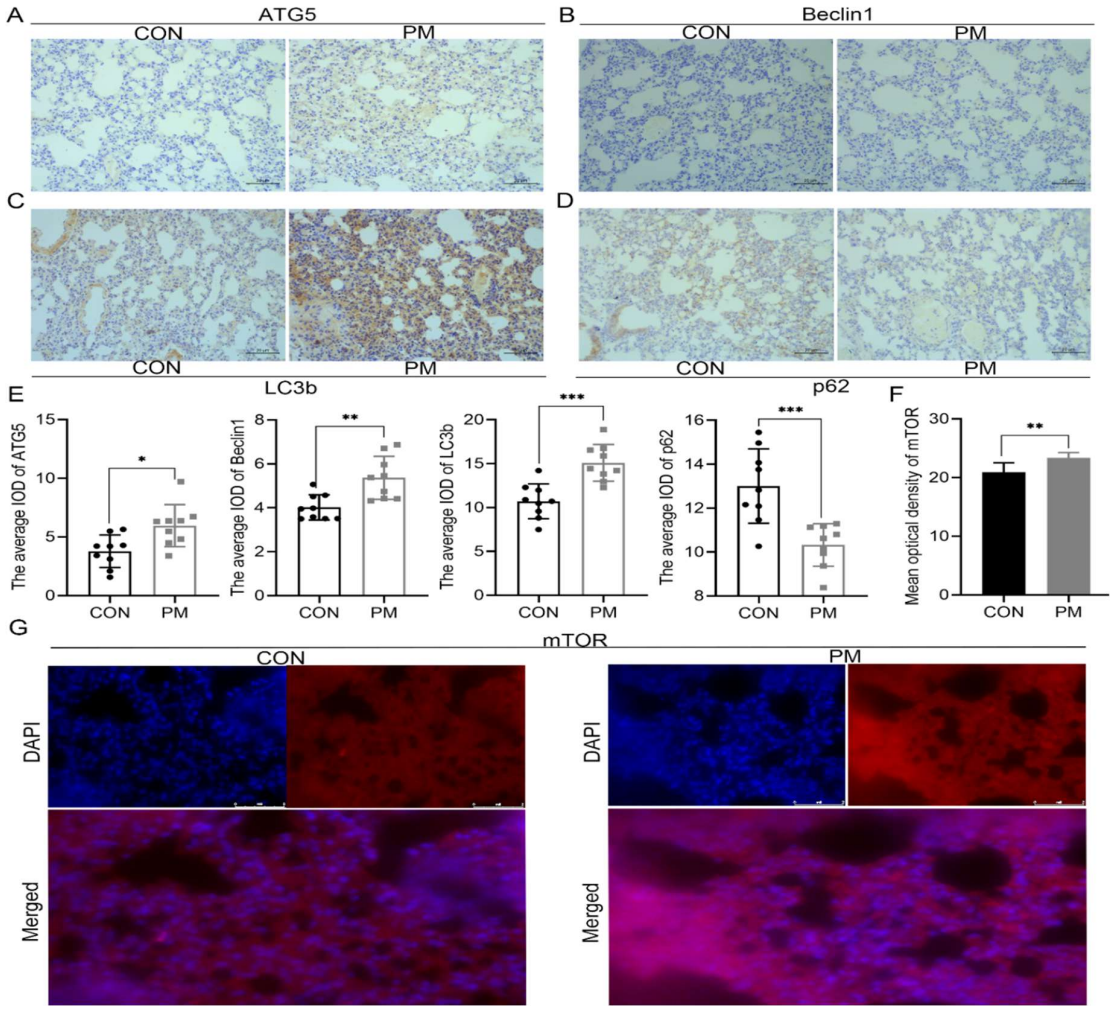

Fig. 6: Expression of proteins associated with lung autophagy. A-E: The protein expression of ATG5, Beclin1, LC3b and p62. F: The mean fluorescence intensity of mTOR. G: Expression of mTOR.

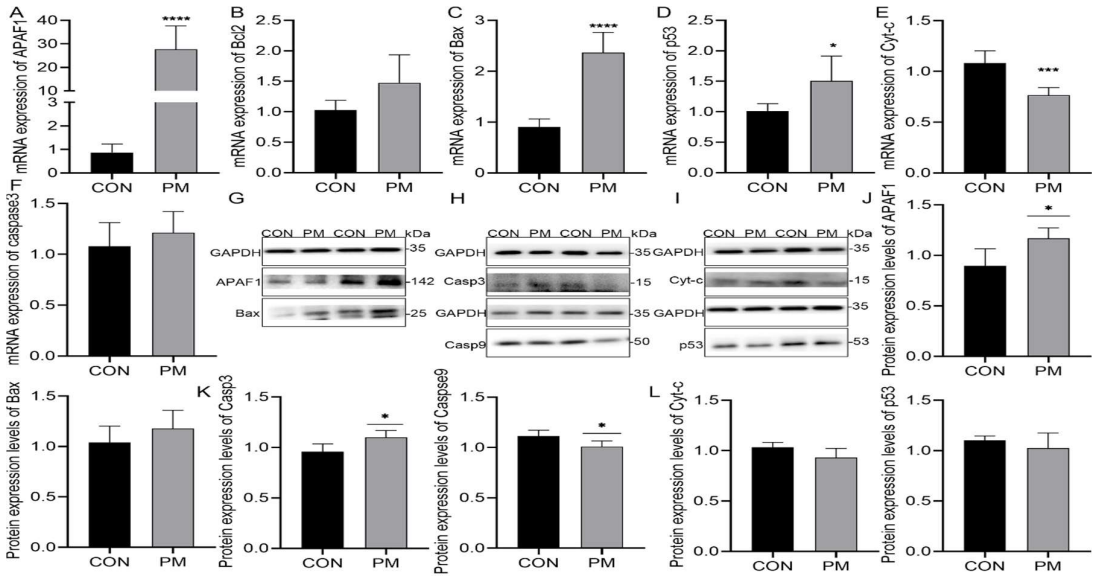

Fig. 7: *P. multocida* infection affected liver apoptosis. A-F: Gene expression of APAF1, Bcl2, Bax, p53, Cyt-c and Caspase3. G: The protein expression of APAF1 and Bax. H: The protein expression of Caspase3 and Caspase9. I: The protein expression levels of Cyt-c and p53. J: The protein expression of APAF1 and Bax. K: The protein expression of Caspase3 and Caspase9. L: The protein expression of Cyt-c and p53.

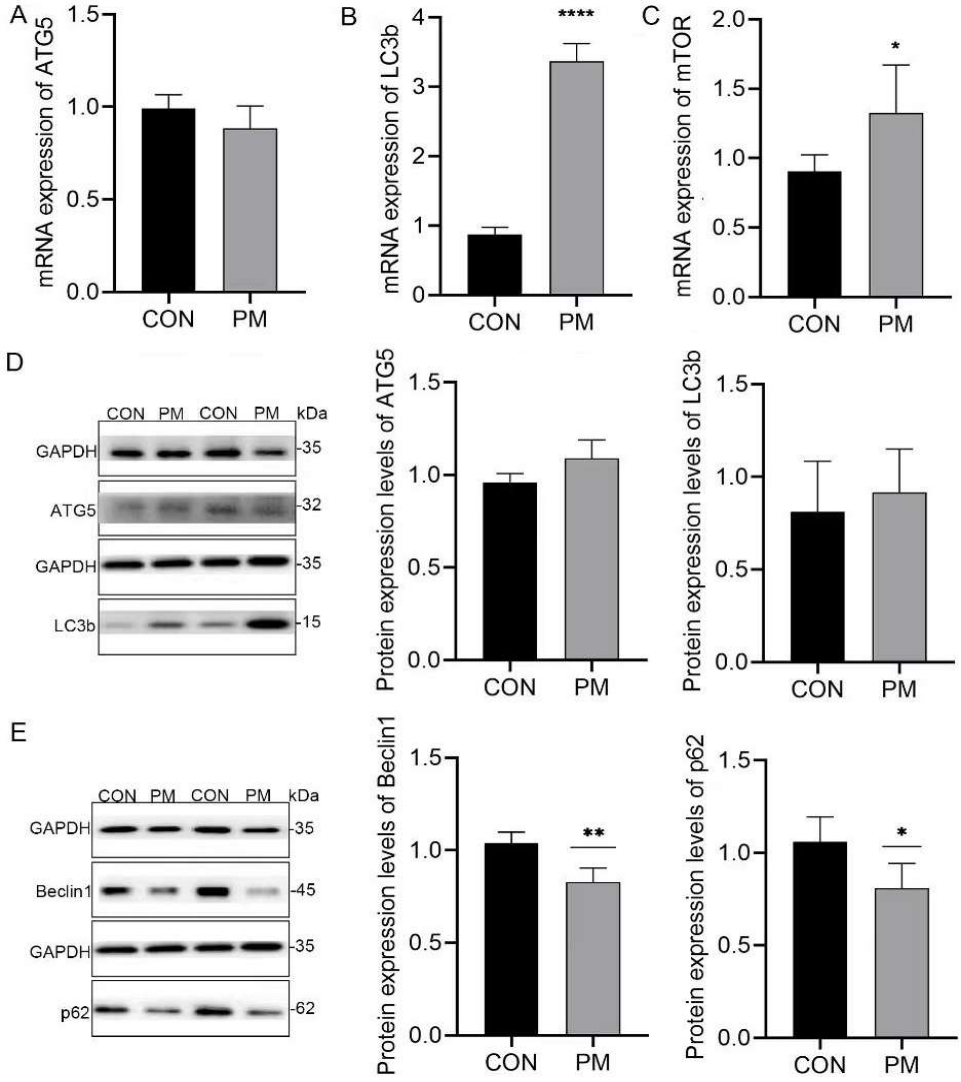

Fig. 8: *P. multocida* infection affected liver autophagy. A-C: Gene expression of ATG5, LC3b, and mTOR. D: Protein expression ATG5 and LC3b. E: Protein expression Beclin1 and p62.

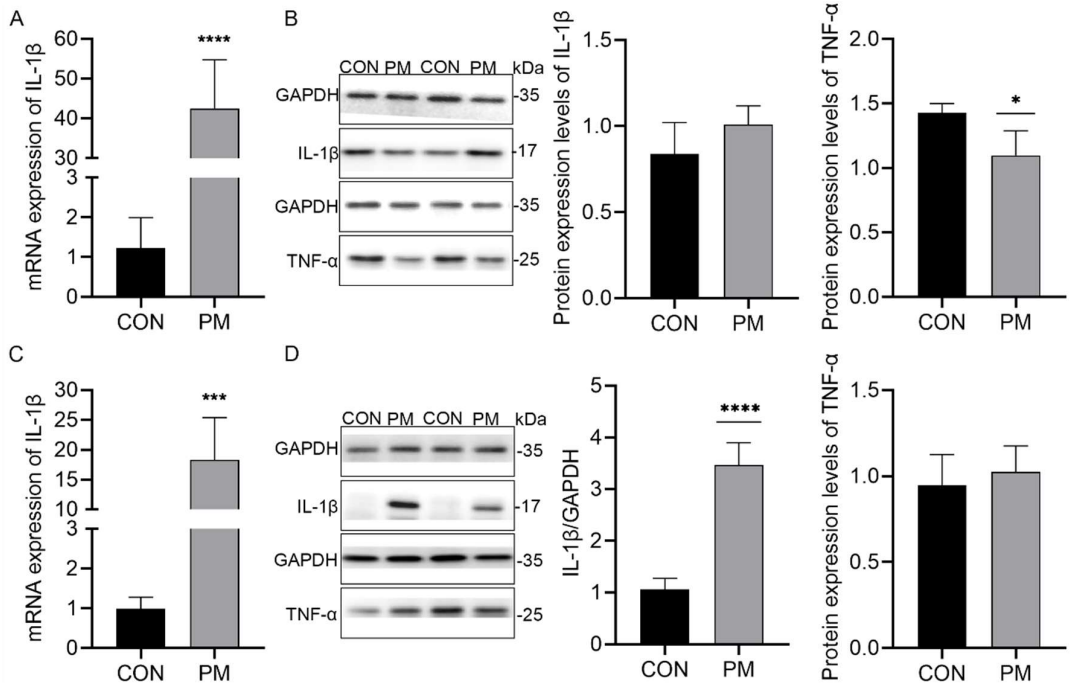

Fig. 9: Effects of *P. multocida* infection on inflammatory factor in lung and liver. A, C: The gene expression of IL-1β in the lung and liver. B, D: The protein expression of IL-1β and TNF-α in the lung and liver.

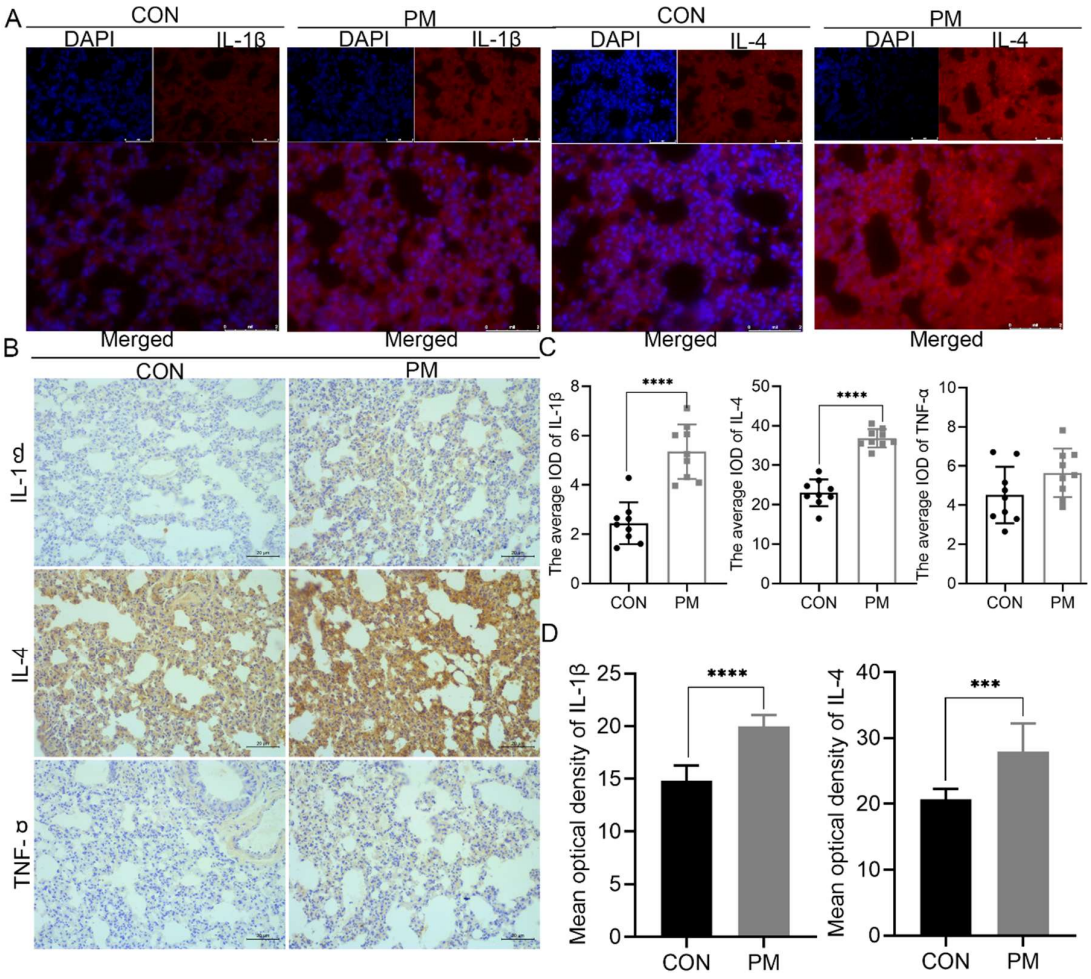

Fig. 10: Expression of proteins associated with lung inflammation. A: IL-1β, IL-4. B, C: IL-1β、IL-4 and TNF-α. D: The mean fluorescence intensity of IL-1β and IL-4.

DISCUSSION

P. multocida, as a significant zoonotic respiratory pathogen, infects humans, livestock, as well as wildlife (Allen *et al*., 2024). According to statistics, respiratory diseases in the world not only lead to billions of dollars' losses to the livestock industry every year but also challenge food security severely. Studies revealed that capsular types A and D of *P. multocida* are predominantly prevalent in pigs, leading to pneumonia and atrophic rhinitis, respectively (Kim *et al*., 2019). The morbidity of *P. multocida* in pigs with pneumonia in South Korea is from 10.3 to 15.6%, while that in pigs with pneumonia or porcine respiratory disease is up to 8% in China (Wu *et al*., 2025). As another point, *P. multocida* contributes to up to 15.6% of United States' respiratory pathogens (Kim *et al*., 2019). Significantly, even though *P. multocida* infections primarily result in respiratory symptoms, it can corrupt other organ systems such as the liver, kidneys, heart, spleen, as well as intestines (Yuan *et al*., 2024). At present, investigatory research on *P. multocida* mostly concentrates on isolates from chickens, ducks, as well as holsteins, while research on *P. multocida* from Tibetan pigs is lacking so far. As such, this study used a mice model to probe the havoc of *P. multocida* from Tibetan pigs on health negatively.

In this research, we noted that *P. multocida* infection can lead to pathological injury of the liver, lungs, kidneys, and heart with overexpression of inflammatory factors (IL-1β and IL-4). In particular, HE staining showed that *P. multocida* infection can lead to coagulative necrosis of the spleen, fatty degeneration of hepatocytes, congestion and hemorrhage of kidney tubules, thickening of alveolar septa, and the occurrence of cellular exudates in bronchiolar lumen. Likewise, earlier research revealed that *P. multocida* infection can significantly impact significant host organs. For example, it was revealed that *P. multocida* infection can lead to enlargement of the liver, hypertrophy of hepatocytes, congestion of sinusoids, as well as cell infiltration in ducks as demonstrated by Xiao *et al*. (2021). Also, it was revealed that *P. multocida* toxin can lead to multiple organ failure as well as death as presented by Yuan *et al*. (2024). The research revealed that liver as well as kidneys is one of the prime target organs that can be damaged due to *P. multocida* infection. Likewise, this research also revealed that *P. multocida* from Tibetan pigs can also jeopardize host health.

Abnormal apoptosis of cells, particularly excessive cell apoptosis, may lead to destruction of the respiratory as well as intestinal barriers (Guo *et al*., 2023). Earlier research indicated that pathogens are capable of employing apoptosis in support of their pathogenic processes (Rodriguez-Gonzalez and Gutierrez-Kobeh, 2023). For example, apoptosis was demonstrated to be amongst the top ten enriched pathways within lung tissue from *P. multocida* infected mice. In this research, we noted that lung epithelial cell apoptosis was induced as a result of *P. multocida* infection leading to lung as well as liver impairment. Interestingly enough, these findings also conformed with those identified from HE staining. Cytochrome C (Cyt-c), a heme-bearing electron transport molecule localized within eukaryotic cell mitochondria, plays a critical role in energy metabolism as well as apoptosis (Csomo *et al*., 2022). Bax is a critical pro-apoptotic molecule within the BCL2 gene family that plays a critical role in apoptosis control (Zhang *et al*., 2016). Previous research indicated that Bax was commonly distributed within hepatocytes, renal tubular epithelial cells as well as respiratory epithelial cells, usually existing as cytoplasmic monomers. Upon becoming activated, Bax relocates from the cytoplam membrane to form mitochondrial membrane oligomers. It was also capable of forming a heterodimer with anti-apoptotic molecule BCL2, while its overexpression is capable of counteracting anti-apoptotic effects of BCL2 thus facilitating apoptosis. In addition, activated Bax is capable of forming pores within mitochondrial membranes thus leading to liberation of Cyt-c, caspase cascade initiation as well as subsequent apoptosis (Zhang *et al*., 2017). In this research, we noted that *P. multocida* infection markedly upregulated protein expression of Bax, Cyt-c as well as APAF1 within lung tissue while downgrading expression of Bcl2 as well as Caspase8 simultaneously. In addition, *P. multocida* infection significantly increased protein expression of APAF1 and Caspase3 in the liver and significantly decreased that of Caspase9. The above results indicate that *P. multocida* infection in Tibetan pigs triggers liver and lung damage through apoptosis mediation.

Previous indicated that appropriate activation of autophagy could prevent apoptosis and support growth and development (Fitzwalter and Thorburn, 2018; Chen *et al*., 2024; Hou *et al*., 2025). Conversely, overactivation of autophagy can induce cell stress, causing the cell death. Additionally, overactivation of autophagy may trigger caspase- and apoptosis-independent DNA damage, causing the cellular environment imbalance, apoptosis or pyroptosis. In this study, we detected the expression of autophagy-related genes and proteins, including mTOR, LC3, ATG5, Beclin1, and LC3b, in the liver and lungs during *P. multocida* infection. mTOR plays a key role in regulating cell growth, metabolism, and autophagy (Deleyto-Seldas and Efeyan, 2021). Elevated mTOR level is also recognized as a vital driver of tumors, metabolic diseases, and neurodegenerative disorders (Gargalionis *et al*., 2022). p62 is a core regulatory protein associated with cellular homeostasis and its dysfunction has been shown to many diseases (Jahanian *et al*., 2024). Previous studies have demonstrated that p62 can bind to ubiquitinated proteins and the autophagosomal membrane protein LC3, thereby targeting them for autophagic degradation and promoting selective autophagy. ATG5 serves as a key promoter of autophagy, forming a complex with the ATG12 protein, which participates in the formation and extension of the autophagosomal membrane and directly influences the initiation and completion of autophagy (Wang *et al*., 2024). Studies indicate that the loss of ATG5 expression or its dysfunctional activity significantly inhibits autophagic processes. Beclin1 is a multifunctional protein that is ubiquitous in eukaryotes and is mainly involved in regulating autophagy and maintaining the balance between cell survival and death (Wang *et al*., 2025). This protein plays a critical role in cancer, neurodegenerative diseases, and immune regulation (Sun *et al*., 2023). As a core regulator of initiation of autophagy, Beclin1 associates with the PI3K-III complex to drive the maturation of autophagosome membranes. Thereafter, it sequester damaged organelles or misfolded proteins and

deliver them to lysosomes for destruction. It is essential for cells to remove metabolic debris and preserve energy homeostasis. In addition to that, Beclin1 associates with BCL2 family proteins, thus indirectly influencing apoptosis pathways. LC3b is a significant marker of autophagosome biogenesis that is involved in the autophagic process through several mechanisms (Li *et al*., 2024). It was studied that LC3b is involved in lipid modification in the formation of autophagosomes and its disordered expression was strongly linked with tumor as well as neurodegenerative disorders (Danish *et al*., 2024). The result presented that mTOR, ATG5, Beclin1, as well as LC3b levels of protein in lung tissue significantly increased while p62 levels drastically decreased during infection with *P. multocida*. In addition to that, *P. multocida* can induce a substantial reduction of p62 protein in the liver tissue. All these results suggested that *P. multocida* can induce lung as well as liver damage through inducing autophagy.

Conclusions: In conclusion, this research investigated the host's health risk of *P. multocida*. Findings demonstrated that *P. multocida* infection is capable of damaging several organs and causing inflammation. In addition, *P. multocida* infection can lead to excessive apoptosis and autophagy activation in lung and liver organs. Our research bears a critical message that excessive apoptosis and autophagy activation may be one of the pathways through which *P. multocida* plays its role in causing its hepatotoxicity as well as its pulmonic impact. In addition, better understanding of host-*P. multocida* interactions as well as its underlying pathogenic processes can lead to the production of efficient control as well as prevention methods that can help alleviate *P. multocida*'s influence on the livestock economy. Lastly, some of this study's limitations also ought to be pointed out, such as its small sample size as well as differences in individual animals.

Authors contribution: YW and ZT provided research idea; YH, XY and YL contributed reagents, materials, analysis tools, and performed research; YW and AL wrote and revised the manuscript; All authors participated in writing and reviewing the manuscript.

Funding: This research was funded by national key research and development program (2022YFD1600904), research and demonstration of integrated control technology for various diarrhea diseases in Tibetan pigs and yaks (XZ202401YD0005), key Science and technology special projects of Xizang (XZ202501ZY0143 and XZ202501ZY0147) and science and technology projects in Linzhi (XDHZ-2025-02).

Conflict of interest: The authors declare that they have no competing interests.

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