Particulate matter in poultry house on poultry respiratory disease: a systematic review

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ABSTRACT Particulate matter (**PM**) is one of the essential environmental stressors for the poultry industry in the world. Given its large specific surface area, PM can adsorb and carry a variety of pollutants, including heavy metal ions, ammonia, and persistent organic pollutants such as pathogenic microorganisms. High concentrations of PM induce poultry respiratory inflammation and trigger various diseases. However, the pathogenic mechanism of PM in poultry houses on respiratory diseases has not been clarified due to its complexity and lack of accurate assays. In terms of pathogenesis, there are 3 ways to explain this phenomenon: Inhaled PM irritates the respiratory tract, decreases immune resistance, and causes a respiratory disease; respiratory tract irritation by compounds presents in PM; infections with pathogenic and non-pathogenic microorganisms attached to PM. The latter 2 modes of influence are more harmful. Specifically, PM can induce the respiratory disease through several toxic mechanisms, including ammonia ingestion and bioaccumulation, lung flora dysbiosis, oxidative stress, and metabolic disorders. Therefore, this review summarizes the characteristics of PM in the poultry house and the impact of poultry PM on respiratory disease and proposes potential pathogenic mechanisms.

Key words: poultry house, particulate matter, respiratory disease, dysbiosis, inflammation

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INTRODUCTION

'I assert, and expect no disagreement, that more than 90% of lung diseases are either initiated by or at least aggravated by inhalation of particles and gases (Brain, 1996).' The role of particulate matter (**PM**) in initiating or exacerbating lung disease has become progressively better known. Because of the limitations of the rearing environment, poultry house air composition varies considerably from the atmospheric composition. Mainly expressed in the production process, feed, feces, feathers, and dander are difficult to be avoided producing large amounts of PM (Shen et al., 2018). Due to the different sources of PM and their temporal and spatial variations, the composition and concentration of PM can change significantly (Fernández et al., 2019). PM in poultry houses was about 10 to 100 times higher in limited spaces than outdoors (Hu et al., 2021). PM with a particle size less than 10 μm (PM_{10}) can reach the upper respiratory tract of broilers, and PM with a particle size less than 2.5 μm ($PM_{2.5}$) can enter the broiler's lungs (Figure 1).

Meanwhile, at high temperatures and humidity, large amounts of microorganisms, secondary particles, and toxic compounds during amino acid metabolism in the animal digestive system are more easily attached to the PM (Dai et al., 2020). In contrast to mammalian lungs, broilers contain multiple bronchi and air sacs. The unique structure places the broiler's lung in a semi-open state and, thereby, more susceptible to PM damage (Ali, 2020). Due to the heterogeneity of PM, long-term exposure to high PM concentrations can make broilers susceptible to different respiratory diseases. The poultry industry has a significant annual loss from respiratory disease. However, little is known about how PM in poultry houses affects respiratory disease. In this review, we aim to explore the underlying pathogenesis by summarizing the link between PM and respiratory diseases in poultry houses.

SOURCES, CHEMICAL COMPOSITION, AND INFLUENCING FACTORS OF PM IN POULTRY HOUSES

PM in poultry houses mainly has primary particles of biological origins, such as fungi, bacteria, viruses,

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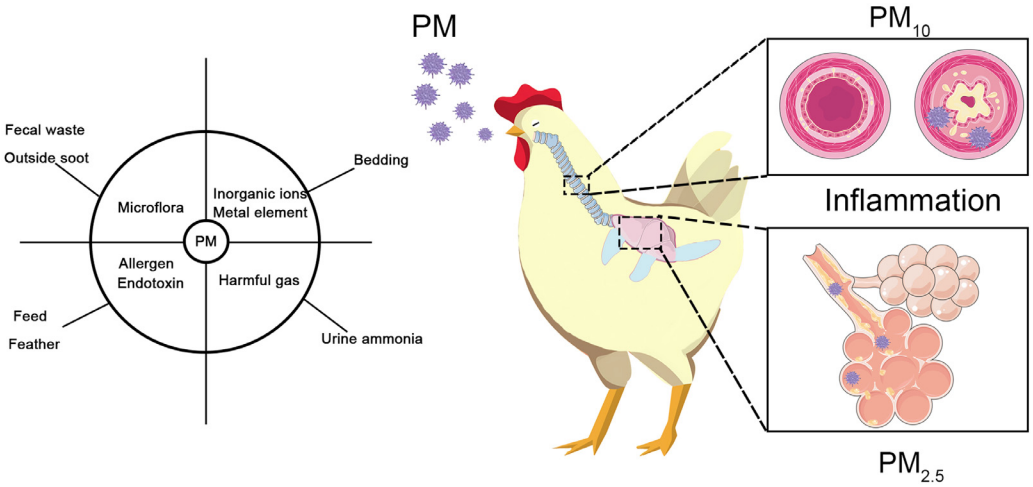

Figure 1. Composition and source of PM in the poultry house. PM carries harmful pollutants from various sources, PM_{10} can enter the respiratory tract, and $PM_{2.5}$ can enter the alveoli, which triggers an inflammatory response. Abbreviation: PM, particulate matter.

endotoxins, and allergens, as well as particles derived from feed, skin, and feces (Cambra-López et al., 2010). In poultry houses, the primary sources of PM are poultry feathers, mineral crystals in the urine, and waste materials (Qi et al., 1992; Amador et al., 2016). In addition, bedding was a significant PM source in litter-fed poultry houses compared to litter-free houses (Liu et al., 2015). The main elements in the PM composition of poultry houses were C, O, N, P, S, Na, Ca, Al, Mg, and K. Elemental components contained in $PM_{2.5}$ (aerodynamic diameter < 2.5 μm) and PM_{10} (aerodynamic diameter $<$ 10 μm) of different origins in broiler houses differed.

PM concentration in poultry houses depends on several factors, including the poultry species, husbandry practices, activity, density of husbandry, the environmental control system, humidity, season, and sampling time (Ellen et al., 2000). The results of studies on broiler houses have shown that the temperature and relative humidity of the houses have a high impact on total suspended particle concentrations (Wood and Van Heyst, 2016). The higher PM concentration in the houses caused by the increasing day age of broilers may be because of the increased dry feces, higher broilers activity, and more feathers with the growing day age of broilers (Yoder and Van Wicklen, 1988). Daily feeding times and light procedures affect the formation and concentration of PM in the house by influencing livestock activity. Walking of workers and poultry daily feeding causes PM dispersion on the surface of the building, resulting in elevated PM concentrations. Relative to broilers, laying hens have more activity during the day and, therefore, a relatively high PM concentration in the poultry house (Wathes et al., 1997). In addition, light exposure can also affect changes in PM concentrations in livestock farms. In poultry houses, PM concentrations were significantly higher when the light is brighter than in the dark due to increased animal activity in the light (Qi et al., 1992).

RESPIRATORY HEALTH HAZARDS OF PM IN POULTRY HOUSE

PM in poultry houses affects respiratory health mainly in 3 ways: inhaled PM irritates the respiratory tract, decreases immune resistance, and causes respiratory disease; irritation of the respiratory tract by compounds present in PM; respiratory diseases are caused by infections with pathogenic and non-pathogenic microorganisms attached to PM. The latter 2 modes of influence are more harmful. Studies have found different amounts of airborne particles of different particle sizes deposited in the poultry respiratory tract. PM_{10} reached the lower respiratory tract of 4-wk-old broilers, and PM_{20} (aerodynamic diameter <20 μm) to PM_1 (aerodynamic diameter <1 μm) deposition in the lungs of 1-day-old broilers increased from 3 to 17% (Corbanie et al., 2006). Broilers exposed to a warm room, as airborne PM increases, were found to have lesions to varying degrees in the bronchi of more than 50% of poultry, where dust particles can be observed (Riddell et al., 1998). Litter-derived PM damages the broilers' tracheal mucosa and air pouch tissues (Terzich et al., 1998). Poultry showed higher immunity levels in houses with higher PM concentrations (Roque et al., 2015). In two studies using mice as a biological model, a higher level of immunity, as well as the occurrence of inflammation, were observed in mice in response to intratracheal instillation of PM in the poultry house and exposure to poultry house air, respectively (Franzi et al., 2017; Liu et al., 2020).

However, PM is a mixture, and understanding its detailed pathogenic factors is highly necessary. To evaluate the relationship between components in PM and poultry immune responses, Lai et al. conducted toxicological tests on various Pathogen-associated molecular patterns (**PAMPs**) in PM. The results showed that PAMPs in PM could all lead to an enhanced immune status in Broilers and potentially affect cardiac morphology and, thus, physiological

status in Broilers (Lai et al., 2012). After incubation, broilers are exposed to PM at all stages of growth and development, and the lungs are affected by PM toxicity for a long time. (de Gouw et al., 2017; Jiang et al., 2020). PM directly irritates the respiratory tract and is far less common than ammonia carried by PM and microorganisms hazards.

Ammonia in Poultry House PM Poses a Respiratory Health Hazard

Ammonia is the most alkaline harmful irritant gas in the poultry house. The combination of airborne ions and volatile particles of ammonia crystals in urine is an essential component of $PM_{2.5}$ in poultry houses. Ammonia is the most hazardous toxic gaseous particulate pollutant in poultry houses. Due to the low ventilation frequency in winter, a high concentration of ammonia is very common in intensive poultry houses (Naseem and King, 2018). When the ammonia content in the poultry house rises to a certain value, a strong ammonia smell will be smelled. Due to the limitation of the detection equipment, the ammonia compounds carried in $PM_{2.5}$ cannot be detected. This situation is often overlooked. High concentrations of ammonia, and ammonia compounds in poultry houses, have been reported to cause multiple organ damage in poultry. Studies have focused on observing immune cells and organs (An et al., 2019; Zhao et al., 2020; Zhou et al., 2020, 2021a,b; Li et al., 2021). However, little is known about the mechanism of respiratory poisoning by ammonia and ammonia compounds. It is generally accepted that the absorption of exogenous ammonia in poultry first causes the breakdown of mucosal barriers in the respiratory tract and lungs, which causes immune imbalance and leads to the development of respiratory inflammation (Wang et al., 2022). Sustained exposure of broilers to ammonia revealed a significant elevation of inflammatory markers, activation of the nuclear transcription factors κB (**NFκB**) pathway, apoptosis, and disturbed immune status in the trachea (Shi et al., 2019). In addition, autolysosomes were induced by ammonia exposure in the ultrastructure of tracheal tissue, and aberrant expression of the upstream genes mir-2188-5p and circ-ifnlr1 were detected (Zhang et al., 2022). Increased reactive oxygen species (**ROS**) levels, reduced antioxidant capacity, and high expression of apoptotic factors can be detected in the lungs of broilers (Bai et al., 2021).In addition to disrupting the mucosal barrier and causing immune disorders, ammonia may cause respiratory inflammation by perturbing microbial distribution and species changes (Liu et al., 2020; Zhou et al., 2021; Wang et al., 2022). During the healthy growth of broilers, the respiratory microbiota changes dynamically with the broilers growing. This dynamic change and the growth environment of broilers have a strong correlation, especially with the quality of air (Chen et al., 2021).

Microorganisms in Poultry Houses Pose a Respiratory Health Hazard

Pathogenic bacteria, endotoxins, and allergens are carried in PM. These factors often lead to respiratory diseases, including chronic bronchitis, asthma, and dust poisoning syndrome (Hamid et al., 2018; Stuper-Szablewska et al., 2018). In a poorly ventilated poultry house, many microorganisms were attached to the $PM_{2.5}$ in the poultry house and increased with higher PM concentrations (Nimmermark et al., 2009). Because of the high temperature and humidity environment in the poultry house, saprophytic bacteria dominated the microorganisms in the PM of the poultry house. High concentrations of microbes and metabolites negatively affect the structure and defense function of the respiratory mucosa. Pathogenic and conditionally pathogenic microbes can cause immunotoxin, allergic effects, and even infectious diseases (Chmielowiec-Korzeniowska et al., 2021). In poultry houses, bacteria that pose a threat to the health of poultry are *Chlamydia* spp., *Staphylococcus aureus, Listeria* spp., *Streptococcus* spp., and a variety of *Salmonella* spp., which can infect the respiratory and lung, causing interstitial pneumonia, airway inflammation, and a range of respiratory diseases (Dai et al., 2020). In addition, the resistance of bacteria has increased due to antibiotic usage problems, and the effectiveness in preventing and treating diseases has declined (Nhung et al., 2017). *Gallinaceous fungi, Aspergillus, Scopulariopsis, Wallemia*, and *Fusarium*, were abundant in the PM of the poultry house. These species are found in plant raw materials and feces. Since fungal spores readily reach the lower respiratory tract with PM, they can cause allergic reactions, respiratory inflammation, and the production of pneumonia (Zukiewicz-Sobczak et al., 2013).

Besides that, microbes' residues and metabolites cause immunotoxicity in the lung immune system. Endotoxin is a cell wall component of gram-negative bacteria and is made of lipopolysaccharide (**LPS**). After binding with PM, it diffuses into the environment. When LPS binds to LPS binding protein (**LBP**) and subsequently to CD14, which is then recognized by toll-like receptor (**TLR**) 4, they activate the innate immune system. LPS binding to the CD14 / TLR4 complex activates macrophages and produces proinflammatory cytokine. Broilers, at high concentrations of LPS, exhibit respiratory and pulmonary tissue lesions and pulmonary arterial hypertension, decreased in vivo immune protein binding capacity, higher interferon expression, and TLR4 expression (Roque et al., 2015; van der Eijk et al., 2022). Mycotoxins produced by fungi in the PM of poultry houses pose hazards to poultry gastrointestinal, respiratory, and immune systems and, under continuous exposure, can even cause death. Of particular note, mold produces β- 1,3-glucan and is an essential factor in causing pneumonia in broilers (Dutkiewicz et al., 2011; Zhang et al., 2021). A study of broiler exposure to PM in poultry houses directly unraveled the impact

Table 1. Effects of PM in poultry house on respiratory disease in animals.

Exposure	Animal	Sample type	Exposure time	Inflammatory indicators	Pathways involved	Reference
Intranasally inoculated	Mice	Lung/Macrophages	14d/6h	IL-6,IL-8,TNF-α	NF-κB	(Li et al., 2020)
Cell addition	Mice	Alveolar Macrophages	12h	N/A	NF-κB mTOR	(Zhang et al., 2022)
Intranasally inoculated	Mice	Lung/BALF	24h	IL-23,IL-5	N/A	(Liu et al., 2020)
Intratracheal instillation	Mice	BALF/Alveolar Macrophages	24h	Inflammatory cell numbers	N/A	(Franzi et al., 2017)
Cell addition	Human	A549 cell	12h	IL-6,IL-8,TNF-α, TRAM2,TICAM1	TLR4-NFkB	(Dai et al., 2019)
Intratracheal instillation	Broiler	trachea	7w	IgM,IgG,IgA	N/A	(Lai et al., 2012)
Air exposure	Broiler	Serum	34d	IgM.IFN-α	TLR4	(van der Eijk et al., 2022)
Air exposure	Broiler	Serum	30d	Inflammatory cell numbers	N/A	(Roque et al., 2015)
Cell addition	chicken	alveolar epithelial cells	24h	NLRP3,IL18, IL1b, RIPK3,Caspase-1	N/A	(Xi et al., 2022)
Air exposure	Broiler	lung	7d	IL-1β, IL-8	Dysbiosis	(Shen et al., 2022)

Note: N/A means not involved.

of microbial and their metabolite perturbations due to PM on lung injury in broilers. Using a combined microbiome and metabolome analysis approach, lung injury and microbial community disruption in broilers were observed, along with a strong correlation in microbial metabolites (Shen et al., 2022). Similar conclusions emerged from other studies in which exposure of rats to $PM_{2.5}$ impaired lung microbiome and immune homeostasis, manifested by a significant increase in the ability of PM to phagocytose bacteria by macrophages and induced changes in immunoglobulin levels (Li et al., 2020).

POTENTIAL RESPONSE MECHANISMS OF POULTRY HOUSE PM-INDUCED RESPIRATORY INFLAMMATION

Because of the complex composition of $PM_{2.5}$ in poultry houses, the mechanisms responsible for respiratory diseases are also different. Little is known about the effects of $PM_{2.5}$ in poultry houses on poultry respiratory disease. We have summarized the results of current trials using PM in poultry house-induced respiratory diseases (Table 1). And we mapped a potential mechanism for PM-induced respiratory disease (Figure 2).

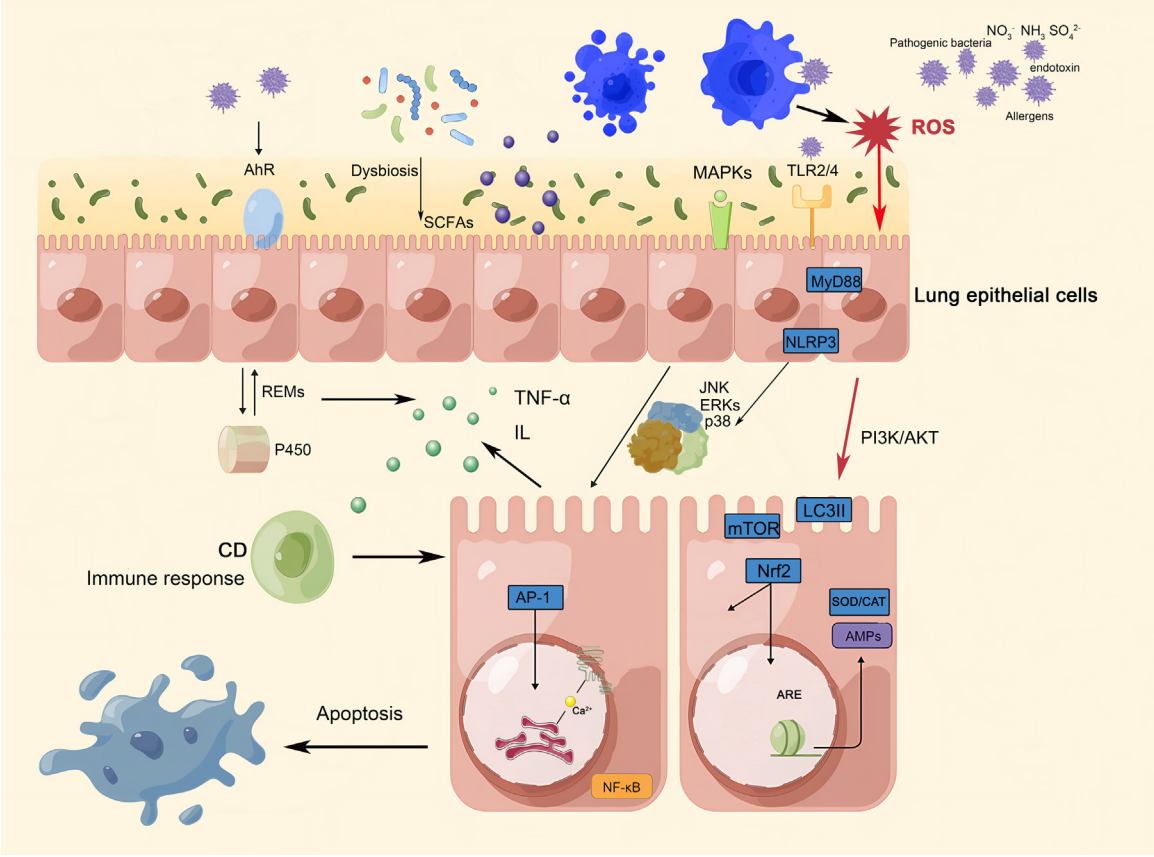

Figure 2. Potential mechanisms of PM-induced respiratory disease in the poultry houses. Abbreviation: PM, particulate matter.

Alveolar Macrophages-ROS Pathway

Inhaled $PM_{2.5}$ can first stimulate alveolar macrophages to produce proinflammatory factors, which stimulate epithelial cells, endothelial cells, and fibroblasts of the alveoli to secrete cytokines and adhesion factors and induce inflammatory cell aggregation, triggering an inflammatory response (Tang et al., 2019; Marcella et al., 2022).

From limited reports, we know that intracellular ROS levels and expression levels of pyroptosis-related genes (NLRP3, IL-18, IL-1B) and necroptosis-related genes (RIPK3) are significantly enhanced in broilers primary alveolar epithelial cells exposed to $PM_{2.5}$ (Dai et al., 2019). PM can stimulate the respiratory tissue cells to produce ROS (Choi et al., 2022; Marques et al., 2022), and it can activate redox-sensitive signal transduction pathways, such as mitogen-activated protein kinases (**MAPKs**) and phosphatidylinositol-3-kinase / protein kinase B (PI3K / Akt) pathways (Li et al., 2021; Xu et al., 2021; Zhu et al., 2022). MAPKs comprise a group of serine/threonine protein kinases (c-Jun NH2 terminal kinase, JNK; extracellular signal-regulated kinases, ERKs; stress-activated protein kinase, p38) that can be activated upon stimulation by extracellular stressors, regulate signal transduction from the cell surface to the nucleus, and ultimately lead to upregulated expression of proinflammatory factors causing cellular inflammatory responses (Ronkina and Gaestel, 2022). Studies have reported that PM can induce alveolar macrophages to produce excessive ROS, which in turn activate MAPKs and induce upregulation of the expression of the transcriptional activator AP-1, inducing cellular inflammatory responses (Ko et al., 2015; Nath et al., 2018; Chen et al., 2022). Diesel exhaust particles induce ROS production in human tracheal epithelial cells, activating ERK1 / 2 and p38, activating the downstream NFκB pathway, ultimately evoking the cell to undergo an inflammatory response (Jiang et al., 2020).

Calcium ion (Ca^{2} +) is indispensable for maintaining life activities and plays a vital role in the body's immune function (Chan et al., 2015). It has been found that oxidative stress in respiratory epithelial cells caused by PM stimulates Ca^{2+} release from the ER and regulates the NFκB expression, which promotes the upregulation of inflammatory factors expression (Xing et al., 2016; Yang et al., 2020; Jheng et al., 2021; Song et al., 2022).

TLR4-NF-κB Pathway

From another study, we know the relevant mechanism of $PM_{2.5}$ toxicity on human alveolar basal epithelial (A549) cells in poultry houses. TLR4-NF-κB pathway mediates inflammation in A549 cells induced by $PM_{2.5}$ in poultry houses; Nrf2 decreases NF-κB by inhibiting oxidative stress and endoplasmic reticulum stress expression, thereby slowing inflammation; autophagy by promoting NF-κB expression, while suppressing Nrf2 expression promotes inflammation (Dai et al., 2019). Co-stimulation of mouse lung tissue with $PM_{2.5}$ in the poultry house and carrier *Pseudomonas aeruginosa* upregulated interleukin (**IL**) - 6, IL-8, TNF α via the nucleus- α The expression levels, which in turn regulate NF-κB expression (Li et al., 2020). In addition, porcine house PM induces immune responses by activating the TLR4 / MAPK / NF-κB pathway and the NLRP3 inflammasome in alveolar macrophages (Tang et al., 2019). TLRs are pattern recognition receptors expressed on the surface of innate immune cells. They can recognize one or more pathogen-associated molecular patterns, which play a role in innate and acquired immune systems. Airborne particulate pollutants have been found to activate the cellular pattern recognition receptors TLR2 and TLR4. Myeloid differentiation factor 88 (**MyD88**) and TIR domain adapter protein (**TRIP**), which are adaptor proteins for all TLRs, are potential downstream proteins whose expression is triggered by particle exposure (Shoenfelt et al., 2009; Ryu et al., 2022). Lung macrophages, upon stimulation by PM, TLR4 associates with trip-related adaptor molecule binding recruits TRIP, which activates p38, causing upregulation of the expression of downstream inflammatory factors, ultimately leading to inflammatory responses in cells (Tang et al., 2019). Disturbances in the microbial flora and metabolites caused by $PM_{2.5}$ in the respiratory tract and lungs may also be a predisposing factor leading to respiratory inflammation. However, further studies are needed to reveal whether changes in the distribution and quantity of microbiota precede or whether inflammation is produced.

Dysbiosis

Mice exposed to $PM_{2.5}$ reduced the abundance and composition of lung and intestinal microflora and found different degrees of metabolic abnormalities in BALF and serum (Ran et al. 2021). In another experiment, it was found that $PM_{2.5}$ could change the composition and abundance of pulmonary microbial flora and cause inflammation and oxidative stress by transplanting the disordered pulmonary flora into the nose (Wang et al. 2022). In addition, after $PM_{2.5}$ disturbs the lung's microbial composition, it increases mice's susceptibility to pneumococcus and exacerbates the deterioration of lung disease (Chen et al. 2020). Interestingly, a probiotic intervention was found to have preventive effects on the occurrence of $PM_{2.5}$-induced pathological injury. The mechanism was associated with inhibiting inflammatory response, regulating Th17/Treg balance and maintaining intestinal internal environment stability (Wu et al. 2022).

These studies showed that exposure to ambient $PM_{2.5}$ caused not only dysbiosis in the lung but also significant systemic and local metabolic alterations. Alterations in lung microbiota were strongly correlated with metabolic abnormalities. They suggest the potential roles of lung microbiota in $PM_{2.5}$-caused metabolic disorders.

CONCLUSIONS

With the continuous development of intensive farming, poultry cannot avoid living in high concentrations

of PM environments until the ventilation system can reach equilibrium with production requirements. While intensive poultry husbandry models bring economic benefits, animal welfare and the natural environment still need to be considered. Currently, PM in the poultry house is mainly responsible for respiratory disease in broilers, as well as contamination of the outside environment. The hazardous effects of high concentrations of $PM_{2.5}$ on the poultry respiratory tract and lungs make it difficult for poultry to be in a state of high-level production. In addition, PM can induce lung disease through several toxic mechanisms, including ammonia ingestion and bioaccumulation, lung flora dysbiosis, oxidative stress, and metabolic disorders. However, these effects largely depend on PM type, composition, and concentration. Poultry contributes to PM formation, disease transmission, and migration to higher nutrient levels. There is no doubt that PM impacts poultry respiratory health, where the poultry industry is responsible for significant annual losses from respiratory disease.

So, we suggest monitoring $PM_{2.5}$ concentration in poultry houses and studying more outstanding efforts about the components of $PM_{2.5}$ in poultry houses on respiratory pathogenicity to clarify the pathogenic mechanism, especially $PM_{2.5}$ stimulates inflammation through effects on the distribution and species changes of respiratory microflora.

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