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Original Article

Chrysin Ameliorates *Mycoplasma pneumonia* Induced Pneumonia in Mice by Down-Regulating Inflammatory Response

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ABSTRACT

Background: Mycoplasma pneumonia, a major respiratory infection characterized by inflammation of the lungs, poses a substantial global health concern, particularly among vulnerable populations such as the elderly, immunocompromised individuals and young children. **Objectives:** The current study has focused on exploring the attenuation of *Mycoplasma pneumoniae* (Mp)-induced pneumonia by chrysin in rodent model. **Materials and Methods:** BALB/c mice were administered 1×10^8 (50 µL) of Mp via nasal drops to induce *Mycoplasma pneumonia*. The mice were then administered with chrysin (50 mg/kg) and/or azithromycin (100 mg/kg) for 3 days. Following the treatment period, the body weights of the experimental mice were evaluated. The Bronchoalveolar Lavage Fluid (BALF) was gathered from the experimental mice and subsequently subjected to analyse the total protein, total cells and inflammatory cytokine concentrations utilizing suitable diagnostic kits. The histopathological examination of the lungs was undertaken to assess histological abnormalities. **Results:** The treatment of chrysin markedly increased the body weight, decreased the total cell counts and total protein concentrations in the BALF of the Mp-infected pneumonia mice. Furthermore, the chrysin treatment led to a reduction in pro-inflammatory cytokine concentrations in the BALF of Mp-infected mice. The findings of the histological study exhibited a notable reduction in lung histopathological abnormalities in the chrysin-treated mice, which evidenced the therapeutic potentials of the chrysin against pneumonia condition. **Conclusion:** The results of this study highlight the beneficial effects of chrysin against *Mycoplasma pneumonia* in mice due to its potential anti-inflammatory properties. Thus, chrysin can be a viable salutary candidate to treat pneumonia.

Keywords: Chrysin, Cytokines, *Mycoplasma pneumonia*, Azithromycin, Inflammatory cells.

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INTRODUCTION

Mycoplasma pneumoniae (Mp) is a major cause of Community-Acquired Pneumonia (CAP), particularly among school-aged children and young adults. This atypical pathogen can cause a wide range of respiratory illnesses, from mild upper respiratory tract infections to serious, life-threatening pneumonia.[1] The global prevalence of *Mycoplasma pneumonia* is significant, with studies estimating it to account for up to 33% of hospitalized cases of CAP. In developed countries, Mp is considered the second most common cause of CAP, following *Streptococcus pneumonia*.[2] The disease burden associated with *Mycoplasma pneumonia* is substantial. It has been estimated that nearly 2 million pneumonia mortalities occur each year in children under the age of 5, predominantly in South-East Asia. Pneumonia can lead to significant morbidity, including respiratory distress, extra pulmonary complications and prolonged hospitalization. The epidemiology of *Mycoplasma pneumonia* is complex, with outbreaks occurring in community settings and distinctive patterns of transmission.[3] Two distinct genotypes of Mp, type 1 and type 2, have been identified and their prevalence can vary across geographic regions and over time. Genotyping reports have confirmed the occurrence of both types in recent outbreaks, highlighting the need for surveillance and the potential utility of molecular typing methods for epidemiological investigations.[4]

Understanding the underlying mechanisms of *Mycoplasma pneumonia* is crucial for improving disease management and prevention strategies. One of the key features of *Mycoplasma pneumonia* is its ability to colonize the respiratory tract mucosa and persist at the site of infection. This persistence is facilitated by the pathogen's strategies to evade the host's specific immune

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response, like variation in surface antigens and abnormal activation of alveolar macrophages.[5] The immune reaction to *Mycoplasma pneumonia* infection is complex, with evidence suggesting that both virulent and attenuated strains may relate to biased differentiation of pro-inflammatory pathogenic T helper 17 and Th1 subsets, respectively. This highlights the intricate interplay between the host's immune system and the pathogen's virulence factors in shaping the disease pathogenesis.[6] Additionally, *Mycoplasma pneumonia* has been said to block the respiratory burst of neutrophils and enhance the release of inflammatory mediators, contributing to the inflammatory response observed in pneumonia. These mechanisms underscore the need for further research to elucidate the precise mechanisms by which Mp evades the host's immune defenses and triggers the development of pneumonia.[7]

The choice of appropriate antibiotic therapy is crucial in effective management of pneumonia and macrolides have emerged as a commonly utilized class of antibiotics to treat pneumonia. Macrolides, including agents such as erythromycin, clarithromycin and azithromycin, have demonstrated efficacy in the management of both CAP and hospital-acquired pneumonia. These antibiotics exert their antimicrobial property by blocking bacterial protein synthesis, targeting the 50S subunit of the bacterial ribosome. This mechanism of action makes macrolides particularly effective against a range of common respiratory pathogens.[8] Nonetheless, the widespread utilization of macrolides has resulted in the emergence of resistance among the pathogens, posing significant challenges in the management of pneumonia. The development of macrolide resistance, driven by various mechanisms such as target site modifications, drug inactivation and drug efflux, has limited the therapeutic options available to clinicians, particularly in regions with high rates of macrolide resistance.[9] While various treatment methods have been developed, the search for more effective and accessible therapies remains a critical challenge. Current treatment approaches, including antibiotic administration and supportive care, have shown limitations in terms of efficacy, accessibility and the rise of antibiotic-resistant pathogens.[10]

The potential of plant-derived bioactive compounds in the treatment of pneumonia has gained increasing attention. These natural compounds, often found in medicinal plants, have demonstrated diverse therapeutic properties, which may be beneficial in managing respiratory infections like pneumonia.[11] Chrysin, a 5,7-dihydroxyflavone is a naturally occurring bioactive flavonoid compound, which is isolated from propolis, passion flowers, honey and honey wax. Chrysin has been reported to demonstrate numerous biological properties, such as hepatoprotective, anti-inflammatory, anti-arthritic, antioxidant, anti-angiogenic and neuroprotective.[12-17] Furthermore, the chrysin also attenuated the allergic airway inflammation and cigarette smoke-induced airway inflammation in an experimental animal model.[18,19] However, there are no scientific reports to claim its beneficial properties against mycoplasma pneumonia. Therefore, the current study has focused on exploring the attenuation of Mp-induced pneumonia by chrysin in rodent model.

MATERIALS AND METHODS

Chemicals

The major chemicals utilized in this work such as azithromycin, chrysin and other reagents were purchased from Sigma Aldrich, USA. The marker specific diagnostic kits to estimate the biochemical parameters were purchased commercially from Elabscience, USA and Abcam, USA, respectively.

Experimental mice and groupings

BALB/c male mice, weighing around 22-27 g, were acquired from institutional animal house and employed in this study. Each experimental group consisted of 6 mice approximately 6-8 weeks of age, including a control (Group I), a Mp infection-only (Group II), a Mp infection group receiving a 50 mg/kg of chrysin (Group III) and a Mp infection group receiving a 100 mg/kg of azithromycin (Group IV). The body weights of each experimental mouse were meticulously noted throughout the studies. All mice were euthanized after the experimental period and samples were obtained from the experimental mice for further experimentations. All experimental procedures are strictly adhered to animal handling procedures sanctioned by the institutional animal ethics committee.

Treatment procedures

Mp was administered by intranasal instillation at a dosage of 1×10^8 Mp in 50 µL per mouse for 2 days. The control group, which was not administered the Mp, received a dose of sterile saline through intranasal instillation. Chrysin (50 mg/kg) and azithromycin (100 mg/kg), respectively were administered 2 hr post-infection via oral route for 3 days. The Bronchoalveolar Lavage Fluid (BALF) and lung tissues were obtained on the 4th day of the experiment for cellular investigation and other biochemical assays.

BALF cell counts and total protein level analysis

After experiments (4th day), animals were terminated via intraperitoneal injection of a fatal dosage of urethane. Lungs were carefully flushed with saline to collect BALF through a cannulated trachea. The cell-free lavage fluid was utilized to evaluate biochemical markers. BALF cells were quantified using an automated cell counter (Countess, Thermofisher, USA) employing Trypan blue exclusion to assess cell viability. The total protein contents in the BALF samples were estimated to be using a commercial diagnostic kit by following the recommended guidelines of the (Abcam, USA).

Analysis of inflammatory cytokines in the BALF

The BALF levels of inflammatory cytokines, including Interleukin (IL)-6, IL-1β and Tumor Necrosis Factor (TNF)-α were studied using a commercial diagnostic kit. Each experiment was performed with three replicates by strictly adhering to the suggested guidelines of the manufacturer (Elabscience, USA).

Preparation of lung tissue and histopathological analysis

The lung tissues were harvested from each experimental mouse after the collection of BALF. The collected lungs were preserved with immersion in 10% formalin. The lung tissues were then paraffinized, sectioned into 5 µm slices using rotary microtome and subsequently stained using eosin and hematoxylin. The stained slides were evaluated using microscope in blinded manner at 40×magnification.

Statistical analysis

The statistical tests were done using Prism software (GraphPad). Data comparisons and significance analysis were conducted using one-way ANOVA accompanied by Tukey's multiple comparison test. Significance was mentioned as follows: * $p<0.01$; ** $p<0.05$.

RESULTS

Effect of chrysin on the body weight changes in the experimental mice

Figure 1 depicts the changes in body weight of both control and experimental mice. The mice with Mp-infected pneumonia exhibited a notable reduction in body weight, which is in contrast with control. Surprisingly, the chrysin at 50 mg/kg concentration demonstrated a significant elevation in the body weight. The administration of the conventional drug azithromycin (100 mg/kg) also resulted in an increase in body weight level of mice with pneumonia.

Effect of chrysin on the total protein in the BALF of experimental mice

The concentrations of total protein in the BALF sample of the experimental mice was studied and the findings are mentioned in Figure 2. The Mp-infected pneumonia mice displayed drastic elevation in the BALF total protein concentrations in comparison with control. Whereas the chrysin treatment at dosage of 50 mg/kg effectively reduced the total protein concentration in the BALF of the Mp-infected mice. Similar outcomes were also noted in the mice administered the azithromycin, further substantiating the efficacy of chrysin.

Effect of chrysin on total cells in BALF of the experimental mice

Figure 3 illustrates the results of chrysin treatment on total cell counts in BALF of the experimental mice. The mice with Mp-induced pneumonia exhibited a substantial elevation in total cells in their BALF. Notably, the 50 mg/kg of chrysin illustrated a considerable reduction in total cell counts in the BALF of Mp-infected mice. Moreover, the azithromycin also remarkably diminished the total cell counts in the BALF of mice with Mp-infected pneumonia (Figure 3).

Effect of chrysin on inflammatory cytokines in BALF of the experimental mice

As demonstrated in Figure 4, the Mp-induced mice had a substantial elevation in the IL-1, IL-6, IL-8, TGF-β and TNF-α concentrations in their BALF. Fascinatingly, the administration of 50 mg/kg of chrysin successfully diminished the IL-1, IL-6, IL-8, TGF-β and TNF-α concentrations in the BALF of Mp-induced mice. In addition, the azithromycin treatment also successfully reduced these cytokines in the BALF of Mp-infected mice, which evident the anti-inflammatory properties of chrysin.

Effect of chrysin on lung histopathology of the experimental mice

Figure 5 displays microphotographs of histopathological analysis of lung tissues from experimental mice. The control mice displayed typical alveolar cell structures and no signs of inflammation or lung tissue damage. In contrast, Mp-infected mice demonstrated notable histological changes, such as thickened alveolar walls, contracted bronchial tubes and heightened inflammatory cell infiltration in their lungs. Remarkably, chrysin at 50 mg/kg concentration effectively diminished lung histological changes in the Mp-infected mice. The findings of azithromycin administration also showed a substantial diminution in lung histological alterations, hence supporting the salutary effectiveness of chrysin.

DISCUSSION

Mp is a significant cause of CAP, accounting for up to 33% of hospitalized cases. This atypical bacterium is known to cause a mild, self-limiting respiratory illness, although it has been rarely associated with complications. CAP is characterized by lower airway infection attained by the patient in non-hospitalized setting, which is connected with clinical signs of severe infection and new opacities described on a chest radiograph.[20] Mp is a unique pathogen that lacks a cell membrane, making it resistant to many common antibiotics that target cell wall synthesis. The organism primarily targets the respiratory epithelium, where it adheres to the mucosal surface and initiates a cascade of inflammatory responses. The host's immune reaction to the infection, including the production of cytokines and chemokines, is believed to contribute to the development of the characteristic pneumonic consolidation. The clinical signs of Mp-infected pneumonia can range from mild, self-limiting condition to serious, life-threatening problems, like acute respiratory distress syndrome and extra pulmonary manifestations.[21] Risk factors for

Mycoplasma pneumonia include age, with children and young adults being most commonly affected, as well as underlying conditions such as chronic lung disease, immunodeficiency and close contact with infected individuals. Accurate diagnosis and prompt treatment are crucial in managing mycoplasma pneumonia, as the condition can lead to significant morbidity and mortality if left untreated. Despite the development of numerous treatment approaches, the pursuit of more effective and accessible remedies continues to be a significant problem due to the less efficacy, poor accessibility and the occurrence of antibiotic-resistant bacteria.[22] The current study aims at investigating the salutary properties of the chrysin against Mp-infected pneumonia in mice.

Pneumonia is a common complication in severely malnourished children, with up to two-thirds of those requiring hospital admission being diagnosed with the condition. Furthermore, severe malnutrition has been reported to enhance the mortality risk in those with pneumonia. Accurately identifying the underlying cause of pneumonia is crucial, as the management approaches can vary significantly depending on the etiology. While the recommended guidelines for pneumonia management are primarily based on the identification of clinical signs. Additionally, efforts to better identify clinical features that could differentiate bacteria from viral pneumonia have been largely unsuccessful, highlighting the need for more objective diagnostic tools.[23] In this context, the analysis of body weight changes in *Mycoplasma pneumonia* could provide valuable insights. Understanding the specific patterns of body weight changes in the *Mycoplasma pneumonia* could help distinguish it from other etiologies, potentially leading to more accurate and timely diagnoses. Furthermore, monitoring body weight changes may also have prognostic value, as severe malnutrition has been linked to poorer outcomes in pneumonia. By closely tracking a patient's weight during the course of disease, clinicians may be better able to diagnose those at higher risk of complications or mortality, allowing for more targeted therapies.[24] In this study, results evidenced that mice with Mp-infected pneumonia exhibited a drastic reduction in body weight. Whereas the chrysin treatment demonstrated a significant elevation in the body weight of Mp-infected mice, which also corroborated by the results of azithromycin treatment.

The analysis of total protein in the BALF of patients with Mp-infected pneumonia may provide valuable insights into the pathophysiology and severity of the disease. Increased total protein levels in the BALF can indicate the extent of lung injury and inflammation, which may be associated with the severity of pneumonia. Additionally, the evaluation of total protein levels can aid in differentiating Mp-infected pneumonia from other types of pneumonia, as the clinical presentation and radiographic findings are often nonspecific.[25] Recent studies have explored the diagnostic and prognostic significance of total protein analysis in the BALF of patients with Mp-infected pneumonia. The findings suggest that the assessment of total protein levels may help to diagnose patients at risk of developing severe complications

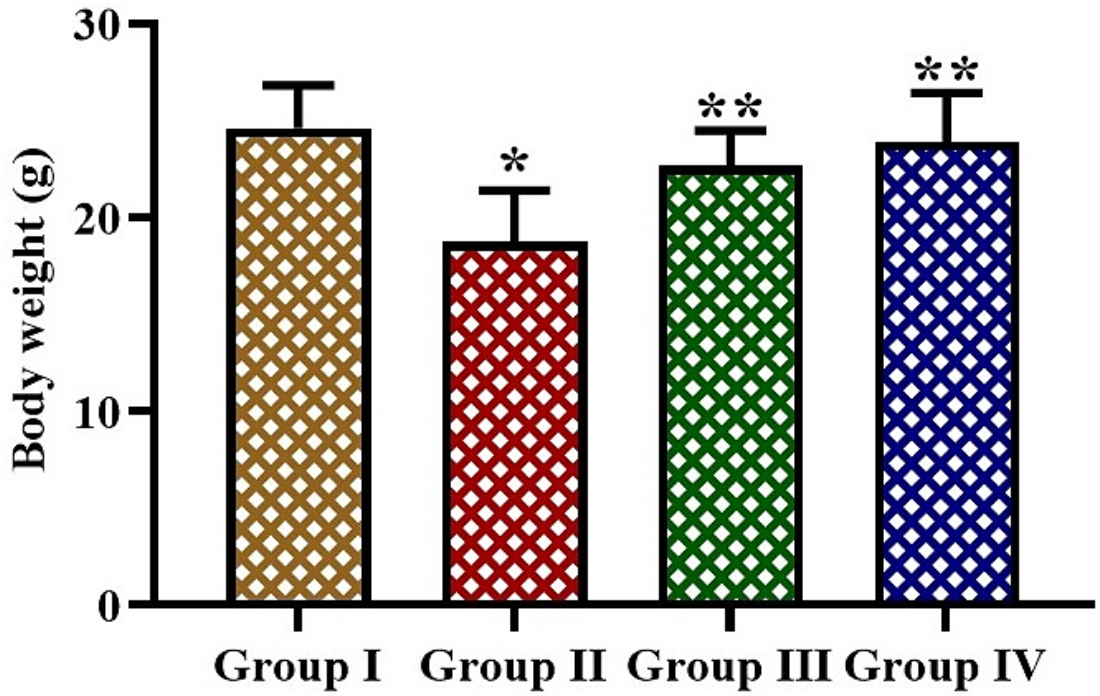

Figure 1: Effect of chrysin on the body weight changes in the experimental mice. Data were depicted in each bar as a Mean±SD of three replicates (n=3). A one-way ANOVA and Tukey's multiple comparison test were done to scrutinize the variations between treatment groups using Prism software (GraphPad). A symbol '*' denotes the significance at p<0.01 when compared with control group; '**' denotes the significance at p<0.05 from pneumonia-induced group.

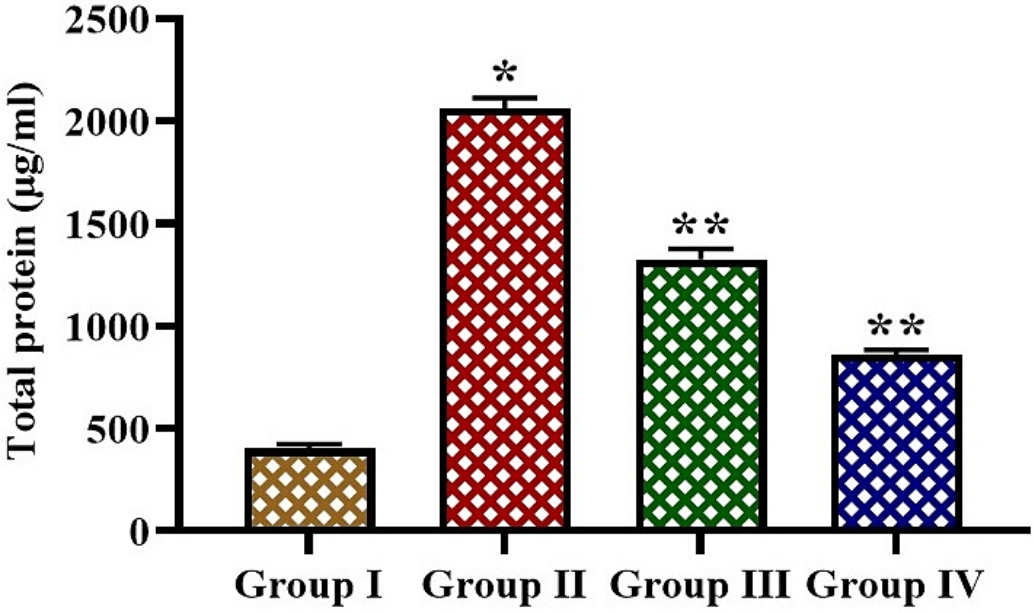

Figure 2: Effect of chrysin on the total protein in the BALF of experimental mice. Data were depicted in each bar as a mean±SD of three replicates (*n*=3). A one-way ANOVA and Tukey's multiple comparison test were done to scrutinize the variations between treatment groups using Prism software (GraphPad). A symbol '*' denotes the significance at $p<0.01$ when compared with control group; '**' denotes the significance at $p<0.05$ from pneumonia-induced group.

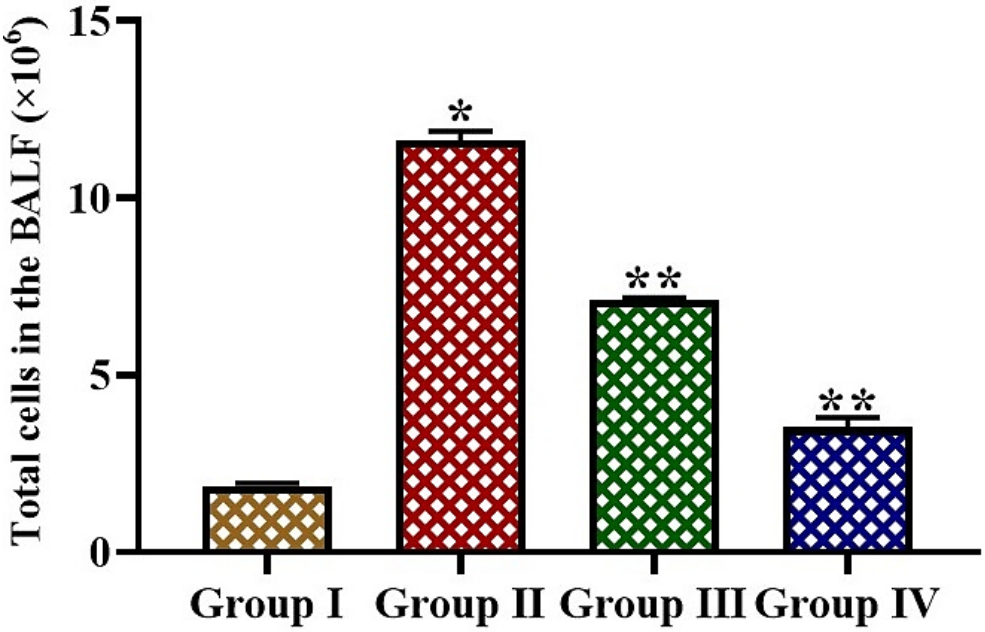

Figure 3: Effect of chrysin on the total cells in the BALF of the experimental mice. Data were depicted in each bar as a Mean±SD of three replicates (*n*=3). A one-way ANOVA and Tukey's multiple comparison test were done to scrutinize the variations between treatment groups using Prism software (GraphPad). A symbol '*' denotes the significance at $p<0.01$ when compared with control group; '**' denotes the significance at $p<0.05$ from pneumonia-induced group.

and guide the management of the disease.[26] Accurate and timely diagnosis of Mp-infected pneumonia remains a challenge, as the clinical signs and symptoms can be nonspecific and vary depending on the patient's physical characteristics. The analysis of total protein levels in the BALF may offer a complementary diagnostic tool that can provide valuable information about the severity and pathophysiology of Mp-infected pneumonia.[27] The current work evidenced that mice with Mp-infected pneumonia displayed severe elevation in total protein in their BALF. Captivatingly, the chrysin treatment significantly reduced the total protein content in BALF of the pneumonia mice.

The clinical presentation of Mp-induced pneumonia can be challenging to distinguish from other respiratory illnesses,

highlighting the need for improved diagnostic tools and a better understanding of the underlying pathophysiology. One area of interest is the analysis of inflammatory cell counts in BALF, which may provide valuable insights into the host immunity and the severity of the condition. Recent studies have shed light on the importance of analyzing total inflammatory cell counts in BALF for Mp-infected pneumonia. Ozone-induced neutrophilic airway inflammation, for instance, has related to higher generation of the pro-inflammatory cytokines.[28] Furthermore, asthmatic inflammation has been shown to develop through the interaction of inflammatory cells with resident cells, generating a series of events that implicate chronic inflammation and clinical manifestations. In the context of Mp-infected pneumonia, understanding the dynamics of inflammatory cell counts in the BALF may provide valuable insights into the pathophysiology of the disease and guide the progression of targeted therapeutic interventions.[29] The findings of study exhibited that mice with Mp-infected pneumonia exhibited a substantial elevation in the total cells in their BALF. Notably, the chrysin treatment caused the diminution of total cells in the BALF of pneumonia mice. These findings highlighted that chrysin has decreased the inflammatory cell infiltrations in the Mp-infected mice.

The analysis of inflammatory cytokines in the patients with *Mycoplasma pneumonia* can offer valuable information about the pathogenesis and immune reaction associated with this disease. Cytokines such as IL-6, IL-8 and TNF-α play crucial roles in the inflammatory process during Mp infection. Elevated concentrations of these cytokines in the BALF have been linked to the severity of pneumonia and the onset of complications.[30] TNF-α are a pivotal pro-inflammatory cytokine that can induce the recruitment of other inflammatory cells, leading to tissue damage and airway inflammation. IL-6 is participated in the acute-phase of inflammatory reaction, while IL-8 is serving as a potent chemoattractant for inflammatory cells, which contributes

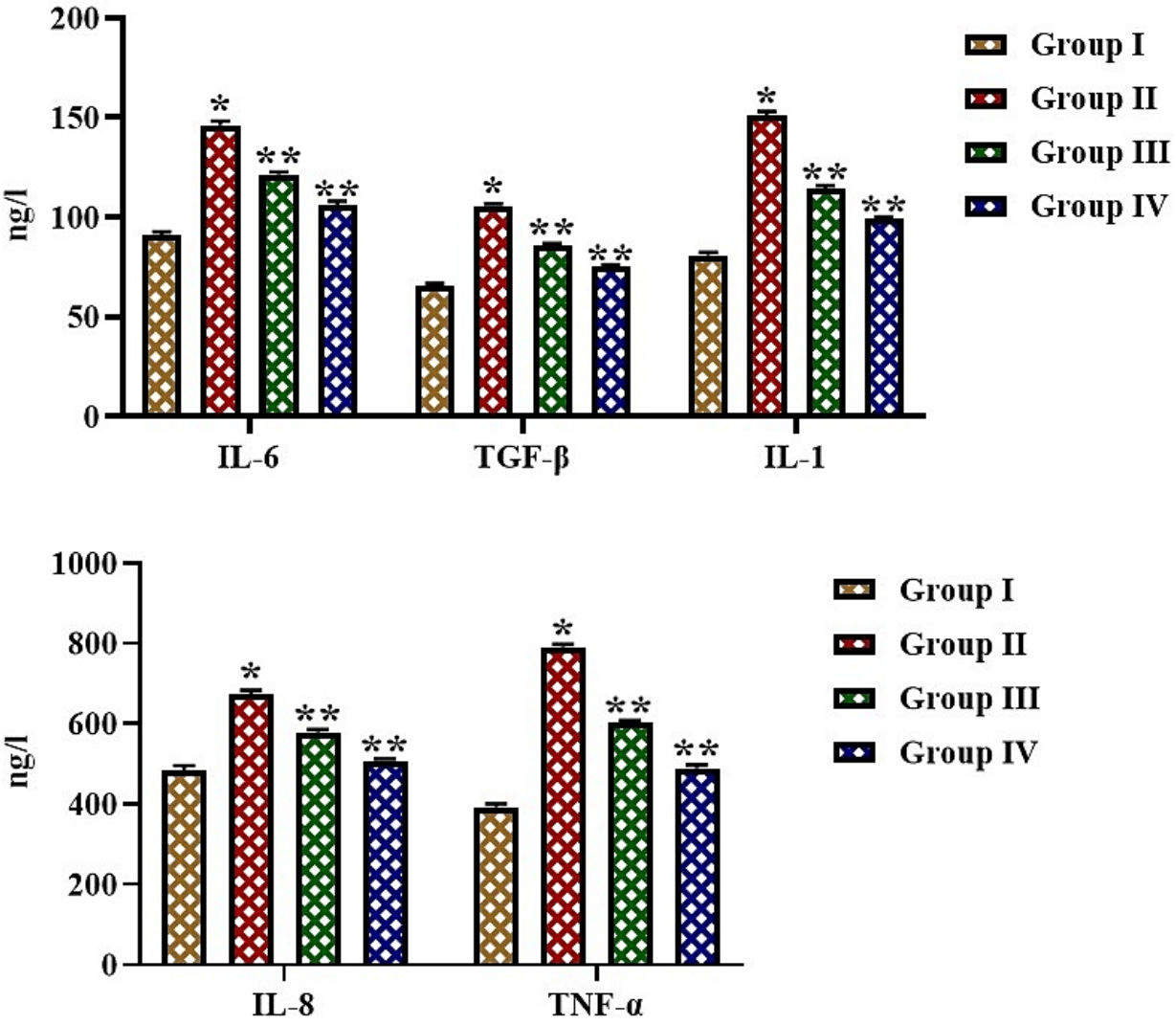

Figure 4: Effect of chrysin on the inflammatory cytokine levels in the BALF of experimental mice. Data were depicted in each bar as a Mean±SD of three replicates (n=3). A one-way ANOVA and Tukey's multiple comparison test were done to scrutinize the variations between treatment groups using Prism software (GraphPad). A symbol '*' denotes the significance at p<0.01 when compared with control group; '**' denotes the significance at p<0.05 from pneumonia-induced group.

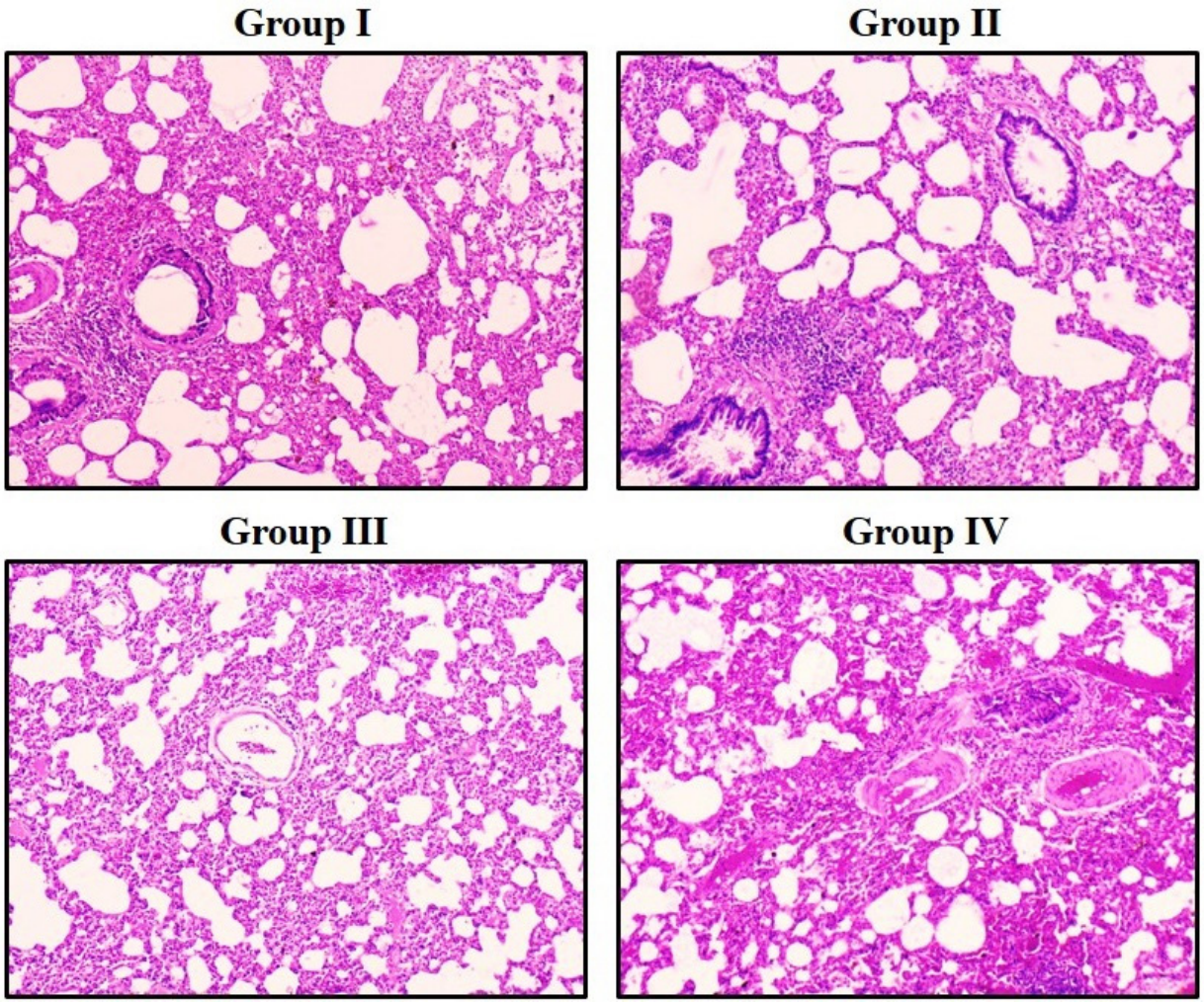

Figure 5: Effect of chrysin on the lung histopathology of the experimental mice. Group I: The control mice displayed typical alveolar cell structures and no signs of inflammation or lung tissue damage; Group II: The Mp-infected mice demonstrated notable histological changes, such as thickened alveolar walls, narrowed bronchial tubes and heightened inflammatory cell infiltration in their lungs; Group III: Chrysin (50 mg/kg) treatment effectively diminished lung histological changes in the Mp-infected mice; Group IV: The results of azithromycin treatment also showed a substantial decrease in lung histological changes.

to the inflammatory cell influx into the lungs. TGF-β is a pivotal immune regulatory cytokine that can lessen the inflammatory response.[31] The analysis of the inflammatory cytokines in the BALF of patients with Mp-infected pneumonia can provide insights about the host immunity and the severity of the disease. The findings of this study evidenced that mice with pneumonia had a drasrric elevation in the pro-inflammatory cytokine levels in their BALF. However, the treatment of chrysin effectively diminished these inflammatory cytokines in the BALF of the Mp-infected mice. These findings evidenced the anti-inflammatory potentials of chrysin against pneumonia condition.

Despite the clinical presentation and radiographic findings of *Mycoplasma pneumonia* are well-documented, the histopathological analysis of lung tissues plays pivotal role in understanding the underlying disease mechanisms. Histopathological examination of lung tissues can provide valuable insights into the pathogenesis of mycoplasma pneumonia. Histopathological analysis can help differentiate Mp-infected pneumonia from other etiologies by revealing the specific histological changes associated with the disease.[32] In mycoplasma pneumonia, the histopathological features often include peribronchial and interstitial inflammatory infiltrates, predominantly composed of lymphocytes, plasma cells and macrophages. These findings can help confirm the diagnosis and guide the appropriate management of the patient. Additionally, histopathological analysis can detect the presence of extra pulmonary manifestations, which may occur in some cases of *M. pneumoniae* infection.

Histopathological analysis can also inform the choice of treatment, as different histological patterns may respond differently to antimicrobial therapy or immunomodulatory interventions. For instance, the presence of significant inflammatory infiltrates may indicate a need for adjunct anti-inflammatory therapy, in addition to antimicrobial treatment.[33] The present results revealed the notable histological changes, such as thickened alveolar walls, contracted bronchial tubes and heightened inflammatory

cell infiltrations in the lung tissues of Mp-induced pneumonia. Captivatingly, chrysin treatment effectively diminished lung histological changes in the Mp-infected mice, which confirms the therapeutic potentials of the chrysin against pneumonia condition.

CONCLUSION

The results of this study highlight the salutary properties of chrysin against *Mycoplasma pneumonia* in mice. The significant increase in body weight, reduction in total cells and total protein levels were observed in Mp-infected mice in response to the chrysin treatment. Furthermore, the chrysin treatment also evidenced the effective reduction in inflammatory cytokines and lung histopathological alterations in the pneumonia mice, which evidence the therapeutic effectiveness of chrysin in treating pneumonia. Thus, chrysin can be a viable salutary candidate to treat pneumonia. Moreover, further studies are strongly recommended to comprehensively elucidate the therapeutic effects of chrysin against *Mycoplasma pneumonia*.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Mp: *Mycoplasma pneumoniae*; **BALF:** Bronchoalveolar Lavage Fluid; **CAP:** Community-Acquired Pneumonia; **IL:** Interleukin; **TNF-α:** Tumor Necrosis Factor-alpha; **TGF-β:** Transforming Growth Factor-beta; **ROS:** Reactive Oxygen Species; **STAT3:** Signal Transduction and Activator of Transcription 3; **SIRT1:** Sirtuin 1; **iNOS:** Inducible Nitric Oxide Synthase; **TCID50:** 50% Tissue Culture Infective Dose; **CPE:** Cytopathic Effect; **CCK-8:** Cell Counting Kit-8; **RIPA:** Radioimmunoprecipitation Assay; **BSA:** Bovine Serum Albumin; **TBST:** Tris-Buffered Saline with Tween; **ELISA:** Enzyme-Linked Immunosorbent Assay; **NF-κB:** Nuclear Factor Kappa B; **IκB:** Inhibitory κB; **MAPK:** Mitogen-Activated Protein Kinase; **p-P65:** Phosphorylated P65; **NC:** Normal Control; **SD:** Standard Deviation; **ANOVA:** Analysis of Variance; **USA:** United States of America; **TCM:** Traditional Chinese Medicine.

SUMMARY

Mycoplasma pneumoniae is a primary etiological agent of Community-Acquired Pneumonia, especially in school-aged children and young adults. Despite the development of several therapeutic modalities, the pursuit of more efficacious and accessible medicines remains a significant challenge. Chrysin is a naturally occurring bioactive flavonoid component derived from propolis, known to exhibit many biological characteristics. The results of the present study underscore the beneficial effects of chrysin against *Mycoplasma pneumonia* in mice. Therefore, chrysin may serve as a promising therapeutic agent for pneumonia.

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