Research Article

Ovalbumin-Induced Asthma in Rats is Alleviated by Resveratrol Treatment

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Abstract | The number of affected people by asthma is rising to reach up to 339 million worldwide. Asthma defined as chronic airway inflammation. A natural substance called resveratrol, which is present in several plants, red wine, and grapes, has been researched for its potential anti-inflammatory, and antioxidant qualities, and to induce relaxation of airway smooth muscle. The current study investigated whether Resveratrol (RES) could lessen allergic asthma that ovalbumin (OVA) causes in rats. Current results revealed that RES improved significantly (P<0.05) allergic asthma attenuation by decreasing the number of infiltrated mononuclear cells in Bronchoalveolar Lavage Fluid (BALF) and non-significantly (P>0.05) the number of infiltrated mononuclear cells intraperitoneally. RES increased lung integrity by reducing Evans blue extravasation in the lung (P<0.05) and liver (P>0.05). Additionally, in the BALF, RES therapy reduced (P<0.05) inflammatory cytokines including interleukin-17 (IL-17) and interferon-gamma (IFN-γ). RES increases (P<0.05) the expression of *Il10* gene in the spleen, which is associated with T-regulatory and anti-inflammatory processes in the immune system. Our findings showed that RES may reduce asthma by activating anti-inflammatory genes, restoring lung barrier integrity, and decreasing proinflammatory cytokines and infiltrating inflammatory cells.

Keywords | Asthma, Rat, Resveratrol, Ovalbumin, Cytokines.

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INTRODUCTION

Traditional classifications of asthma as an atopic disease triggered by allergens, affecting approximately 300 million individuals worldwide, have made it a significant public health concern (Masoli et al., 2004). Asthma has many signs such as bronchial hyperreactivity, clinical airway inflammation, and reversible airway obstruction. According to studies, asthma patients' lungs have T-helper-2 cells that play a role in controlling cytokine and immunoglobulin synthesis. Breathing difficulties, chest tightness, and a lingering cough are the clinical symptoms of asthma (Woodrow et al., 2023; Holgate et al., 2015).

In reaction to stress, injury, fungal infection, or UV exposure, phytoalexins are generated in plants (Aggarwal et al., 2004; Soleas et al., 1997). Resveratrol, a natural phytoalexin is known to possess multiple biological activities that were linked to human health (Brown et al.,, 2024). Even though resveratrol comes in both trans and cis isomers, it is thought that trans-resveratrol is the biologically active isoform because of its steric stability (Terla et al., 1996). Red wine, as well as different foods like grapes, peanuts, mulberries, and legumes, contain phytoalexin resveratrol. When resveratrol was found in red wine and used in traditional Chinese and Japanese medicine, it became clear that it has biological significance (Lopez et al., 2007). Resveratrol has been shown in many different studies to have positive impacts on cellular systems. The 'French Paradox' of France's high wine consumption shows that it pro-

tects against coronary heart disease (Shimuzu et al., 2005). Resveratrol is lipid-associated and prevents lipid oxidation (Gimeno-Mallenc et al., 2019; Delmas et al., 2007), prevents platelet aggregation (Stef et al., 2006) and also has antioxidant properties (Bhat et al., 2001). In the present investigation, the main hypothesis was that resveratrol could inhibit immune cell hyperactivation and proinflammatory cytokines caused by asthma and protect tissue integrity.

MATERIALS AND METHODS

Ethical statement

Before performing experimental procedures, the protocols of experiments were tested by an ethical committee to ensure compliance of the Animal Use Protocol with the guidelines of the University of Baghdad and then approved under reference number 1438/P.G. Animals and treatment.

Sixty adult male Wister albino rats, 8-week-old, weighing 195-200g on average were used in the current investigation. The rats were acclimated in the College of Veterinary Medicine's animal house at the University of Baghdad in Baghdad, Iraq. All animals were fed a standard pellet during the entire experiment period, provided with unlimited access to water, and housed in plastic cages with good ventilation and at temperature of 20 to 25 degrees Celsius. Throughout the experiment, the rats were subjected to 12-hour alternate periods of light and darkness. Twice a week, the bed was changed. Four equal groups of rats were formed at random. The initial group was regarded as naive (G1), the rats in the 2nd group (G2) were given daily 100 mg of resveratrol supplement orally for 14 days (Alghetaa et al., 2023), and the third group (G3) were sensitized with 100µl intraperitoneal injection of 250µg of ovalbumin (OVA) from chicken eggs (Sigma-Aldrich, USA) and aluminium hydroxide 4mg/ml on day 0. The mice that had been sensitized received 50 g of OVA suspended in 50 µl of sterile phosphate buffer saline intranasal on day 7 as described by Alharris et al. (2022). The rats in the fourth group (G4) were given mix treatment as in G2 and induction of asthma as in G3.

BALF collection and infiltrated mononuclear cells count

To obtain broncho alveolar lavage fluid (BALF), the trachea was sutured before the lung and trachea were surgically removed. To aspirate the fluid, sterile, ice-cold phosphate buffer saline was inoculated into the trachea. The gathered BALF was separated in a centrifuge to obtain the cytokine-containing supernatants. Enzyme-linked immunosorbent assay (ELISA) was done using MAXTM standard kits (Biolegend, California, USA) as per the manufacturer's workflow to identify the cytokines present in BALF (Sultan et al., 2021). The cells in the tubs after centrifugation were collected and stained count the number of infiltrated mononuclear cells with an autoanalyzer (Sultan et al., 2021).

Lung vascular leak measurement

Prior to killing the experimental animals, 100 µL of Evans blue stain (Sigma-Aldrich, USA) was administered intravenously two hours beforehand. The whole lung lobes were removed and preserved for 48 hours at 37 degrees Celsius in formamide (Fisher Scientific, USA) as described by Alghetaa et al, (2018).

Real-Time Quantitative PCR

According to Ahmed and Mohammed (2022), Q-PCR was used to ascertain the expression of *Il10* in the spleen. To this end, from each group, total RNA was extracted and utilized to create cDNAs using the Real MODTM Green W2 2x qPCR mix (Ahmed and Mohammed, 2022). Primer for *Il10* used was, Reverse: 5′AGGCTTGGCAACCCAAGTAA 3′ Forward: 5′ TCCGGGGTGACAATAACTGC 3′.

Statistical analysis

All collected data were statistically analyzed by utilizing the GraphPad Prism v8 Software (San Diego, CA, USA). Five mice per group were considered in each experiment, each experiment was repeated at least three times. The multiple comparisons were undertaken using a one-way ANOVA and then Tukey's post hoc analysis was performed. Statistics were deemed significant at $P<0.05$ (Mohammed et al., 2020).

RESULTS

Resveratrol attenuated the number of infiltrated mononuclear cells in BALF and intraperitoneal fluid.

As can be seen in Figure-1A, the number of infiltrated mononuclear cells in BALF in G3 group rats significantly ($P<0.05$) increased in comparison to the G1, G2, and G4 groups. Figure-1B showed no significant differences in the infiltrated mononuclear cells in the intraperitoneal fluid. Although, there is an insignificant elevation of the number of cells in the G3 group relative to other groups.

Resveratrol protects tissue integrity in the lung and liver

As shown in Figure-2A, the concentration of Evan blue extravasation in rat lungs in group G3 was significantly ($P<0.05$) increased in comparison to the G1, G2, and G4 groups. While in Figure 2B, there was no statistical difference in the level of Evans blue dye in the liver among the groups. However, the concentration of G3 was elevated in contrast to other groups.

Resveratrol decreased proinflammatory cytokines.

Figure-3A indicates that IL-17 level in BALF was significantly (P<0.05) higher in the G3 group than in the G1, G2, and G4 groups. Figure-3B reveals that IFN-γ cytokines dramatically raised (P<0.05) in the G3 group compared to the G1, G2, and G4 groups. In addition, there was a significant increase (P<0.05) in this cytokine in G2 and G4 groups in comparison to G1 group.

Splenic *Il10* gene validation

As shown in Figure-4, the *Il10* gene expression was significantly (P<0.05) downregulated in the G3 group rats compared to the G4 group. In addition, *Il10* gene expression statistically elevated (P<0.05) in the G2 group as compared to the G1, G3, and G4 groups.

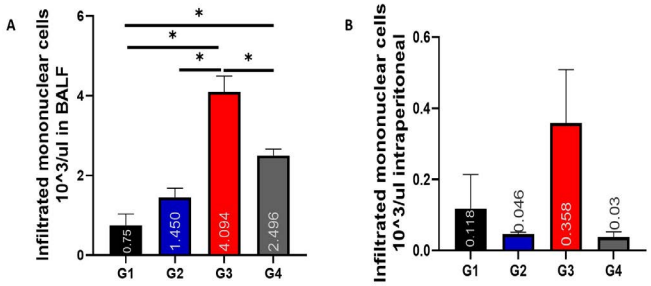

Figure 1: The effect of RES, Ova- induced Asthma, and their combination on the number of infiltrated mononuclear cells in BALF and intraperitoneal fluid in mature male rats. * P<0.05 is the statistical threshold for group differences. A: number of infiltrated mononuclear cells in BALF. B: Number of infiltrated mononuclear cells in intraperitoneal fluid. G1: rats received only drinking water, G2: Rats orally received resveratrol 100 mg/kg, G3: Rats were induced asthma, G4: Rats received both resveratrol and induced asthma.

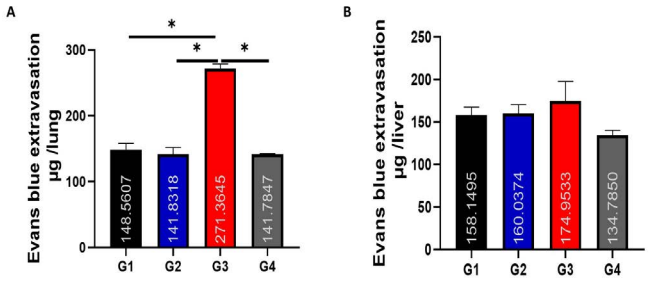

Figure 2: The effect of RES, Ova-induced asthma, and their combination on lung vascular leak by Evans blue dye in adult male rats * P<0.05 is the statistical threshold for group differences. A: Amount of Evans blue stain in the lung. B: Concentration of Evans blue stain in the liver. G1: rats received only drinking water, G2: Rats orally received resveratrol 100 mg/kg, G3: Rats were induced asthma, G4: Rats received both resveratrol and induced asthma.

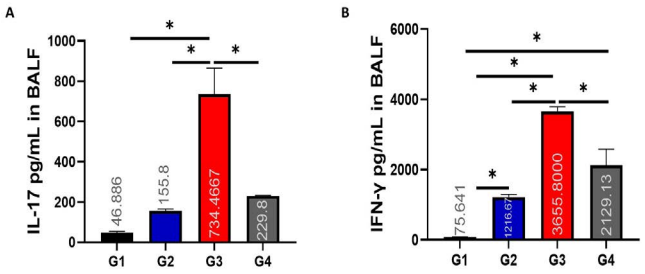

Figure 3: The effect of RES, Ova-induced asthma, and their combination on the concentration of IL-17 and IFN-γ in adult male rats. * P<0.05 is the statistical threshold for group differences. A: Concentration of IL-17 in BALF. B: Concentration IFN-γ in BALF. G1: rats received only drinking water, G2: Rats orally received resveratrol 100 mg/kg, G3: Rats were induced asthma, G4: Rats received both resveratrol and induced asthma.

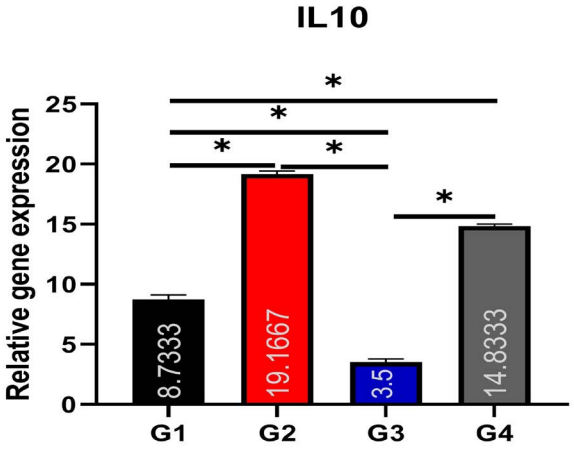

Figure 4: The effect of RES, Ova-induced asthma, and their combination on *Il10* gene expression in adult male rats. * P<0.05 is the statistical threshold for group differences. G1: rats received only drinking water, G2: Rats orally received resveratrol 100 mg/kg, G3: Rats were induced asthma, G4: Rats received both resveratrol and induced asthma.

DISCUSSION

The specific mechanisms by which resveratrol decreases the number of infiltrated mononuclear cells and reduces inflammation are not fully understood, but several proposed mechanisms have been studied. Resveratrol may exert its anti-inflammatory effects by reducing the quantity and kind of leukocytes in BALF (Zhang et al., 2014). Additionally, a cytogenetic analysis of resveratrol on healthy human blood lymphocytes showed a significant reduction of the mutagen's ability to induce mitosis (Mohammed et al, 2011). Previous published research demonstrated that resveratrol may ameliorate asthma by preventing the production of inflammatory mediators, increasing airway remodeling, and suppressing inflammation that is brought

on by asthma (Alharris et al., 2018). However, there is limited scientific evidence available to support the claim that resveratrol directly reduces tissue permeability. In order to evaluate the impact of the inflammatory process on the integrity of the mucosal barrier, alveolar epithelial cells type II were cultured with splenocytes that had been pre-treated with RES (Alghetaa et al., 2021). Although, most of the research on resveratrol's anti-inflammatory effects has focused on its modulation of inflammatory signaling pathways and immune cell function, rather than its impact on tissue permeability. Resveratrol markedly attenuated the effects of H2O2 on the defect *Tunica albuginea*, disorganized germ cells, necrosis of spermatogonia, and azoospermia (Abdulla et al., 2022). The physical barrier may be protected by resveratrol, which may be connected to the control of tight junction protein expression and the reduction of oxidative stress (Buckley et al., 2018). In male rats, hydrogen peroxide-induced kidney damage was lessened by resveratrol (Khudair and Al-Okaily, 2022). In dogs with *T. brucei* infection, resveratrol administration reduces oxidative stress and liver damage (Chigozie et al., 2022).

IL-17 is a pro-inflammatory cytokine produced by various immune cells, including T helper 17 (Th17) cells. It plays a role in the recruitment and activation of immune cells during inflammation. Resveratrol has been found to inhibit the production of IL-17 by suppressing the differentiation of Th17 cells and reducing their activity. By reducing IL-17 levels, resveratrol may help attenuate the inflammatory response (Manni et al., 2014) which was also observed in our study. Contrasted with the control and vaccination groups, the transfer factor recipient lambs' serum levels of the cytokines IL-17, IFN, and MIF was significantly higher. According to the findings, the generated particular *M. bovis*-BCG transfer factor was successful in raising the serum level of cytokines in recipient lambs and causing cell-mediated immunity via delayed-type hypersensitivity (Elaf et al., 2021). IFN-gamma is another pro-inflammatory cytokine that is primarily produced by natural killer (NK) cells and activated T lymphocytes. It has an impact on promoting inflammation and enhancing immune responses. Resveratrol has been administered to lower the production of IFN-gamma, and IL-2 by T cells and NK cells. By reducing IFN-gamma levels, resveratrol may help modulate the immune response and potentially alleviate inflammation (Fuggetta et al., 2016). Lung tissue is not just affected by inflammation; exposure to dietary additives, such as monosodium glutamate, can result in a variety of histopathological alterations, such as a significant infiltration of inflammatory cells, emphysema, hemorrhage, hyperplasia, and endothelial cell hypertrophy. In addition, fibroid deposition all over the bronchioles, particularly in pregnant women (Sanabel et al., 2022). In vitro, IL-1, IL-6, and TNF-gamma production were shown to be dose-dependently suppressed by resveratrol, and IL-17 mRNA expression and protein release were reported to be downregulated (Gao et al., 2001). Following thoracic surgery, tissue damage, or lung infection all contributed to the infiltration of inflammatory cells. Additionally, the release of cytokines by inflammatory cells within the wounded tissue would draw them to the injury site (Al-Hyani, 2023). The potential cancer treatment properties of resveratrol, which can disrupt erroneous signaling mechanisms in altered colorectal cancer (HRT) cell lines, are thought to be the main causes of this impact (Khayoon and Al-Rekabi, 2021). Immune cells, especially regulatory T cells, release the anti-inflammatory cytokine *Il10*. It has strong anti-inflammatory properties and can stop other immune cells from producing cytokines that cause inflammation. It has been shown that resveratrol increases *Il10* production, adding to its anti-inflammatory effects (Song et al., 2014). Also, by reducing ROS and nitric oxide (NO) production, resveratrol can produce anti-inflammatory effects across a variety of illnesses, including long-term inflammation and tumors, oxidative stress brought on by the buildup of ROS contributes to inflammation (Meng et al., 2021). Resveratrol is well-defined for its anti-inflammatory and antioxidant properties. In the preclinical trial of significant respiratory disorders including chronic obstructive pulmonary disease (COPD), it has already been shown that resveratrol has a shield-like function in disorders of the respiratory system (Liu et al., 2016). The therapeutic effect of RES in reducing inflammation and avoiding lung injury through a variety of possible molecular pathways was demonstrated using a variety of procedures to create acute lung inflammation. Similar research demonstrated that RES therapy enhances lung structural changes, reduces pulmonary edema, enhances lung function, and reduces neutrophil infiltration as well as myeloperoxidase protein production and activity in lung tissue (Cao et al., 2011; Zhang et al., 2014). Resveratrol has positive impacts on the body via decreasing superoxide levels, activating potassium channels, and increasing endothelium-dependent vasodilation (Goh et al., 2007).

CONCLUSIONS

Resveratrol increases *Il10* gene expression, which had a significant effect on immune responses by reducing excessive inflammation and promoting immunological tolerance. Additionally, resveratrol improved tissue integrity and remodeling of the lung tissue after asthma induction, featured by lowering the number of infiltrating cells as well as extravasated Evans blue stain.

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CONFLICTS OF INTEREST

None.

AUTHORS DECLEARATION

We hereby confirm that all the Figures in the manuscript are ours.

ETHICAL CLEARANCE

The project was approved by the local ethical committee in the College of Veterinary Medicine at the University of Baghdad and received approval to conduct this scientific investigation in file No. 1438/P.G.

NOVELTY STATEMENT

This study has linked between the anti-inflammatory properties of resveratrol with the outcomes of asthma condition through enhancing the pulmonary-blood barrier integrity.

AUTHORS' CONTRIBUTION

Amira Mohammed designed all the experiments. Bushra AL-Khaqani performed all experiments, collected the data, and wrote the draft of the manuscript. Amira Mohammed contributed to analyses of the data to finalize the manuscript for journal submission. All authors checked and approved the final version of the manuscript for publishing in the Journal of Animal and Health Production.

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