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Original Article

Pulmonoprotective Action of *Zataria Multiflora* in an Experimental Model of Lung Inflammation Induced by Ochratoxin-A in Mice

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A B S T R A C T

Introduction: Ochratoxin-A (OTA) represents one of the primary secondary metabolites produced by Penicillium and Aspergillus species. Acratoxin was recognized in 1965 as the most significant carcinogenic mycotoxin found in agricultural products. Given that the vital function of the lungs in maintaining other bodily organ system, it was examined the role of the *Zataria multiflora* extract in an experimental model of lung inflammation induced by Ochratoxin-A in mice.

Materials and Methods: This study was designed around a 14-day gavage administration of OTA in mice. Markers of oxidative stress and apoptotic factors (Bax/Bcl2, Caspase 3 Caspase 9) were also evaluated.

Results: OTA-induced toxicity provokes lung inflammation and apoptosis in a dose-dependent manner. The administration of *Zataria multiflora* (at dosages of 25 and 50 mg/kg) resulted in a significant alleviated of lung inflammation, oxidative damage, inflammatory cytokines, and levels of apoptosis protein when compared to the group treated with OTA alone.

Conclusion: The results of the study indicate that *Zataria multiflora* exerts robust antioxidant effects that counteract the inflammation and apoptosis associated with OTA-induced toxicity in lung tissue.

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Introduction

Mycotoxins are among the most important metabolites produced by fungi and can exert diverse physiological effects [1]. Mycotoxins come in a variety of forms; six groups of them have significant toxic effects produced by *Fusarium, Alternaria, and Penicillium* and *Aspergillus* groups [2]. Ochratoxin-A (OTA) produced by a broad spectrum of fungi -especially *Aspergillus ochraceus*- is a white crystalline substance that dissolves readily in fats and polar organic solvents [3, 4]. OTA has been reported in a wide range of food sources, including cereals, coffee, dried fruits, grape juice, and meat products [5-7]. Nonetheless, cereals and cereal-based items are known the primary contributors to human exposure. OTA, which has the chemical formula C20H18O6NCl, is regarded as a major mycotoxin that shows good solubility in polar organic solvents [8, 9]. According to the American Cancer Research Institute, OTA is categorized as a class B carcinogen. Among more than 300 known mycotoxins, OTA stands out as a key toxin with immunotoxic, and nephrotoxic properties [10, 11]. This toxin negatively affects the kidneys and liver and can cross the placenta; it also causes vasoconstriction and suppresses immune system activity [12, 13]. Due to its particular features related to cellular toxicity, OTA is considered as major contributor to infertility, including male infertility and fetal mortality [12, 14].

OTA inhibits cell proliferation, suppresses B and T lymphocytes, degrades immune organs, and decreases antibody production. It alters cytokine production, which affects both the number and function of immune cells. OTA inhibits the death of immune cells by inhibiting protein synthesis by intensifying the death of immune cells and reducing their replacement rate [15].

Alongside its liver damage, nerve damage, immune damage, teratogenesis, and carcinogenesis of OTA, authors indicated that it easily effects on bronchial epithelial cells- within four hours of human exposure) [16, 17]. Various studies have shown that OTA specifically induces oxidative stress and activates the Nrf2 signaling pathway, ultimately leading to cytotoxicity and cell death [17, 18]. Another study by Okutan et al. similarly reported OTA's toxic effects on the lungs and heart, noting that oxidative stress and degradation of cellular proteins are the main mechanisms responsible for toxicity in these organs [19]. Despite numerous studies into OTA's toxicity, no study has yet clarified the molecular mechanisms OTA-induced lung damage or examined the protective effect of *Zataria multiflora (Z. multiflora)* In this context. *Z. multiflora* is a perennial plant known for its wide range of medical benefits and has attracted researchers' attention for many years [21-23]. Iran and Afghanistan are recognized as the primary regions fot the growth and distribution of this species. Studies highlight their notable soothing and anti-inflammatory properties. In Iran, *Z. multiflora* is commonly used for its anti-inflammatory and antiseptic actions. The antioxidant effects of this plant are due to its most important active ingredient called Carvacrol [24, 25]. It affects the muscarinic

receptors and β-adrenoceptors receptors [26]. Numerous therapeutic effects have been demonstrated for both the plant and Carvacrol, especially regarding respiratory disorders. Another pharmacological action of Carvacrol is its ability to reduce cell death. Therefore, it was examined OTA-induced pulmonary inflammation and apoptosis in mice, as well as the protective effects of *Z. multiflora* and carvacrol in an experimental model of pulmonary inflammation.

Materials and Methods

Chemicals

OTA, glutathione (GSH), MDA, SOD, catalase (CAT), Thiol, NO and other materials were purchased from Sigma-Aldrich, (St. Louis, MO, USA). Anti-serum against β-actin, BAX, Bcl2, Caspase 3-9-cleaved (Respectively #4970, #2772, #2870, #9664, #7237). In addition, anti-mouse and rabbit horse radish peroxidase labeled IgG (#7076 and #7074, Cell Signaling, USA) were used for check protein levels by western blot method. For Nrf2 pathway analysis (1: 1000) diluted of anti-Keap1, anti-Nrf2, anti-MnSOD, anti-HO-1, anti-toll-like receptor 4 (TLR4), anti-tumor necrosis factor (TNF)-α, interleukine (IL)-1β, IL-6 and IL-10 were used (Sigma- Aldrich, St. Louis, MO, USA).

Animals and the experimental protocol

In this research 30 male albino mice (weighing 20 to 30 g) were purchased and randomly divided into 5 groups (n=6). Animals were housed in cages at 22 ± 1 °C with temperature conditions of 26-19 26 °C, relative humidity of 70-75%, light intensity of 300 lux, exposure of 12: 12 (light / dark), in additions food, water, and everything else they needed was available in sterile conditions.

Adult mice received a dose of OTA (0.5 µg/kg) by gavages in 14 day. Group 1: control group normal saline (0.5 µg/kg); Group 2: OTA (0.5 µg/kg) negative control group; Group 3: OTA (0.5 µg/kg) + *Zataria multiflora* (ZM) (25 mg/kg); Group 4: OTA (0.5 µg/kg) + ZM (50 mg/kg); Group 5: Vitamin E 20 mg/kg + OTA (2µg/rat) were treated group.

Biochemical assessment

After treatment, the animals were sacrificed, and their lung tissues were dissected and kept at -80 °C for biochemical analyses. The samples were homogenized in ice-cold normal saline at a volumes of 9 g/L (1: 9 w/v). After centrifuging the homogenates at 4000 rpm/min for 10 min at 40 °C, the supernatant was collected for testing [27]. A spectrophotometer (Jenway 6105 UV/Vis, UK) was used according to the procedures outlined in the assay kits. The broncho alveolar fluid (BALF) supernatants were used for the evaluation of activities of MDA, GSH, SOD, Thiol, NO and CAT [28, 29].

Western blotting

The western blot technique was employed to study molecular damage induced by OTA. Lung tissues from mice were homogenized and the extracted proteins were separated, then transferred from the gel onto a proteins-binding membrane such as nitrocellulose, where their positions are preserved [30, 31]. Antibodies were used as the primary means of detecting specific proteins in the membrane. Protein concentrations were measured in the tissue supernatant with a protein measurement kit. All separation and

detection steps followed kit protocols and referenced other studies [32, 33].

Histopathological analysis

At the end of the treatment period, the animals were sacrificed and their lungs were maintained in 4% paraformaldehyde. Washed lung tissue samples were embedded in paraffin and cut into 5 µm sections for histopathological studies. Hematoxin and eosin (H&E) as well as periodic acid-Schiff (PAS) staining were used to investigate damage scores [34, 35].

BALF analysis

To examine the BALF, the trachea was first washed using phosphate-buffered saline (PBS), and lavage fluid was recovered. Protein concentration (Beyotime Kit, China) and number of cells (Beckman Coulter) were measurred in the collected samples [36].

Wet-to-dry (W/D) ratio assay

To determine the W/D lung weight ratio, lung samples were dried in an oven at 60 °C for 7 days and their weights were recorded [32]. After drying again, the weights were reassessed, and the W/D ratio was calculated [31, 37].

Evaluation of myeloperoxidase (MPO) activity

MPO is a leukocyte-derived enzyme that generates reactive oxidant species, making it usefulas an additional indicator of inflammation and tissue damage. MPO activity is quantified based on the reaction between Tetramethyl benzidine (TMB) and H_2O_2, which is read at a wavelength of 650 nm. Neutrophil levels rise substantially during pulmonary inflammation. Pulmonary homogeneous samples are prepared and measured based on the kit protocol [38]. MPO detection followed the manufacturer's guidelines for the mouse MPO Nampox™ MPO activity assay kit.

Statistical analysis: All statistical analyses were performed using one-way ANOVA, followed by Tukey's post hoc test. A P-value lower than 0.05 was considered statistically significant. Partial Eta-squared values were also reported to represent effect sizes.

Results

Extract characterization

Z. multiflora extract, provided by the Pharmacological Research Center of the School of Medicine, was prepared using a Soxhlet extraction system and then analyzed by high-performanceliquid chromatography (HPLC) to check the concentration of the active compound, carvacrol. The results of HPLC confirming the presence of carvacrol in the extract are presented in Fig. 1.

Effect of *Z. multiflora* on oxidative stress

As shown in Fig. 2A and F, exposure to OTA (0.5 µg/kg) significantly increased level of MDA and NO as compared to control respectively ($P < 0.001$). Treatment with *Z. multiflora* (25 and 50 mg/kg) and Vitamin E (20 mg/kg) reduced MDA content in comparison with OTA (0.5 µg/kg) ($p<0.01$, $p < 0.001$). In the OTA (0.5 µg/kg) treated group, GSH content was decreased in lungs (Fig. 2B, $p<0.01$, $p<0.001$).

Treatment with *Z. multiflora* (25 and 50 mg/kg) and Vitamin E (50 mg/kg) significantly increased GSH content compared to OTA treated rats ($p<0.001$). Similar results have been obtained from CAT (Fig. 2C, $p<0.01$-$p < 0.001$) and SOD (Fig. 2D, $p < 0.001$ for all cases). According to results Thiol level as well as CAT

and SOD activities were decreased (Fig. 2E, p<0.01- p<0.001).

Effect of *Z. multiflora* on apoptotic factors (Bax/Bcl‑2, Caspase 3 and Caspase 9)

As indicated in Fig. 3A protein expression of Bax/Bcl2 was increased in OTA group (P<0.001). In addition, the protein levels of cleaved caspases 3 and 9 were up-regulated by administration of OTA (0.5 µg/kg). Co-treatment of OTA (0.5 µg/kg) with *Z. multiflora* (25 and 50 mg/kg) or vitamin E significantly decreased the ratio of Bax/Bcl2 in comparison with OTA group (p<0.001 and P<0.001, respectively). Furthermore, administration of *Z. multiflora* (25 and 50 mg/kg) or vitamin E (50 mg/kg) plus OTA inhibited the activation of caspases 3 and 9 (Fig. 3B and C).

Effect of *Z. multiflora* on the structural damage in mice lungs

Structural alternations associated with lung inflammation are shown in Fig. 4. H&E (A) and PAS staining (B) were performed to observe the lung injury score (C), W/D ratio (D), evaluation of total protein content, and (E) lung inflammatory cell counts in BALF from different groups. (F) Lung MPO activity was also determined among the groups (G) (p<0.01- p<0.05- p<0.001).

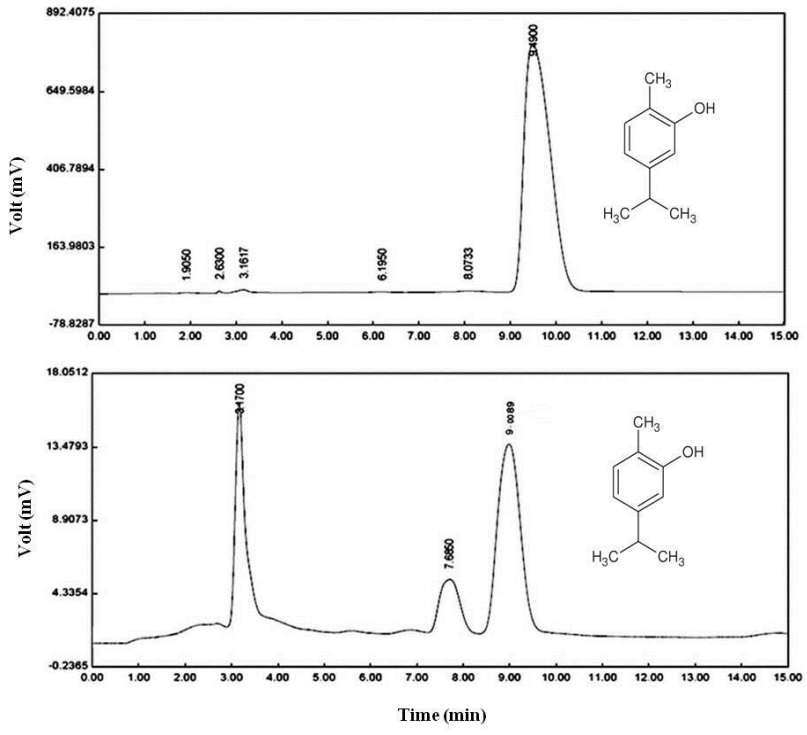

Fig. 1: The results of high-performanceliquid chromatography based on the presence of the active ingredient carvacrol in the *Z. multiflora* (50 mg/kg) extract. (C10H14O, 5/1000)

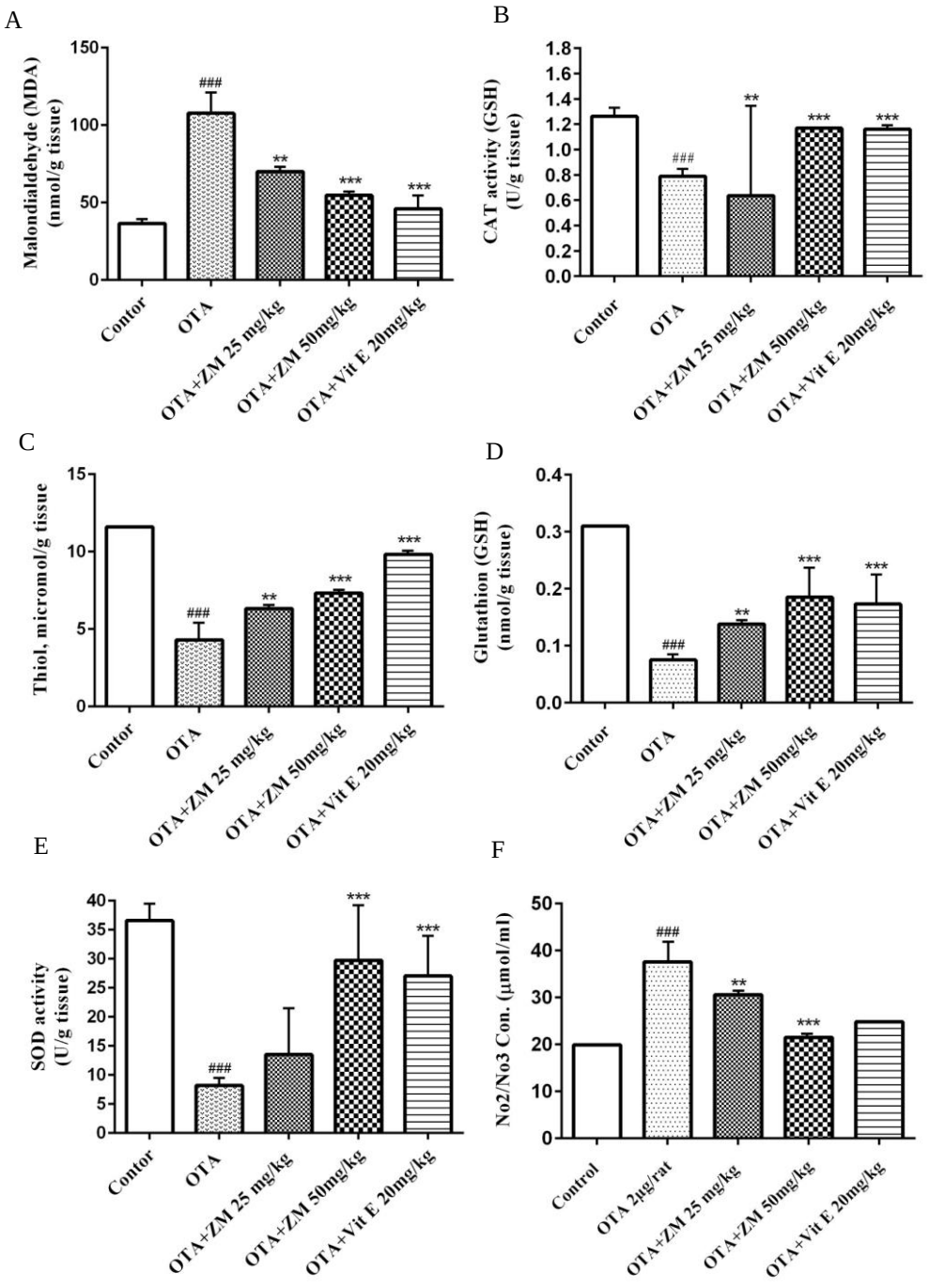

Fig. 2: Effects of *Zataria multiflora* (ZM) extract on Malondialdehyde (MDA) concentrations (A), Glutathione (GSH) (B), Catalase (CAT) activity (C), SOD activity (D), Thiol (E) and NO_2 (F) in the lung tissues mice's. $^{###}p<0.001$ vs. control, $^{***}p<0.001$ compared to Ochratoxin A group. *Zataria multiflora* resin (Carvacrol). OTA= Ochratoxin-A; Vit E= Vitamin E

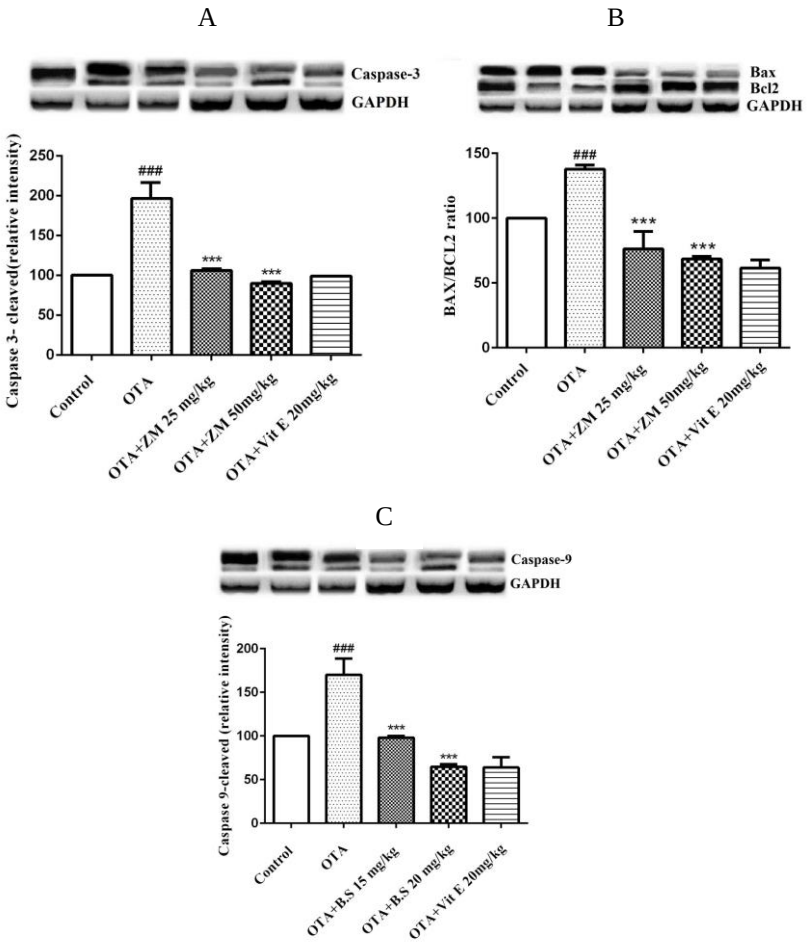

Fig. 3: Effects of *Zataria multiflora* (ZM) (25 and 50 mg/kg) on expressions of apoptotic factors following exposure to Ochratoxin-A (OTA) in mice's. The blots and the bars exhibiting the densitometry analysis of western blots for Bax/Bcl-2 (A) ratio, Caspase 3 (B) and Caspase 9 (C) proteins, consecutively. $^{###}$P<0.001 vs. control, **P<0.01 and ***P<0.001 compared to OTA-administered mice's.

Discussion

The results of the present study investigated the antioxidant, and anti-inflammatory properties of *Z. multiflora* and its constituent, carvacrol in an experimental model of lung inflammation induced by OTA in mice. Although various studies have documented OTA toxicity in the brain, heart, and kidneys, this study highlights its considerable ability to trigger inflammation, apoptosis, and destruction in lung tissue [39, 40]. Previous studies have revealed that OTA can cross the blood-brain barrier and exert neurotoxic effects in laboratory rodents [41, 42]. The experimental examined pulmonary toxicity, apoptosis, and OTA-induced inflammation following 14 days of treatment in rats. After the administration period, the animals were examined for weight changes, and the results showed an increase in weight in the samples. The study again elevated pulmonary toxicity, apoptosis, and OTA-induced inflammation after 14 days of gavage administration in treated rats. Post-treatment examination also revealed weight gain in the samples.

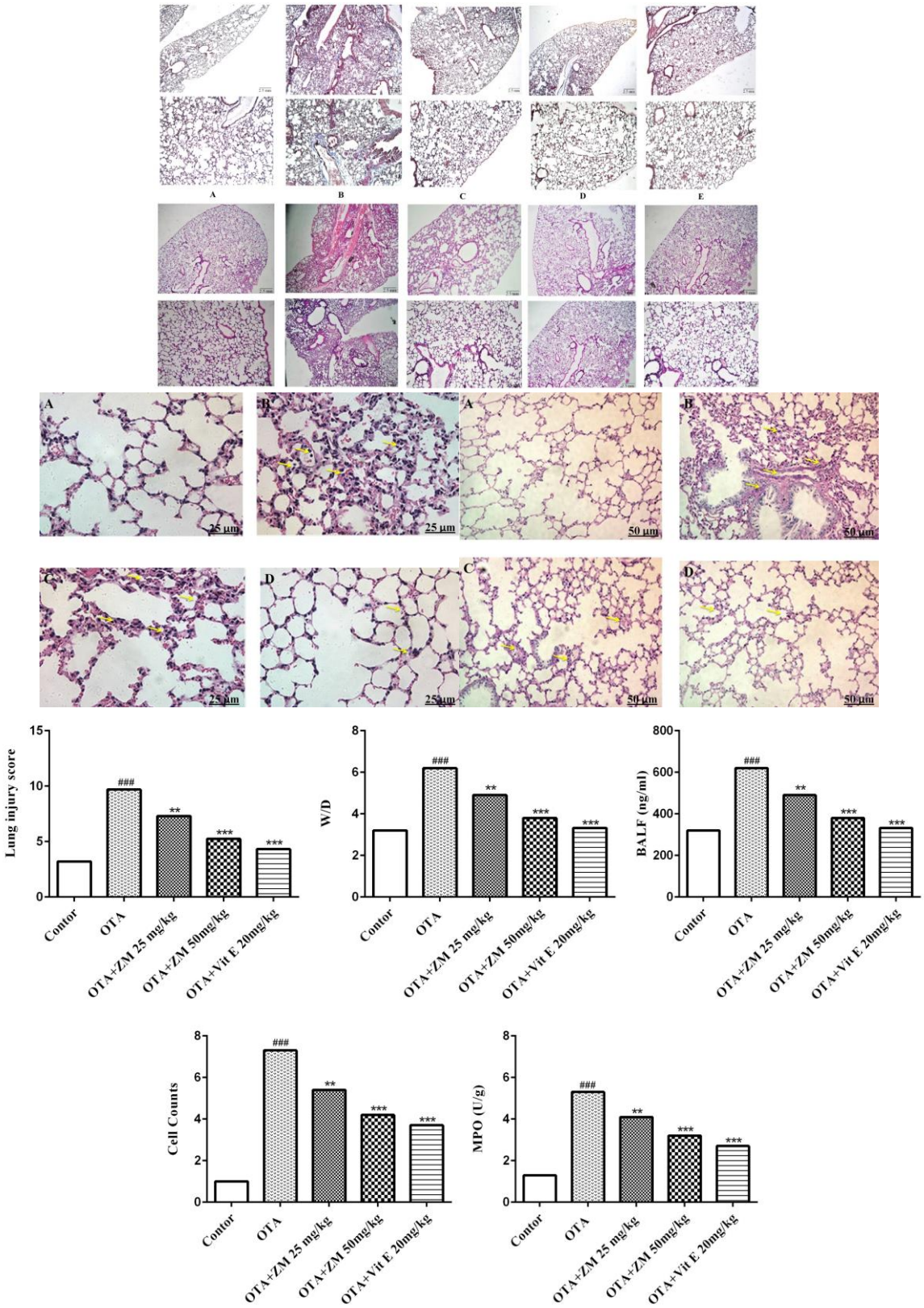

Fig. 4. Effects of *Zataria multiflora* (ZM) in structural damage of lung inflammation. H&E (A) and PAS staining (B) were performed to observe the lung injury score (C), wet-to-dry ratio (D), evaluation of the Broncho alveolar lavage fluid (E) lung inflammatory cell counts in broncho alveolar fluid from different groups (F) and evaluation of myeloperoxidase (G). OTA= Ochratoxin-A; Vit E= Vitamin E

Pathobiological studies indicate inflammation and tissue destruction in groups that received OTA. The results show the antioxidant and anti-inflammatory effects of *Z. multiflora* receptor groups.Our results indicated that lung levels of MDA and NO metabolites were significantly increased, whereas GSH, CAT and other oxidative-stress-related indicators such as thiol and SOD displayed a significant reduction in the OTA-exposed groups. The results of antioxidant studies align with other research demonstrating that OTA induces oxidative stress in treated specimens [43-45]. According to the present results, apoptosis was particularly observed in toxin-exposed groups. The proteins in this family, especially Bcl-2 and Bax, regulate the apoptotic pathway. By determining the ratio of these two proteins, the rate of cell death can be determined. Activation of these pathways at the cellular level can lead to the formation of apoptosis and eventually the activation of caspases (especially caspase-3, and caspase-9) [46].

Given that Nrf2 is a key pathway in examining the rate of inflammation in various organs and tissues, it was examined the most important factors involved in this pathway. Various studies have shown the effective role of Nrf2 in many diseases caused by oxidative stress [47]. Consequently, it was examined proteins involved in this pathway. Antioxidant enzymes in this pathway such as HO-1, and MnSOD, which are regulated by Nrf2, contribute to pathogenesis when altered [48]. According to the results of other researchers on the anti-inflammatory effects of *Z. multiflora* [39], the results of this study indicate a decrease in inflammatory factors in the groups receiving *Z. multiflora*. So far, the analgesic and anti-inflammatory effects of the total extract and the essential oil and flavonoid fractions of this plant have been studied. Key inflammatory mediators include TNF-α, IL-1β, and IL-6. Although the results of this study are similar to those of other studies in terms of the anticancer effects of Z. *multiflora* [49] and the toxic effects of OTA, due to the increase in the level of inflammatory factors as well as OTA appears to cause a specific toxicity in the lung tissue.

According to the results of this study and the toxic effects of OTA and the activation of apoptosis signaling pathways, the protective effects of *Z. multiflora* and its combination with carvacrol has a special ability in an experimental model of lung inflammation.

Conclusions

Our study demonstrated that apoptosis signaling pathways, oxidative stress and inflammation were involved in OTA-induced experimental model of lung inflammation. The present study showed a significant reduction in oxidative stress, inflammation, and apoptosis in the samples receiving *Z. multiflora* through the apoptosis signaling pathway.

Ethical Considerations

The study was approved by the research ethics of Islamic Azad University of Shahrekord, NUM:1402.049.

Funding Statement
The responsible author covered the experiment and other associated costs.

Conflict of Interest
The authors declared no conflict of interest.

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Data Availability Statement
The data presented in this study are available on request from the corresponding author.

Authors' Contributions
F.N. and H.C.M. were responsible for designing the review protocol, conducting the literature review, providing feedback on the manuscripts, writing the manuscript and improving the interpretation of the results. M.S. and E.T. were responsible for writing the manuscript, assembling data, analyzing data, and interpreting analyses.

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