

Protective Effects of Walnut (*Juglans regia* L.) Septum Extract Against Isoniazid-Induced Pulmonary Inflammation in Rats

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ABSTRACT

Aim: Isoniazid (INH) is a first-line antituberculosis drug that can induce oxidative stress and tissue damage. Walnut (*Juglans regia* L.) septum extract contains high levels of antioxidant compounds with potential therapeutic applications. This study aimed to investigate the protective effects of walnut septum methanolic extract against isoniazid (INH)-induced pulmonary inflammation in rats.**Material and Methods:** Thirty-two adult male Wistar-Albino rats (250-300 g) were randomly divided into four groups (n=8): Control (saline), INH (400 mg/kg), INH + walnut septum extract 100 mg/kg, and INH + walnut septum extract 250 mg/kg. All treatments were administered orally for 7 consecutive days. Lung tissues were analyzed for lipid peroxidation (LPO), glutathione (GSH), and catalase (CAT) levels, accompanied by comprehensive histopathological examination.**Results:** INH administration significantly increased LPO levels and decreased GSH content and CAT activity in lung tissue compared to controls (p<0.05). Walnut septum extract dose-dependently reduced LPO levels and restored GSH content and CAT activity. Histopathologically, INH induced interalveolar cellular infiltration and peribronchial lymphoid tissue hyperplasia. Walnut septum extract, particularly at 250 mg/kg, significantly preserved normal pulmonary architecture and attenuated inflammatory changes.**Conclusion:** Walnut septum methanol extract exhibited significant protective effects against INH-induced pulmonary inflammation likely through its antioxidant properties, suggesting potential therapeutic value in preventing INH-associated pulmonary toxicity.**Keywords:** Isoniazid, walnut septum, pulmonary inflammation, oxidative stress, antioxidant activity.

INTRODUCTION

Tuberculosis (TB) remains a significant global health threat, representing one of the most serious bacterial infectious diseases affecting humanity throughout history. This disease, caused by *Mycobacterium tuberculosis*, primarily affects the lungs and can be fatal if left untreated. The advent of antituberculosis chemotherapy marked a pivotal milestone in modern medicine, transforming TB from a predominantly fatal disease to a treatable condition. Isoniazid (INH), one of the cornerstone drugs in tuberculosis treatment, is utilized both for treating active disease and as prophylactic therapy in high-risk individuals to prevent disease development (1).

INH exerts its antimycobacterial effect by targeting specific components of the *Mycobacterium tuberculosis* cell wall, thereby inhibiting bacterial growth and replication. This medication is typically administered in combination with other anti-tuberculosis agents to enhance therapeutic efficacy and reduce the risk of resistance development. Despite its proven efficacy in active tuberculosis treatment, the clinical utility of INH is significantly limited by its adverse effect profile (2,3).

The most commonly reported adverse effects associated with INH therapy include gastrointestinal disturbances, hepatotoxicity, peripheral neurotoxicity, and central nervous system-related complications (4). These adverse effects can significantly complicate the treatment process

and increase therapy-related morbidity, potentially leading to treatment discontinuation and therapeutic failure. Although the primary target organs of INH toxicity are the liver and peripheral nervous system, after oral absorption, INH is rapidly distributed to almost all body fluids and tissues, including the bronchi and pulmonary alveoli (2,3). Reactive metabolites formed during INH metabolism, particularly hydrazine and acetylhydrazine, can also cause oxidative stress in lung tissue (4). Furthermore, CYP2E1, a key enzyme involved in the oxidative metabolism of INH metabolites and the formation of reactive oxygen species, has been shown to be expressed in bronchial, bronchiolar, and alveolar epithelium, as well as in alveolar macrophages; this provides a mechanistic basis for INH-induced pulmonary oxidative damage (5,6).

Oxidative stress emerges as one of the principal mechanisms underlying INH-induced cytotoxicity. This pathological condition occurs when excessive reactive oxygen species (ROS) are generated within cells, overwhelming the endogenous antioxidant defense systems and resulting in cellular damage to vital macromolecules.⁴ Research has suggested that INH metabolism may contribute to elevated ROS generation, which can perpetuate cellular damage and tissue injury through oxidative mechanisms (2,5-8).

In this context, natural plant extracts with antioxidant

properties have attracted considerable interest as potential therapeutic agents for preventing oxidative stress-mediated damage. These bioactive compounds may counteract the harmful effects of ROS, thereby potentially mitigating cellular damage during treatment.

The walnut (*Juglans regia* L.) belongs to the Juglandaceae family and is an economically important tree species cultivated worldwide, particularly in the Americas, Mexico, and Asia. In Türkiye, walnut cultivation is primarily concentrated in the Northeastern and Eastern Anatolia regions. Comprehensive physicochemical analyses have revealed that walnut components contain exceptionally high concentrations of fatty acids, proteins, phytosterols, and various phenolic compounds (9).

The phytochemical profile of walnut (*Juglans regia* L.) septum is characterized by a rich array of bioactive compounds, including juglone (5-hydroxy-1,4-naphthoquinone), ellagic acid, gallic acid, tannins, and flavonoids (9,10). Among these compounds, juglone is the most pharmacologically distinctive constituent of the *Juglandaceae* family and is present in notably high concentrations in the septum fraction. Juglone has demonstrated both antioxidant and pro-oxidant properties depending on the cellular redox environment; while it can quench reactive oxygen species under certain conditions. It is also capable of undergoing redox cycling to generate superoxide radicals, particularly at higher concentrations (11). Ellagic acid and gallic acid, both hydrolysable tannin-derived compounds abundant in walnut septum, are well-established free radical scavengers with potent anti-inflammatory activity (9). The methanol extraction solvent employed in the present study has been reported to yield the highest total phenolic content and antioxidant capacity from walnut septum fractions (10).

Walnut septum has been reported to possess high antioxidant content and demonstrate potent radical scavenging activity (11,12). Based on these properties, the present study was designed to evaluate the protective effects of walnut septum extract against isoniazid (INH)-induced pulmonary injury, with the hypothesis that its rich bioactive compound profile may attenuate oxidative stress and associated tissue damage.

MATERIAL AND METHODS

Experimental Protocol and Animals

The experimental design included 32 adult male Wistar-Albino rats weighing 250-300 g, randomly allocated into four distinct groups (n=8 per group). Prior to experimental procedures, all animals underwent a 7-day acclimatization period to ensure adaptation to laboratory conditions. Extracts and pharmaceutical agents were prepared at appropriate concentrations and administered at literature-validated dosages for 7 consecutive days. The administration sequence and timing were kept consistent throughout the experimental period (3,13).

Group 1 (n=8) Isoniazid Group: Animals received isoniazid (400 mg/kg) dissolved in physiological saline for 7 days via oral gavage.

Group 2 (n=8) Walnut Septum Methanol Extract 100 mg/kg: Animals received walnut septum extract (100 mg/kg) dissolved in physiological saline for 7 days via oral gavage. Thirty minutes after extract administration, isoniazid (400 mg/kg) was administered via oral gavage.

Group 3 (n=8) Walnut Septum Methanol Extract 250 mg/kg: Animals received walnut septum extract (250 mg/kg) dissolved in physiological saline for 7 days via oral gavage. Thirty minutes after extract administration, isoniazid (400 mg/kg) was administered via oral gavage (13).

Group 4 (n=8) Control Group: Animals received physiological saline for 7 days via oral gavage. All administrations were performed at the same time each day to ensure standardization and minimize circadian variations. Although methanol was used during the extraction process, it was completely removed by evaporation under low pressure using a rotary evaporator prior to application. To ensure standardization, all substances were dissolved in physiological saline. In this way, the potential biological effects of methanol were eliminated (14-16). The dosages of walnut septum extracts were selected based on literature-supported phenolic potency, reducing capacity, and antioxidant properties. Following the 7-day treatment period, animals were sacrificed 24 hours post-final administration using high-dose anesthesia. Lung tissues obtained post-sacrifice were subjected to comprehensive biochemical and histological analyses.

The absence of a walnut-only group was based on previously published safety data demonstrating significant oxidative or inflammatory effects of *Juglans regia* extracts at comparable doses in rodent models, and was further constrained by the number of animals approved under the institutional ethics protocol (16,17).

Pharmaceutical Agents

Isoniazid (INH): The INH dosage selection (I.N.H. 300 mg Tablet, Koçak Pharma) was based on established literature protocols (13).

Preparation of Walnut (*Juglans regia* L.) Septum Methanol Extract

Walnuts were obtained from authorized vendors and cracked to extract the inner septums. The collected septums were pulverized using liquid nitrogen in a mortar to achieve fine powder consistency. Four hundred grams of pulverized walnut septum samples were subjected to methanol extraction using a shaking water bath for seven days (methanol 60°C, 200 ml ×8 extractions). The extracts were filtered, dried, and the well-drained methanol extract was administered to experimental animals.

Tissue Collection and Preparation for Biochemical Analyses

Following experimental procedures, animals were euthanized using high-dose anesthetic agents (xylazine hydrochloride 300 mg/kg, ketamine hydrochloride 40 mg/kg). Excised lung tissues were initially cleaned with physiological saline, with portions preserved in 10% buffered formaldehyde solution for histological examination. Histopathological evaluations were performed by an independent pathologist blinded to the experimental group assignments. Findings were assessed descriptively using hematoxylin and eosin stained sections. Remaining tissue samples were stored at -80°C for biochemical enzyme analyses.

Lung tissues were pulverized using liquid nitrogen in a mortar to achieve powder consistency. From each tissue sample, 0.5 g was weighed and 4.5 ml of appropriate buffer solutions (utilizing different buffer systems for each parameter) were added. Samples were homogenized using an ultra-turrax homogenizer for 10 minutes on ice.

Homogenates were filtered through filter paper and centrifuged using a refrigerated centrifuge at literature-specified speeds at 4°C for each enzyme. The resulting clear supernatant was utilized for biochemical enzyme activity determinations.

Lipid Peroxidation (LPO) Determination: Lipid peroxidation levels in lung tissue were assessed by measuring malondialdehyde (MDA) content using the thiobarbituric acid reactive substances (TBARS) method as described by Ohkawa et al. (18).

Total Glutathione (GSH) Determination: Total reduced glutathione (GSH) levels were measured using an established method with minor modifications (19). Following homogenization of the brain tissues, the supernatants were collected, and GSH content was determined spectrophotometrically. GSH levels were expressed as nmol/g tissue.

Catalase (CAT) Activity: Catalase activity was measured according to principles consistent with the literature (20). The amount of enzyme required for the decomposition rate of H₂O₂ at 240 nm was determined. Results were expressed as mmol/min/mg tissue.

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed

using the Shapiro-Wilk test. Since the data followed a normal distribution, parametric statistical methods were employed for all analyses. Differences between experimental groups were evaluated using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. All results were expressed as mean $\pm$ standard deviation (SD). A p-value less than 0.05 was considered statistically significant.

RESULTS

Biochemical Parameters

INH administration resulted in a significant increase in LPO levels in lung tissue compared to the control group. A dose-dependent significant reduction in LPO levels was observed in the walnut methanol extract-treated groups compared to both control and INH groups. GSH levels demonstrated significant reduction in the INH-treated group. While an increase was observed in the control group compared to INH treatment, more pronounced elevations were detected in walnut methanol extract-treated groups. An analysis of CAT activity in lung tissue revealed a significant increase in activity in the group treated with INH, while both doses of walnut methanol septum extract showed a significant decrease in activity (Table 1, Figure 1).

Table 1. Effects of walnut septum methanol extract (100 mg/kg and 250 mg/kg), isoniazid (400 mg/kg) and control groups on the amount of GSH and LPO, activities CAT in isoniazid-induced rat lung tissue.

Treatment	LPO Level (nmol/g tissue)	Cat Activity (nmol/min/mg tissue)	GSH Level (nmol/mg tissue)
Isoniazid (400 mg/kg)	14.1 $\pm$ 0.1d	131.0 $\pm$ 0.4d	2.8 $\pm$ 0.2a
Walnut septum methanol extract (100 mg/kg)	11.4 $\pm$ 0.2c	122.7 $\pm$ 1.0c	4.9 $\pm$ 0.2b
Walnut septum methanol extract (250 mg/kg)	8.3 $\pm$ 0.1b	111.0 $\pm$ 0.5b	7.0 $\pm$ 0.2c
Control	7.1 $\pm$ 0.1a	99.8 $\pm$ 0.6a	8.1 $\pm$ 0.1d

Means in the same column by the same letter are not significantly different to the Duncan test P < 0.05). Mean damage index $\pm$ SE of eight animals in each group.

Histopathological Findings

Control group rats exhibited normal histological lung architecture with only mild alveolar hyperemia. INH-treated group rats demonstrated increased interalveolar tissue due to cellular infiltration and peribronchial lymphoid tissue hyperplasia. Walnut extract treatment, particularly at the 250 mg/kg dose, significantly preserved normal histological architecture. In the 100 mg/kg walnut methanol extract group administered with INH, interalveolar cellular infiltration-related thickening and peribronchial lymphoid tissue hyperplasia were relatively attenuated compared to the INH-only group. In the 250 mg/kg walnut methanol extract group administered with INH, lung alveoli predominantly maintained normal histological structure, with increased interalveolar cellular infiltration observed only in limited regions (Figure 2).

DISCUSSION

This study investigated the protective effects of walnut septum methanol extract against INH-induced pulmonary injury. Our findings demonstrate that INH induces oxidative stress and inflammation in lung tissue, whereas walnut septum extract significantly attenuates these harmful effects. Despite being a first-line agent in

tuberculosis treatment, INH carries substantial organ toxicity risks. INH toxicity is associated with reactive metabolites generated through metabolic activation, which form covalent bonds with cellular macromolecules, leading to mitochondrial dysfunction and oxidative stress (3). During INH metabolism, reactive metabolites such as hydrazine and acetylhydrazine are generated through CYP2E1-mediated pathways, contributing to increased oxidative stress (2).

The elevated LPO levels observed in our study align with literature findings demonstrating INH-induced oxidative stress enhancement. INH-related hepatic injury has been associated with oxidative stress, mitochondrial dysfunction, drug-metabolizing enzymes, and endoplasmic reticulum stress (21). Our findings indicate that INH also exerts toxic effects in pulmonary tissue. Literature contains rare case reports describing INH-induced pulmonary fibrosis and interstitial lung disease (6,22). While INH is primarily recognized for its hepatotoxic and neurotoxic effects, its potential to induce pulmonary injury through systemic oxidative mechanisms warrants consideration. INH metabolites, including hydrazine and acetylhydrazine, generate reactive oxygen species via CYP2E1-mediated pathways (2,8).

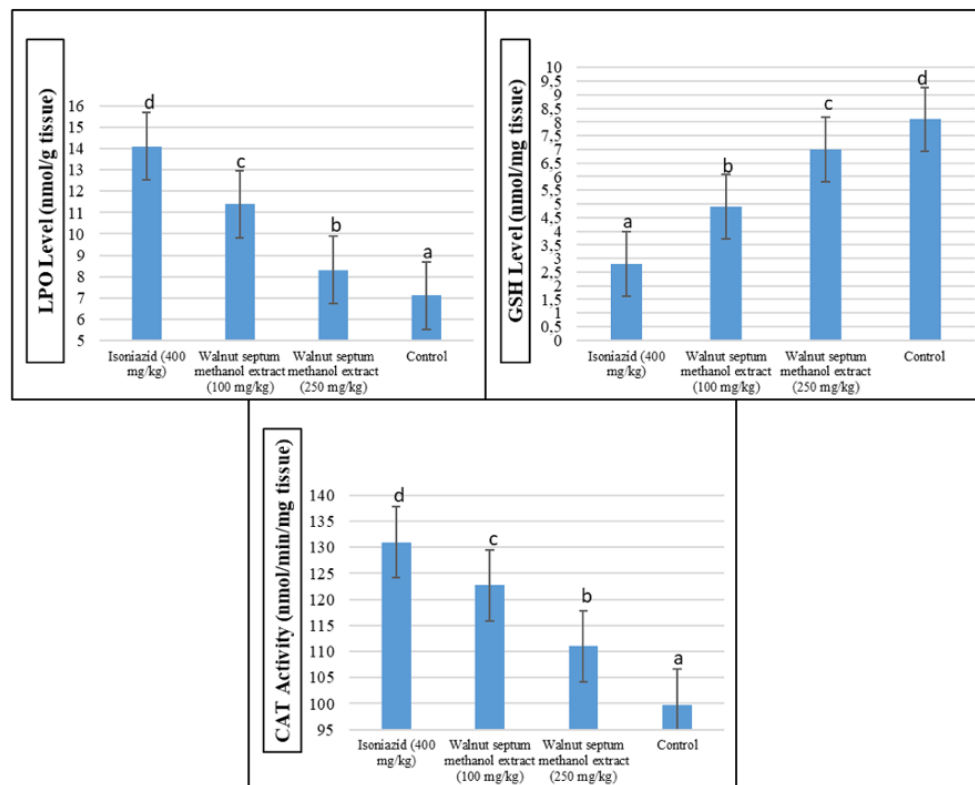


Figure 1. Effects of walnut septum methanol extract on reduced glutathione (GSH), lipid peroxidation (LPO) level and catalase (CAT) enzyme activities in isoniazid-induced lung tissue. Data are presented as mean $\pm$ SE. Different superscript letters indicate statistically significant differences between groups (one-way ANOVA followed by Scheffé's test, $p < 0.05$).

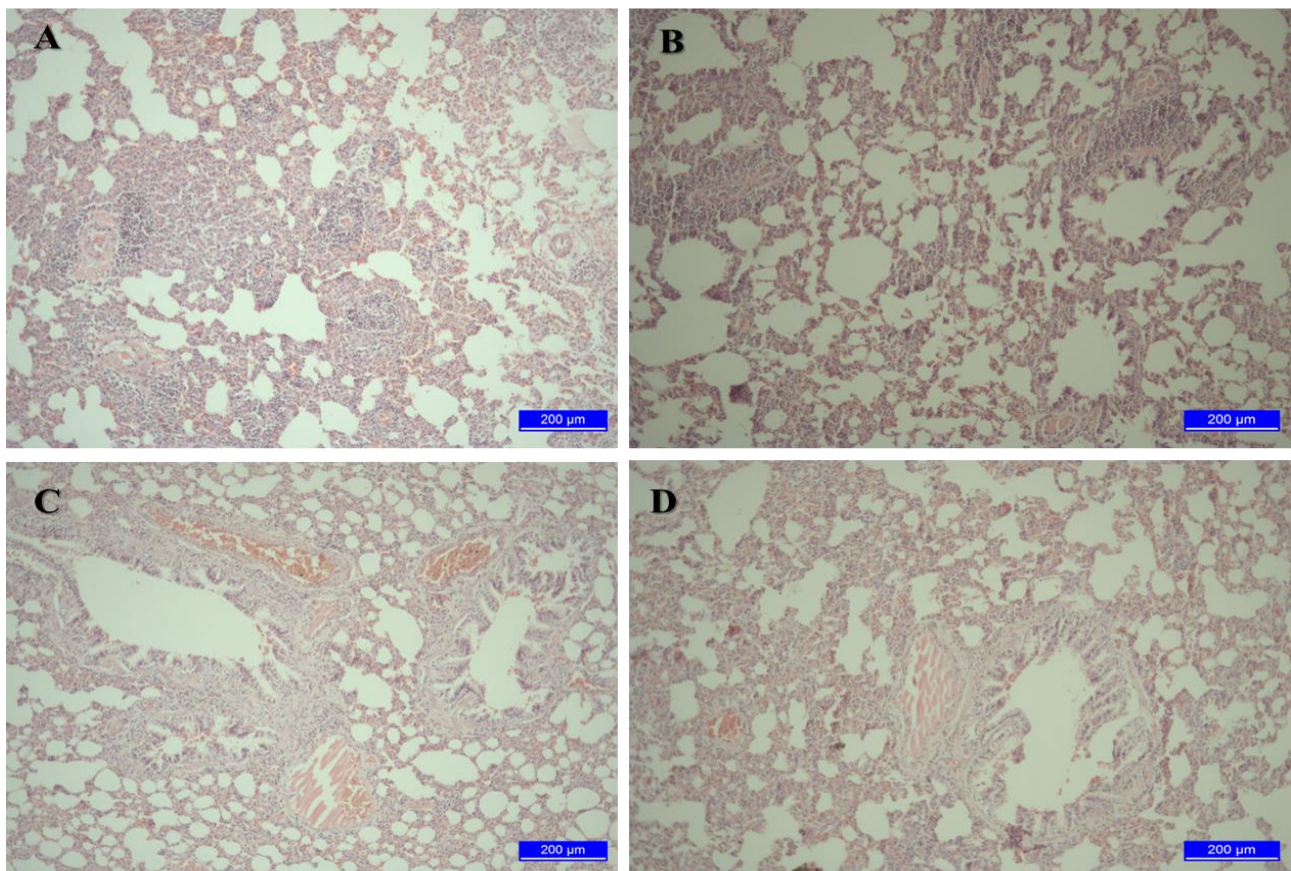


Figure 2. The isoniazid-treated rat lung tissues, (A-Control, B- isoniazid 400 mg/kg, C- Walnut septum methanol extract 100 mg/kg, D- Walnut septum methanol extract 250 mg/kg).

Importantly, CYP2E1 is expressed not only in hepatocytes but also in pulmonary bronchial and alveolar epithelial cells, suggesting that reactive metabolites reaching the lung via systemic circulation may induce local oxidative damage (5,23). This mechanistic rationale is further supported by clinical case reports documenting INH-induced pneumonitis and interstitial lung disease (6). The oxidative stress parameters observed in our study (increased LPO and decreased GSH and CAT activity in animals treated with INH) are consistent with this mechanistic framework. The interalveolar cellular infiltration and peribronchial lymphoid tissue hyperplasia observed in our study indicate that INH induces inflammatory responses in pulmonary tissue. The increased LPO levels and decreased GSH content in the INH group demonstrate enhanced lipid peroxidation and impaired antioxidant defense mechanisms, both of which are characteristic features of oxidative stress.

LPO represents a crucial biomarker resulting from ROS-mediated lipid attack and is utilized for oxidative stress assessment in various pathological conditions (24). Catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) enzymes collectively constitute the primary defense system against ROS-induced oxidative stress (25). The reduced CAT activity observed in our INH group indicates compromised antioxidant defense mechanisms.

These findings are further supported by studies examining various parts of *Juglans regia*, although it should be noted that different plant fractions possess distinct phytochemical profiles. Specifically, walnut septum extract, which is rich in juglon and tannins similar to the septum fraction used in the present study, has been shown to demonstrate protective effects against pulmonary inflammation through antioxidant enzyme stimulation and reduction of IL-6 concentrations (26). In contrast, *Juglans regia* kernel extract, whose composition is dominated by polyunsaturated fatty acids and polyphenols rather than naphthoquinones, has demonstrated protective effects against cigarette smoke-induced pulmonary toxicity (27). Additionally, a total methanolic walnut extract has been reported to attenuate bleomycin-induced pulmonary oxidative stress and inflammation by modulating alveolar macrophage responses (16). While these studies collectively support the pulmonary protective potential of *Juglans regia*, the mechanistic contributions may differ across fractions due to their varying bioactive compound profiles.

The more pronounced protective effect observed with the 250 mg/kg dose compared to 100 mg/kg in our study indicates dose-dependent antioxidant activity of walnut septum extract. Walnut septum extracts obtained using different solvents exhibit varying antioxidant activities, with ethyl acetate extract demonstrating the highest radical scavenging activity (13).

Various components of *Juglans regia* possess potent antioxidant activity with IC₅₀ values against reactive oxygen species at µg/mL levels (28). *Juglans regia* leaf extract has been shown to exert anti-inflammatory effects in diabetic nephropathy by inhibiting the NF-κB pathway (29). The histopathological findings observed in our study, which are consistent with previous reports in the literature, suggest that walnut extract exerts protective effects against pulmonary inflammation. The interalveolar cellular

infiltration and peribronchial lymphoid tissue hyperplasia observed in the INH group represent indicators of acute inflammatory response. The substantial preservation of histological architecture in walnut septum extract-treated groups, particularly at high doses, indicates the anti-inflammatory and tissue-protective effects of the extract. Some limitations of this study must be acknowledged. First, the absence of a walnut septum extract-only group represents a methodological limitation. However, this decision was based on two considerations: the restrictions on animal numbers imposed by institutional ethics committee and published studies showing that *Juglans regia* extracts administered at dose ranges do not exhibit significant pro-oxidant or cytotoxic effects in healthy rodent tissue. Nevertheless, future studies should include a walnut septum extract-only group to more comprehensively evaluate the effects of the extract on lung tissue and to better characterize the contribution of juglone to these effects. Furthermore, the histopathological assessment was descriptive rather than quantitative. The absence of a validated semi-quantitative scoring system such as the Ashcroft scale represents a limitation; future studies should incorporate standardized scoring criteria to allow for a more objective and reproducible assessment of lung tissue changes.

Another limitation of this study is that the experimental model did not include tuberculosis infection. The biological effects of isoniazid and walnut septum extract may differ in the presence of active infection due to disease-related metabolic changes. Therefore, the findings of this study should be interpreted within the context of an experimental model without infection, and further studies using infection-based models are needed to better elucidate potential therapeutic effects.

CONCLUSION

This study suggests that walnut septum methanol extract may exert significant protective effects against INH-induced pulmonary oxidative stress in a rat model. These findings are supported by improvements in oxidative stress parameters, enhanced antioxidant defense activity, and attenuation of histopathological changes. Our results indicate that walnut septums may represent a promising source of natural antioxidants warranting further investigation; however, comprehensive mechanistic and safety studies are required before any translational implications can be drawn. Future research should focus on identifying active compounds responsible for the protective effects, optimizing extraction methods, and conducting dose-escalation studies to establish therapeutic windows.

DECLARATIONS

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plagiarism, and no instances of plagiarism were detected.

Use of AI Tools: The authors declare that no Artificial Intelligence (AI) tools were used in the creation of this article.

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