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Research Article

Histopathological Effects of Garlic Extract in Cigarette Smoke–Induced Lung Injury in Wistar Rats: A Comparative Study with Vitamin C

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ABSTRACT

Cigarette smoke contains various free radicals that can damage lung tissue. Natural antioxidants such as garlic extract (*Allium sativum* L.) are believed to neutralize free radicals. An in vivo study was conducted using 30 male Wistar rats. Twenty-five rats were allocated into five experimental groups (cigarette smoke and distilled water group, cigarette smoke and vitamin C 50 mg/kgBW group, garlic extract 50 mg/kgBW group, garlic extract 100 mg/kgBW group, and a combination of vitamin C and garlic extract 100 mg/kgBW group), while an additional five rats served as a non–smoke-induced baseline group for descriptive comparison. Cigarette smoke induction was performed for 21 days with exposure to 3 cigarettes per day. After treatment, the rats' lungs were observed histopathologically for alveolar lumen widening, alveolar septal thickening, and inflammatory cell infiltration. The data were analyzed in SPSS version 24 to evaluate significant differences among treatment groups. Lung damage data across all groups were homogeneous. Vitamin C produced the greatest improvement compared to the other treatment groups. Vitamin C effectively improved lung damage in Wistar rats induced by cigarette smoke compared to garlic extract. Garlic extract (50 mg/kgBW) has the potential to improve lung damage in cigarette smoke–induced Wistar rats, with no additional benefit at higher doses.

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INTRODUCTION

Smoking is the act of burning a cigarette, inhaling the smoke, and exhaling it, thereby producing cigarette smoke (Mufida & Isni, 2022). Cigarettes contain free radicals that can damage the thin-walled cellular layers of elastin and collagen fibers, thereby disrupting cellular permeability and causing alveolar lumen dilation. Free radicals from cigarette smoke also activate neutrophils in the alveolar walls, leading to increased protease activity and subsequent lung tissue damage, characterized by inflammatory cell infiltration. Thickening of the alveolar walls results from the accumulation of inflammatory cells (Triantara et al., 2019).

Free radicals in cigarette smoke can be neutralized by antioxidants. Antioxidants are chemical compounds that reduce the activity of free radicals, thereby lowering the risk of oxidative stress and protecting cellular components from damage (Shraideh et al., 2024). Vitamin C is a water-soluble antioxidant that is effective in counteracting free radicals (Sanggamele et al., 2020). However, vitamin C may cause side effects, including headache, flushing, nausea or vomiting, and dizziness. In large quantities, it may increase the risk of kidney stones as well as elevate uric acid and oxalate levels due to urine acidification (Abdullah et al., 2025). Alternative antioxidants may be obtained from spices, including garlic (*Allium sativum L.*). The chemical constituents in garlic that possess antioxidant activity include allicin and flavonoids (Romsiah et al., 2020).

Previous studies have demonstrated that garlic exhibits significant antioxidant activity. This antioxidant activity supports the mitigation of oxidative damage to the liver and kidneys in rats exposed to cigarette smoke. Furthermore, other studies have shown that a combination of garlic and honey can improve sperm motility in mice induced with cigarette smoke, indicating the broader potential of garlic in counteracting the adverse effects of cigarette smoke. Additional studies also indicate that garlic extract exerts antioxidant effects that alleviate oxidative damage caused by cigarette smoke induction, further reinforcing the hypothesis that garlic extract may reduce the detrimental impact of cigarette smoke on body organs (Hasanudin et al., 2024; Romsiah et al., 2020; Shraideh et al., 2024). Therefore, this study aims to evaluate the effects of garlic extract on cigarette smoke-induced lung damage in male Wistar rats.

METHODS

Experimental Animals

The study used 30 male Wistar rats aged 2 months, healthy, free of physical abnormalities, and weighing 150–200 grams. Twenty-five rats were included in the experimental groups, while five rats were assigned to a non–smoke-induced baseline group. The baseline (non–smoke-induced) group was not included in the inferential statistical analysis and was used solely for descriptive comparison to represent normal lung histology prior to cigarette smoke exposure

Study Procedure

A total of 25 rats were allocated into five groups, with each group consisting of five rats, as follows: (1) Negative Control (KN): Rats induced with cigarette smoke and administered distilled water; (2) Positive Control (KP): Rats induced with cigarette smoke and administered vitamin C at 50 mg/kgBW; (3) B50: Rats induced with cigarette smoke and administered garlic extract at 50 mg/kgBW; (4) B100: Rats induced with cigarette smoke and administered garlic extract at 100 mg/kgBW; (5) B100C: Rats induced with

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cigarette smoke and administered both vitamin C at 50 mg/kgBW and garlic extract at 100 mg/kgBW. Additionally, one non–smoke-induced group (five rats) was prepared to serve as a pre-induction baseline. Cigarette smoke induction was carried out in the afternoon using three cigarettes daily for 21 consecutive days. After the cigarettes had completely burned, the rats received garlic extract and vitamin C according to their respective dosage groups.

Sample Collection

After 21 days, the rats were euthanized by inducing depression of the cortical neural system. Euthanasia was performed using intramuscular ketamine at 75 mg/kg, in accordance with ethical guidelines and by employing the most humane method possible to minimize animal suffering. All four extremities were fixed using restraining pins to prevent movement during the surgical procedure. Necropsy began by incising the lower abdomen up to the thoracic cavity, after which the lungs were carefully removed.

Preparation of Hematoxylin–Eosin (H&E) Slides

The right lung of each Wistar rat was fixed in formalin for 12 hours and embedded in paraffin. Following fixation, tissues were processed and sectioned sagittally at a thickness of 5 µm. Tissue sections were stained with hematoxylin–eosin, mounted on slides, and examined under a light microscope. Slide preparation was performed at Barokah Laboratory in Palembang.

Each slide was evaluated in five microscopic fields (four corners and one central field) at 100× and 400× magnification. Lung damage assessment was performed by an anatomical pathology specialist who was blinded to the treatment groups, ensuring a double-blind study design. Lung injury scoring was based on alveolar lumen dilation, alveolar wall thickening, and inflammatory cell infiltration using the following criteria:

Score 0 = 0% of the microscopic field

Score 1 = <1–33% of the microscopic field

Score 2 = 34–66% of the microscopic field

Score 3 = 67–100% of the microscopic field

Statistical Analysis

Statistical analysis was performed using SPSS version 24 to evaluate lung damage in male Wistar rats induced by cigarette smoke, based on the parameters of alveolar lumen dilation, alveolar wall thickening, and inflammatory cell infiltration. Statistical analyses were performed only on the five cigarette smoke–induced groups (n=25), excluding the baseline group. Data normality was assessed using the Shapiro–Wilk test, followed by a homogeneity test. A paired t-test was used to assess pre- and post-treatment effectiveness, an independent t-test was used to compare post-treatment values between two groups, and one-way ANOVA followed by an appropriate post-hoc test was applied when the ANOVA p-value was <0.05.

RESULTS

Cigarette smoke induction resulted in significant increases in alveolar lumen dilatation and alveolar wall thickening compared with the normal (pre-induction) condition across all groups ($p < 0.05$), indicating the successful establishment of lung injury in this model.

A significant difference was observed between the negative control (KN) and positive control (KP) groups ($p = 0.037$), indicating that vitamin C administration at 50 mg/kg BW significantly reduced alveolar lumen dilatation and alveolar wall thickening induced by cigarette smoke exposure.

However, no significant differences were found among the cigarette smoke–induced

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treatment groups ($p > 0.05$), suggesting that the variations in mean values were insufficient to indicate a clear treatment effect.

Similarly, cigarette smoke exposure significantly increased inflammatory cell infiltration compared with the normal condition ($p < 0.05$). The positive control group (KP) showed a significant reduction in inflammatory cell infiltration compared with the negative control group (KN) ($p = 0.003$), indicating the protective effect of vitamin C.

In addition, overall differences in inflammatory cell infiltration were observed among the cigarette smoke–induced groups ($p < 0.05$), suggesting a treatment-related effect. Post hoc analysis demonstrated that both the vitamin C group (KP) and the garlic extract group at 50 mg/kgBW (B50) differed significantly from the negative control group (KN) ($p < 0.05$), indicating that both interventions reduced inflammatory cell infiltration, with vitamin C exhibiting a more pronounced effect.

Table 1. Effectiveness of Garlic Extract on Alveolar Lumen Dilatation, Alveolar Wall Thickening, Inflammatory Cell Infiltration, and Inflammatory Cell in Rats Exposed to Cigarette Smoke

Group	Mean Alveolar Lumen Dilatation and Alveolar Wall Thickening (Mean ± SD)		P *value* (*)	Mean Inflammatory Cell Infiltration (Mean ± SD)			Mean Inflammatory Cell Infiltration (Mean ± SD)	P *value*
	Before	After		Before	After			
KN (IAP)	0.5600 ± 0.26077	2.2400 ± 0.40988	0.001*	0.3200 ± 0.22804	2.6000 ± 0.31623	0.000*	2.6000 ± 0.31623	
KP (IAP+VC)	0.5600 ± 0.26077	1.4800 ± 0.54037	0.002*	0.3200 ± 0.22804	1.6800 ± 0.36332	0.002*	1.6800 ± 0.36332	
B50 (IAP+B50)	0.5600 ± 0.26077	2.2400 ± 0.21909	0.000*	0.3200 ± 0.22804	2.0400 ± 0.29665	0.000*	2.0400 ± 0.29665	0.001**
B100 (IAP+B100)	0.5600 ± 0.26077	2.1600 ± 0.43359	0.000*	0.3200 ± 0.22804	2.4000 ± 0.20000	0.000*	2.4000 ± 0.20000	
B100C (IAP+B100C)	0.5600 ± 0.26077	2.3200 ± 0.70143	0.001*	0.3200 ± 0.22804	2.3600 ± 0.21909	0.000*	2.3600 ± 0.21909	

Paired T test *p <0,05, *One way* **ANOVA, p value < 0,05*

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Table 2. Comparison of the Effectiveness of Garlic Extract on Alveolar Lumen Dilatation, Alveolar Wall Thickening, and Inflammatory Cell Infiltration Between Pairs of Rat Groups Exposed to Cigarette Smoke

Group	Mean ± SD	Comparison Group	Alveolar Lumen Dilatation and Alveolar Wall Thickening (Mean ± SD)	P Value	Inflammatory Cell Infiltration (Mean ± SD)	P Value
KN (IAP)	(2.2400 ± 0.40988)	KP (IAP+VC)	(1.4800 ± 0.54037)	0.037*	(1.6800 ± 0.36332)	0.003*
		B50 (IAP+B50)	(2.2400 ± 0.21909)	1.000	(2.0400 ± 0.29665)	0.020*
		B100 (IAP+B100)	(2.1600 ± 0.43359)	0.772	(2.4000 ± 0.20000)	0.266
		B100C (IAP+B100C)	(2.3200 ± 0.70143)	0.831	(2.3600 ± 0.21909)	0.201
KP (IAP+VC)	(1.4800 ± 0.54037)	B50 (IAP+B50)	(2.2400 ± 0.21909)	0.031*	(2.0400 ± 0.29665)	0.124
		B100 (IAP+B100)	(2.1600 ± 0.43359)	0.059	(2.4000 ± 0.20000)	0.005*
		B100C (IAP+B100C)	(2.3200 ± 0.70143)	0.067	(2.3600 ± 0.21909)	0.007*
B50 (IAP+B50)	(2.2400 ± 0.21909)	B100 (IAP+B100)	(2.1600 ± 0.43359)	0.726	(2.4000 ± 0.20000)	0.055
		B100C (IAP+B100C)	(2.3200 ± 0.70143)	0.814	(2.3600 ± 0.21909)	0.088
B100 (IAP+B100)	(2.1600 ± 0.43359)	B100C (IAP+B100C)	(2.3200 ± 0.70143)	0.676	(2.3600 ± 0.21909)	0.771

*Independent T-test. *p< 0.05*

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Table 3. Evaluation of the Effect of Garlic Extract on Alveolar Lumen Dilatation and Alveolar Wall

Variable	KN (IAP)	KP (IAP+VC)	B50 (IAP+B50)	B100 (IAP+B100)	B100C (IAP +B100C)
KN (IAP)		0.139	1.000	0.999	0.999
KP (IAP+VC)	0.139		0.139	0.218	0.085
B50 (IAP+B50)	1.000	0.139		0.999	0.999
B100 (IAP+B100)	0.999	0.218	0.999		0.984
B100C (IAP+B100C)	0.999	0.085	0.999	0.984	

Post hoc Tukey, $p < 0,05$

Table 4. Evaluation of the Effect of Garlic Extract on Inflammatory Cell Infiltration

Variable	KN (IAP)	KP (IAP+VC)	B50 (IAP+B50)	B100 (IAP+B100)	B100C (IAP+ B100C)
KN (IAP)		0.000*	0.040*	0.801	0.677
KP (IAP+VC)	0.000*		0.305	0.006*	0.010*
B50 (IAP+B50)	0.040*	0.305		0.305	0.416
B100 (IAP+B100)	0.801	0.006*	0.305		0.999
B100C (IAP+B100C)	0.677	0.010*	0.416	0.999	

Post hoc Tukey, $p < 0,05$

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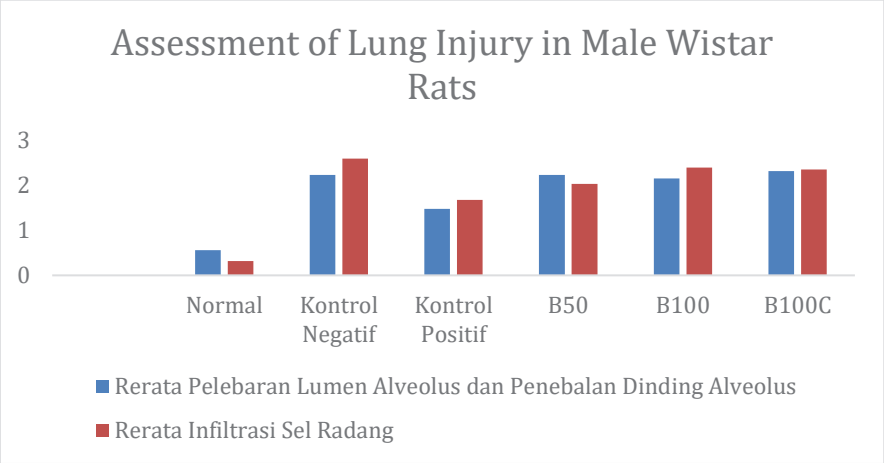

Figure 1. Assessment of Lung Injury in Male Wistar Rats. Normal group: non–smoke-induced rats; Negative control group (KN): rats induced with cigarette smoke and distilled water; Positive control group (KP): rats induced with cigarette smoke and vitamin C 50 mg/kgBW; B50 group: rats induced with cigarette smoke and garlic extract 50 mg/kgBW; B100 group: rats induced with cigarette smoke and garlic extract 100 mg/kgBW; B100C group: rats induced with cigarette smoke, vitamin C 50 mg/kgBW, and garlic extract 100 mg/kgBW.

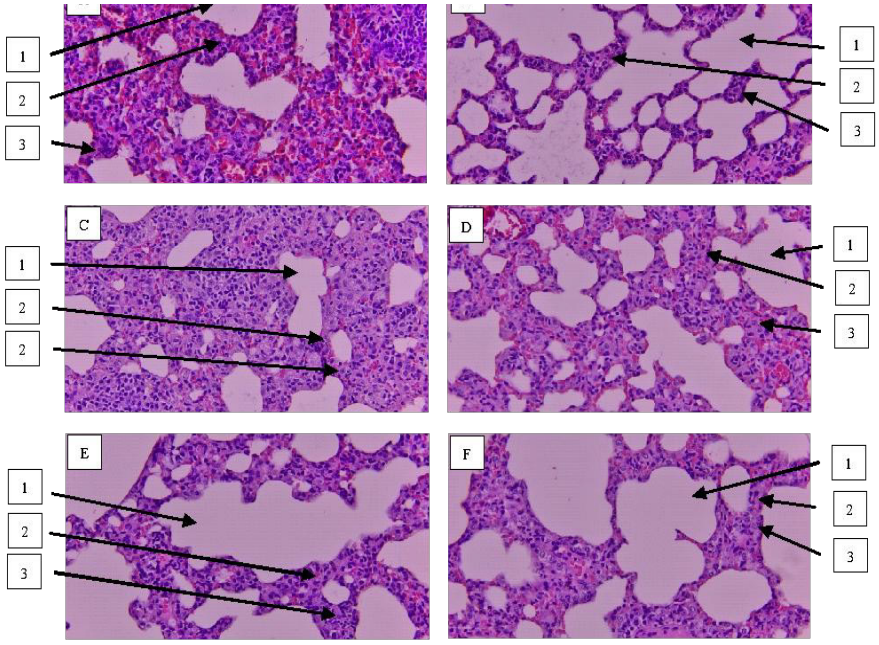

Figure 2. Histological Features of Alveolar Lumen Dilatation, Alveolar Wall Thickening, and Inflammatory Cell Infiltration. (a) Normal group: non–smoke-induced rats; (b) Negative control group (KN): rats induced with cigarette smoke and distilled water; (c) Positive control group (KP): rats induced with cigarette smoke and vitamin C 50 mg/kgBW; (d) B50 group: rats induced with cigarette smoke and garlic extract 50 mg/kgBW; (e) B100 group: rats induced with cigarette smoke and garlic extract 100 mg/kgBW; (f) B100C group: rats induced with cigarette smoke, vitamin C 50 mg/kgBW, and garlic extract 100 mg/kgBW. Legend: (1) Alveolar lumen dilatation; (2) Alveolar wall thickening; (3) Inflammatory cell infiltration. Magnification 400×.

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DISCUSSION

This study demonstrates the antioxidant effects of garlic extract (*Allium sativum L.*) on lung injury in male Wistar rats induced by cigarette smoke. Cigarette smoke is a well-established stimulus capable of triggering pulmonary damage (Binarsa et al., 2022). Rats exposed to cigarette smoke develop pathological changes similar to those observed in humans, including increased free radical production as a marker of oxidative stress (Joe et al., 2024; Seo et al., 2023). Cigarette smoke induction for 21 days has been shown to cause oxidative stress (Yuniarifa et al., 2022).

In this study, cigarette smoke exposure increased alveolar lumen dilatation, alveolar wall thickening, and inflammatory cell infiltration. These results are consistent with findings by Idrus et al., who reported lung damage characterized by alveolar lumen dilatation, alveolar wall thickening, and leukocyte infiltration following cigarette smoke induction. Cigarette smoke stimulates epithelial cells to produce cytokines that activate neutrophils and macrophages (Al Idrus et al., 2016). It also inactivates antiproteases, leading to increased protease activity—particularly neutrophil elastase—which degrades elastin and collagen within the alveoli, thereby causing alveolar dilation (Caliri et al., 2021). Lung injury characterized by inflammatory cell infiltration arises from free radicals in cigarette smoke, which trigger immune responses, including leukocyte infiltration into alveolar walls and pulmonary vessels. The accumulation of inflammatory cells in the alveolar walls leads to wall thickening (Al Idrus et al., 2016). While these mechanisms are biologically plausible, they were not directly evaluated in this study and remain speculative.

Under physiological conditions, the body maintains redox homeostasis through antioxidant defense systems. However, various stimuli can disrupt this balance, triggering oxidative stress due to elevated levels of reactive oxygen species (ROS) (Pizzino et al., 2017). Cigarette smoke induces ROS formation through both gas and tar phases. The gas phase forms during tobacco combustion and is inhaled as mainstream smoke, whereas the tar phase contains relatively stable free radicals, such as quinone or hydroquinone complexes, that can reduce molecular oxygen to superoxide and generate additional radicals. Smoke particles deposited in the lungs form a tar layer that undergoes redox cycling, producing reactive species including phenols, quinones, heavy metals, and free radicals. Excess oxidants disrupt the balance between oxidants and antioxidants, leading to oxidative stress. This state, in turn, activates the NF-κB pathway, promoting the accumulation of inflammatory cells in lung parenchyma and increasing cytokine and chemokine levels, thus creating a vicious cycle wherein oxidative damage exacerbates inflammation and further increases macromolecular injury (Caliri et al., 2021).

Vitamin C administration reduced lung injury through its antioxidant mechanism. Vitamin C neutralizes oxidative stress via electron transfer, donating electrons to prevent the oxidation of other compounds and scavenging hydroxyl radicals, superoxide anions, and lipid hydroperoxides (Cahyanto et al., 2020). This finding aligns with Awuy et al., who reported that vitamin C effectively countered cigarette smoke–induced free radicals, improving the quality of spermatozoa in smoke-exposed rats (Awuy et al., 2021)

The potential protective effect of garlic extract on lung tissue may be attributed to its bioactive compounds, particularly allicin and flavonoids, which exhibit antioxidant and anti-

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inflammatory properties. These compounds are known to scavenge reactive oxygen species (ROS), inhibit lipid peroxidation, and modulate inflammatory signaling pathways, including the suppression of pro-inflammatory cytokines (Iwar et al., 2024; Shraideh et al., 2024). In cigarette smoke–induced injury, excessive ROS production activates inflammatory cascades that lead to structural damage of alveolar walls (Pizzino et al., 2017). By reducing oxidative stress and inflammatory cell recruitment, garlic extract may contribute to the attenuation of histopathological damage observed in this study.

In addition to vitamin C, several antioxidant and anti-inflammatory agents have been reported to exert protective effects against cigarette smoke–induced lung injury, including N-acetylcysteine (NAC) and other bioactive compounds. NAC, in particular, has been shown to attenuate cigarette smoke–induced oxidative stress, reduce inflammatory cytokine production, and protect alveolar epithelial cells from injury (Messier et al., 2013; Mokra et al., 2025). These effects are mediated by the enhancement of intracellular glutathione levels and the modulation of oxidative stress pathways (Messier et al., 2013). Compared with these agents, the effect of garlic extract observed in this study appears relatively modest, suggesting that while it possesses biological activity, its efficacy may be less pronounced or context-dependent.

Garlic extract at a dose of 50 mg/kgBW reduced inflammatory cell infiltration in cigarette smoke–induced rats. Garlic extract possesses antioxidant potential that can mitigate oxidative damage, as previously demonstrated in smoke-induced reproductive toxicity models (Hasanudin et al., n.d.). Garlic extract suppresses the formation and release of pro-inflammatory cytokines that normally facilitate inflammatory cell recruitment into lung tissue. In treated lungs, reduced numbers of lymphocytes and inflammatory cells indicate decreased inflammation. Additionally, garlic extract enhances anti-inflammatory cytokine production, further inhibiting pro-inflammatory signaling. Structural improvements such as reduced inflammatory infiltration to limited alveolar areas support these mechanisms (Savira et al., 2023).

Conversely, garlic extract at 100 mg/kgBW did not significantly reduce lung injury in male Wistar rats. This may be attributable to dose-dependent variations in antioxidant activity. Although garlic contains bioactive compounds such as flavonoids and allicin with known antioxidant potential (Iwar et al., 2024), these compounds may not have exerted sufficient protective effects at the tested concentration. This finding may also be influenced by the absence of a non–smoke-treated group, which limits the interpretation of whether the lack of additional benefit at higher doses is due to reduced efficacy or potential dose-related adverse effects. Similar findings have been reported in previous studies, which noted that allicin is most effective at doses below 100 mg/kg BW (Ni'mah et al., 2017). Another study concluded that garlic extract is non-toxic and non-allergenic at doses below 5000 mg/kgBW. With a human equivalent dose conversion factor (50 kg adult equivalent to 200 g rat), the effective antioxidant dose range of 30–60 mg/kgBW corresponds to a rat dose of 50 mg/kgBW (Fadly, 2022).

The lack of additional benefit at the higher dose (100 mg/kgBW) may be explained by several factors. First, antioxidant compounds may exhibit non-linear or biphasic dose–response relationships, in which optimal effects occur within a specific concentration range, while higher doses confer no additional benefit (Calabrese, 2008; Mattson, 2008). Second, excessive concentrations of antioxidant

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compounds may disrupt redox homeostasis and potentially exert pro-oxidant effects under certain conditions, thereby attenuating their protective activity (Pizzino et al., 2017). Third, the bioavailability and metabolic stability of key bioactive compounds in garlic, particularly allicin, are limited by rapid degradation and conversion into other sulfur-containing metabolites, which may reduce their biological effectiveness at higher doses (Amagase, 2006). Furthermore, higher concentrations of phytochemicals may alter cellular signaling pathways or trigger compensatory responses that diminish their net protective effect. In addition, the absence of a non–smoke-treated group in this study further limits the interpretation of whether the reduced efficacy at higher doses reflects pharmacodynamic limitations or potential dose-related adverse effects.

The interpretation of a dose–response relationship in this study should be approached with caution. Although the 50 mg/kg BW dose appeared to have a more favorable effect than the higher dose, the small sample size (n=5 per group), overlapping standard deviations, and the absence of biochemical oxidative stress markers limit the strength of this conclusion. Therefore, the observed pattern may reflect an exploratory finding rather than a definitive dose–response relationship. Further studies with larger sample sizes and the inclusion of objective biomarkers of oxidative stress are required to confirm these findings.

The combination of vitamin C and garlic extract did not reduce lung injury in smoke-induced rats. Previous reports show that combining petroleum ether garlic extract with vitamin C did not produce antifungal activity against *Candida albicans* (Khaira et al., 2016). This may be due to interactions between vitamin C and garlic extract that impair antioxidant enzyme activity, thereby diminishing their protective effects (Eniola, 2011).

This study has several limitations related to its experimental design and the absence of mechanistic correlates. All treatment groups were exposed to cigarette smoke, and no group received garlic extract without smoke exposure. Therefore, the baseline effects of garlic extract on normal lung tissue could not be evaluated. In addition, the absence of a non–smoke-treated group limits the ability to assess potential intrinsic effects of garlic extract, including possible pro-oxidant or toxic effects at higher doses, such as 100 mg/kgBW. Furthermore, the relatively short duration of cigarette smoke exposure (21 days) may not fully reflect the chronic pathological processes observed in long-term smoking models, thereby limiting the extrapolation of these findings to chronic lung disease conditions. The assessment of lung injury also relied solely on histopathological evaluation, without measuring oxidative stress biomarkers such as malondialdehyde (MDA), superoxide dismutase (SOD), or glutathione peroxidase (GPx), without evaluating inflammatory mediators such as TNF-α, IL-6, or NF-κB signaling pathways, nor assessing functional pulmonary outcomes. Consequently, the mechanistic interpretation of the protective effects of garlic extract remains limited. Future studies should include a non–smoke-exposed group receiving garlic extract, extend the duration of exposure to better simulate chronic conditions, and incorporate biochemical and functional parameters to provide a more comprehensive understanding of its safety profile and underlying mechanisms in cigarette smoke–induced lung injury.

CONCLUSION

This study concludes that cigarette smoke induction causes lung injury in male Wistar rats, characterized by alveolar lumen dilatation, alveolar wall thickening, and inflammatory cell

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infiltration. Vitamin C effectively reduced lung injury induced by cigarette smoke based on all assessed parameters, demonstrating stronger protective effects than garlic extract. Garlic extract showed a potential protective effect at 50 mg/kgBW; however, this effect was modest, and no additional benefit was observed at higher doses. These findings should be interpreted with caution and may represent preliminary evidence rather than definitive evidence of therapeutic effect.

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