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(RESEARCH ARTICLE)

Peperomia pellucida Extract Mitigates Cigarette Smoke-Induced Hepatic Histopathological Injury in Wistar Rats: A Post-Exposure Treatment Study

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Abstract

Tobacco smoke is a systemic toxicant whose health effects extend beyond the cardiopulmonary system to metabolically active organs such as the liver. Because interventions are often initiated only after exposure has occurred, post-exposure strategies that facilitate hepatic recovery warrant investigation. *Peperomia pellucida* is a phytochemical-rich medicinal herb with reported antioxidant and anti-inflammatory activity; however, its therapeutic potential against smoke-associated hepatic injury in a post-exposure setting remains incompletely defined. In this controlled, parallel-group study, an ethanolic extract of authenticated *P. pellucida* was evaluated in male Wistar rats. Thirty rats (6-8 weeks; 220-280 g) were randomized to SHAM, SMOKE, or SMOKE+EXTRACT (n=10/group). The SMOKE and SMOKE+EXTRACT groups underwent cigarette smoke exposure for 4 weeks (1 cigarette/rat/day), followed by a 4-week treatment phase in which SMOKE+EXTRACT received *P. pellucida* (200 mg/kg body weight, orally once daily) and the remaining groups received vehicle. At week 8, livers were processed for H&E staining and assessed on anonymized slides by a blinded pathologist (Olympus BX43) using an ordinal 0-3 grading system for steatosis, inflammation, necrosis, and fibrosis. Smoke exposure induced marked architectural disruption with inflammatory infiltration and congestion and increased injury scores across all domains versus SHAM ($p < 0.0001$). Post-exposure *P. pellucida* significantly reduced injury severity, with the largest effects on steatosis and necrosis ($p < 0.01$) and smaller but significant improvements in inflammation and fibrosis ($p < 0.05$). These data provide preclinical evidence that *P. pellucida* may promote histological recovery following cigarette smoke exposure.

Keywords: *Peperomia pellucida*; Cigarette Smoke Exposure; Liver Injury; Histopathology

1. Introduction

Tobacco smoke exposure remains one of the most persistent and preventable drivers of global morbidity and mortality [1,2]. The World Health Organization estimates that tobacco use kills more than 7 million people each year, and that approximately 1.6 million non-smokers die annually from exposure to second-hand smoke, underscoring that harm extends well beyond active smokers [3]. With roughly 1.3 billion tobacco users worldwide, and a disproportionate burden concentrated in low- and middle-income settings, the downstream health consequences of sustained smoke exposure continue to challenge public health systems and clinical practice [4].

Although the respiratory and cardiovascular sequelae of smoking are widely recognized, the liver is an equally relevant target organ because it is central to xenobiotic metabolism and systemic inflammatory regulation [5]. Cigarette smoke contains a complex mixture of reactive oxidants and toxicants that can disrupt hepatic redox homeostasis and promote inflammatory signaling. Consistent with this biological plausibility, clinical and translational evidence increasingly links

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smoking to worse liver-related outcomes, including higher incidence and severity of fatty liver disease, accelerated fibrosis progression, and increased risk of hepatocellular carcinoma, particularly when combined with other metabolic or toxic exposures[6,7]. Importantly, emerging epidemiologic work also suggests that second-hand smoke exposure may not be benign for hepatic health, with associations reported between passive exposure and liver injury-related outcomes in population-based analyses [8].

Mechanistically, tobacco smoke-driven hepatic injury is thought to arise through converging pathways: oxidative stress (with lipid peroxidation and mitochondrial dysfunction), amplification of pro-inflammatory cytokine cascades, and metabolic dysregulation that favors steatosis and fibrogenesis. Experimental models of chronic smoke exposure further support these mechanisms, demonstrating redox imbalance and inflammatory remodeling that translate into structural liver alterations and activation of profibrotic processes [5,6,9]. Yet, despite the compelling mechanistic rationale, therapeutic strategies that can attenuate or reverse smoke-associated hepatic histopathology remain limited.

Smoking cessation and exposure reduction are fundamental, but they do not fully resolve the clinical problem. Many individuals experience prolonged or repeated exposure before cessation, and a substantial proportion of non-smokers remain involuntarily exposed in homes, workplaces, and public environments [5]. From a translational standpoint, interventions with post-exposure efficacy are especially relevant because they better reflect real-world scenarios, where treatment often begins after the injurious exposure has already occurred, rather than concurrently with it. However, most preclinical studies evaluating protective agents against smoke toxicity emphasize prophylactic or co-exposure designs, leaving a gap in evidence regarding restorative approaches initiated after exposure ends [10].

Against this backdrop, *Peperomia pellucida* has attracted growing interest as a source of bioactive compounds with potential hepatoprotective properties. This herb is reported to contain abundant polyphenols and flavonoids, alongside other constituents (including pellucidin) that have been linked to antioxidant and anti-inflammatory activities [11,12]. Preclinical findings across disease models indicate that *P. pellucida* extracts can modulate inflammatory mediators, including reductions in key cytokines such as TNF-α and IL-1β, supporting a possible mechanism for mitigating toxin-induced tissue injury [13–15]. Nevertheless, whether *P. pellucida* can meaningfully improve smoke-induced hepatic histopathological damage when administered as a post-exposure therapy remains insufficiently characterized. Therefore, this study aimed to determine whether post-exposure treatment with *P. pellucida* extract mitigates cigarette smoke-induced hepatic histopathological injury in Wistar rats, thereby providing preclinical evidence for its potential role as a restorative intervention following cessation of smoke exposure.

2. Material and methods

2.1. Plant material and extract preparation

Peperomia pellucida was harvested from Batu, East Java, Indonesia in December, 2023. The plant material was taxonomically authenticated by East Java Provincial Government, Health Service, Technical Implementation Unit (UPT) Herbal Materia Medica Laboratory, and a voucher specimen was deposited in the same institution under accession number (No. 000.9.3/2684/102.20/2023). The aerial parts were rinsed to remove adhering soil and debris, then shade-dried at ambient temperature to constant mass. Dried material was ground to a fine powder. A measured amount of powder was extracted with 96% ethanol using a maceration approach at a plant-to-solvent ratio of 1:10 *w/v* for 72 hours with periodic agitation. The mixture was filtered, and the residue was re-extracted three times under the same conditions. Filtrates were pooled and concentrated under reduced pressure (rotary evaporation, ≤ 45°C) to remove solvent, followed by freeze-drying to obtain a dry crude extract [13].

For animal administration, the extract was freshly suspended in distilled water to the required concentrations and delivered at 200 mg/kg body weight. Preparations were protected from light and prepared within one day prior to dosing to limit oxidative degradation. The remaining dried extract was stored in airtight containers at −20°C until use.

2.2. Study design, experimental animals and intervention protocol

A controlled, parallel-group post-exposure treatment experiment was conducted to determine whether *P. pellucida* extract mitigates hepatic histopathological injury following subchronic cigarette smoke exposure. A total of 30 Wistar rats (6-8 weeks old; 220-280 g) were used. Animals were maintained under standardized laboratory conditions (22 ± 2 °C, 55 ± 10% relative humidity, 12 h light/12 h dark cycle) with free access to standard chow and water, following an acclimatization period of 7 days. All procedures complied with institutional and national guidelines for animal care and were approved by Institutional Animal Ethics Committee, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya (Approval No. 79/SLE/FK/UWKS/2023).

Rats were allocated into three groups (n = 10 per group): SHAM, SMOKE, and SMOKE+EXTRACT. The SHAM group served as unexposed controls and underwent the same handling schedule without cigarette smoke. For exposure induction, rats in the SMOKE and SMOKE+EXTRACT groups were subjected to cigarette smoke for 4 weeks, at a standardized dose of one cigarette per rat per day. Smoke exposure was delivered using a controlled experimental setup designed to provide consistent daily exposure across animals, while minimizing non-exposure stressors through uniform handling procedures.

Immediately after completion of the 4-week smoke exposure period, the therapeutic phase commenced. Rats in the SMOKE+EXTRACT group received *P. pellucida* extract at 200 mg/kg body weight, administered orally once daily for 4 weeks. To control for administration-related effects, rats in the SHAM and SMOKE groups received the corresponding vehicle distilled water on the same schedule. Animals were monitored daily for general health and signs of distress, and body weight was recorded at regular intervals to support dose adjustment and to document exposure- and treatment-related systemic effects [10,14].

2.3. Tissue collection and histopathological evaluation

At study completion (week 8), rats were fasted overnight and euthanized under deep anesthesia in accordance with institutional animal welfare guidance (ketamine-xylazine, intraperitoneal). After a midline laparotomy, the liver was rapidly excised, gently rinsed with cold phosphate-buffered saline to remove residual blood, blotted dry, and weighed. To minimize sampling variability, tissue blocks were collected in a standardized manner from comparable lobar regions in all animals and fixed in 10% neutral-buffered formalin for 24-48 h at room temperature. Specimens were processed using routine graded dehydration and paraffin embedding. Serial sections (4-5 μm) were prepared and stained with hematoxylin and eosin (H&E) for light microscopic assessment [16].

All slides were anonymized using coded identifiers prior to evaluation and were read by a blinded pathologist who was unaware of group allocation throughout scoring. Microscopic examination and image acquisition were performed using a light microscope (Olympus BX43, Tokyo, Japan). Hepatic injury was graded using a predefined semi-quantitative system across four domains: steatosis, inflammation, necrosis, and fibrosis (Table 1) [16]. Each scored on a 0-3 ordinal scale. Steatosis was graded by the estimated proportion of hepatocytes involved (0 <10%, 1 10-30%, 2 31-60%, 3 >60%). Inflammation was scored as 0 (none), 1 (moderate; scattered inflammatory cells), 2 (marked; focal aggregates), or 3 (severe; diffuse infiltrates). Necrosis was graded according to estimated extent (0 = 0%, 1 <10%, 2 10-50%, 3 >50%). Fibrosis was scored as 0 (absent), 1 (mild; pericentral thickening around the centrolobular vein [CLV]), 2 (marked; prominent pericentral fibrosis), or 3 (severe; cirrhotic remodeling). For each animal, multiple non-overlapping fields were assessed at a standardized magnification (200× and 400×) across the section, and representative photomicrographs were captured using identical acquisition settings for figure preparation.

Table 1 Liver injury scoring system

Histological criteria	Severity	Description	Score
Steatosis	Absent	< 10%	0
	Mild	10-30%	1
	Marked	31-60%	2
	Severe	> 60%	3
Inflammation	None		0
	Moderate	Scattered	1
	Marked	Foci	2
	Severe	Diffuse	3
Necrosis	Absent	0%	0
	Mild	< 10%	1
	Marked	10-50%	2
	Severe	> 50%	3
Fibrosis	Absent		0

	Mild		1
	Marked		2
	Severe		3

2.4. Statistical analyses

All analyses were performed using GraphPad Prism v9.0. Because the histopathological outcomes were recorded on an ordinal scale (0-3), data are presented as median (interquartile range [IQR]). Between-group comparisons for each domain score (steatosis, inflammation, necrosis, and fibrosis) and for the composite injury score (sum of domain scores) were conducted using the Kruskal-Wallis test. When the overall test was significant, Dunn's post hoc test with an appropriate adjustment for multiple comparisons (Bonferroni) was applied to identify pairwise group differences. All tests were two-sided, and $p < 0.05$ was considered statistically significant

3. Results

This study evaluated whether post-exposure oral administration of *P. pellucida* extract (200 mg/kg body weight for 4 weeks) could attenuate cigarette smoke-induced hepatic histopathological injury in Wistar rats. As shown in Figure 1, livers from the SHAM group (Figure 1A) exhibited preserved lobular architecture, with well-organized hepatocyte plates and patent sinusoidal spaces, without appreciable inflammatory aggregates or overt necrotic change in the representative field.

In contrast, the SMOKE group (Figure 1B) demonstrated clear structural derangements consistent with smoke-related hepatic injury. These sections showed disrupted parenchymal organization accompanied by conspicuous inflammatory cell infiltration concentrated along vascular/tract regions and evidence of vascular/sinusoidal congestion, indicating an inflammatory and hemodynamic component to the tissue response following chronic smoke exposure.

Notably, post-exposure treatment with *P. pellucida* extract was associated with a visible improvement in hepatic morphology. The SMOKE+EXTRACT group (Figure 1C) displayed better-preserved tissue architecture relative to the SMOKE group, with less prominent inflammatory infiltrates and reduced congestion, suggesting partial normalization toward the control phenotype. Taken together, these representative H&E sections support that post-exposure *P. pellucida* treatment mitigates key histopathological features of cigarette smoke–induced liver injury.

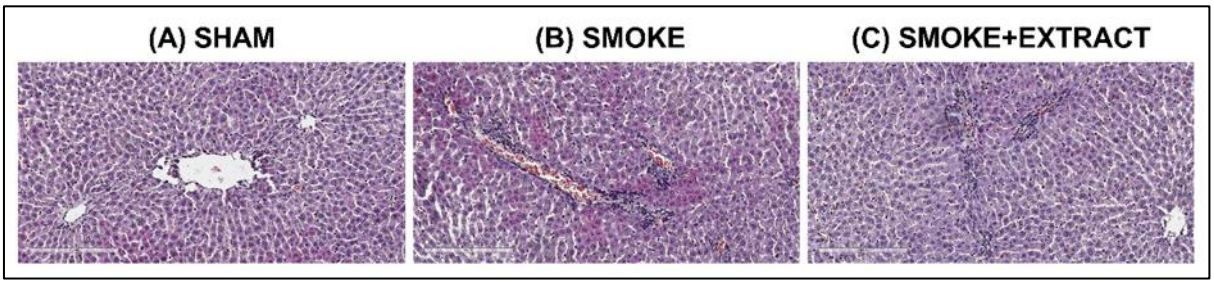

Figure 1 Representative hematoxylin and eosin (H&E)-stained liver sections illustrating the effect of post-exposure *Peperomia pellucida* extract on cigarette smoke-induced hepatic injury in Wistar rats. (A) SHAM: preserved lobular architecture with orderly hepatocyte plates and patent sinusoidal spaces. (B) SMOKE: structural disorganization with prominent inflammatory cell infiltration in peri-vascular/tract regions and vascular/sinusoidal congestion. (C) SMOKE+EXTRACT: partial restoration of hepatic architecture with reduced inflammatory infiltrates and congestion following post-exposure oral *P. pellucida* treatment (200 mg/kg body weight, 4 weeks) after 4 weeks of cigarette smoke exposure (1 cigarette/rat/day). Scale bar, 200 μm

Moreover, semi-quantitative grading of liver sections demonstrated that cigarette smoke exposure imposed a broad injury phenotype, with coordinated increases across all four prespecified domains (Figure 2A-D). Compared with the SHAM group, where scores clustered at the lower end of the scale, the SMOKE group showed a pronounced upward shift in steatosis, inflammation, necrosis, and fibrosis, consistent with multi-component parenchymal injury and remodeling (SMOKE vs SHAM: $p < 0.0001$ for each domain, Kruskal–Wallis with Dunn's multiple comparisons).

Initiating *P. pellucida* treatment after cessation of smoke exposure was associated with a significant attenuation of injury severity. The SMOKE+EXTRACT group exhibited lower grades than SMOKE across domains, with the clearest reductions observed for steatosis and necrosis ($p < 0.01$; Figure 2A and 2C), indicating that post-exposure therapy mitigated both lipid-associated parenchymal change and overt tissue injury. Improvements in inflammation and fibrosis were also evident, although the magnitude of separation from the SMOKE group was smaller ($p < 0.05$; Figure 2B and 2D). Overall, the distribution of individual scores in the SMOKE+EXTRACT group shifted toward the SHAM phenotype, supporting a restorative effect of post-exposure *P. pellucida* administration on cigarette smoke-induced hepatic histopathology.

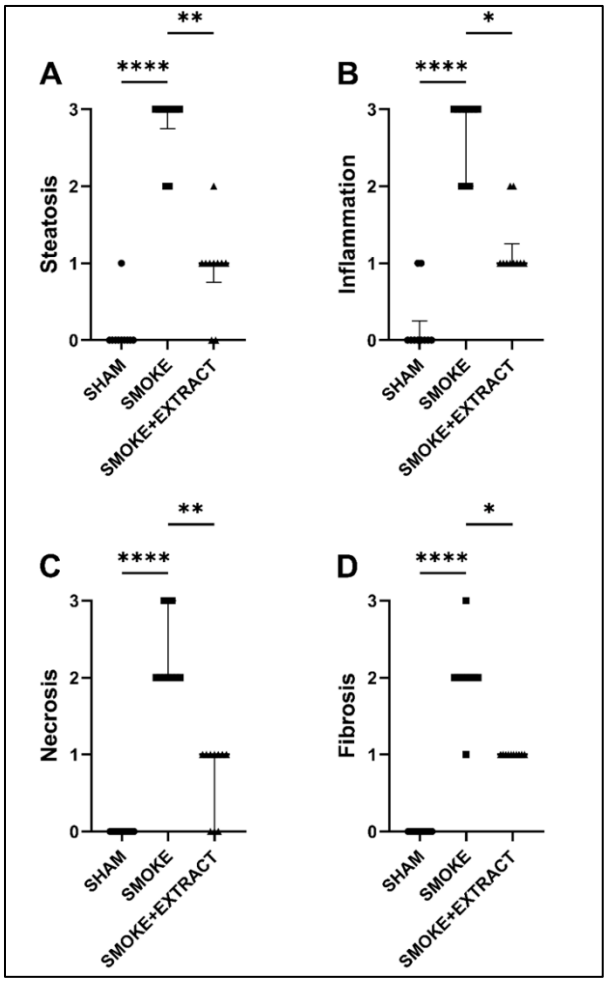

Figure 2 Post-exposure *Peperomia pellucida* extract attenuates cigarette smoke-induced liver injury scores. Semi-quantitative ordinal grading (0-3) of hepatic histopathology for (A) steatosis, (B) inflammation, (C) necrosis, and (D) fibrosis in SHAM, SMOKE, and SMOKE+EXTRACT groups. Points represent individual animals; horizontal bars indicate group median with interquartile range. Statistical comparisons were performed using Kruskal-Wallis followed by Dunn's multiple-comparisons test. ****$p < 0.0001$; **$p < 0.01$; *$p < 0.05$

4. Discussion

Cigarette smoke exposure is increasingly recognized as a systemic toxicant with clinically relevant hepatic consequences, extending beyond its established cardiopulmonary effects [17]. Epidemiologic syntheses indicate that active smoking is associated with a higher likelihood of fatty liver disease, and that passive exposure may also increase risk, supporting the concept that inhalational toxicants can contribute to metabolic liver injury even in the absence of direct hepatic exposure to combusted products [9,18–20]. Consistent with these human observations, experimental studies have shown that cigarette smoke can aggravate hepatosteatosis and promote progression toward steatohepatitis, in part through redox imbalance and inflammatory activation. Within this framework, the present post-exposure model is clinically pertinent because many individuals reduce or cease exposure only after harm has begun, and a key translational question is whether hepatic injury remains modifiable during the recovery phase.

A central implication of the current findings is that smoke-related liver injury appears to involve a coupled phenotype spanning metabolic disturbance (steatosis), immune activation (inflammation), parenchymal injury (necrosis), and early remodeling (fibrosis) [21,22]. This multidomain pattern aligns with contemporary mechanistic understanding summarized in hepatology reviews: cigarette smoke can disrupt lipid handling, amplify oxidative stress, and stimulate inflammatory and cell-death pathways that, when recurrent, may prime fibrogenic signaling [23]. The liver is particularly susceptible because of its role in xenobiotic metabolism and the sensitivity of Kupffer cells and hepatic stellate cells to circulating danger signals [24]. Notably, even secondhand smoke has been linked experimentally to hepatic steatosis through mechanisms involving stress-responsive signaling and metabolic reprogramming, reinforcing plausibility for injury in passive exposure contexts [8].

The post-exposure improvement observed with *P. pellucida* extract is biologically credible given the plant's reported phytochemical profile and pharmacological activities. Recent reviews summarize *P. pellucida* as containing multiple bioactive constituents, including polyphenols and flavonoids, and describe antioxidant and anti-inflammatory properties across experimental settings [11,12,25]. In the context of smoke-induced liver injury, these activities are relevant because oxidative stress is repeatedly implicated as a key driver linking smoke exposure to hepatocellular damage and steatohepatitis-like changes in animal models [21,26]. A reasonable interpretation is that *P. pellucida* may support the transition from injury propagation to resolution by dampening redox-driven lipid peroxidation and restraining inflammatory amplification, processes that can persist after exposure ends and delay tissue recovery. Importantly, the post-exposure design strengthens this interpretation: rather than preventing toxin contact, the intervention is positioned to modify the downstream biology of damage and repair.

The pattern of improvement across domains also fits what is known about the tempo of hepatic lesion reversibility. Steatosis and inflammatory activity are often more labile than fibrosis, which tends to reflect cumulative remodeling and may regress more slowly. Human studies support the clinical relevance of this point: smoking has been associated with greater fibrosis severity in NAFLD, suggesting that tobacco exposure may accelerate remodeling in susceptible livers [21,23,27]. In a short-duration model, a reduction in fibrosis grade should therefore be interpreted cautiously as an early signal of attenuated remodeling rather than definitive collagen regression. Methodologically, this underscores the value of pairing H&E-based grading with collagen-sensitive stains (e.g., Sirius red or Masson's trichrome) and quantitative morphometry in future studies to more precisely characterize extracellular matrix changes.

Several limitations merit consideration when positioning these. First, the study uses a single extract dose and duration; dose–response relationships and the minimal effective post-exposure window remain undefined. Second, while daily cigarette exposure is pragmatic, exposure verification (e.g., chamber particulate monitoring or cotinine) would strengthen inferences about delivered dose and inter-animal variability. Third, histopathological grading captures clinically meaningful endpoints, yet mechanistic depth would be enhanced by linking morphology to serum biochemistry (ALT/AST), oxidative stress indices, and markers of inflammatory/fibrogenic signaling. Finally, because the outcomes are ordinal, reporting effect sizes alongside nonparametric testing can better convey biological magnitude and reproducibility, particularly in small-to-moderate group sizes.

Despite these constraints, the present study contributes a clear translational message: hepatic injury attributable to cigarette smoke exposure is not necessarily fixed at the point of exposure cessation, and a phytochemical-rich intervention initiated post-exposure can shift the injury phenotype toward histological recovery. Given the epidemiologic links between smoking (including passive exposure) and fatty liver disease risk, these findings support further investigation of *P. pellucida* as a candidate adjunct aimed at restoring hepatic homeostasis after toxicant exposure. Next-step studies should incorporate (i) multi-dose and time-course designs, (ii) exposure biomarkers, (iii) collagen-specific histochemistry and quantitative image analysis for fibrosis, and (iv) targeted molecular readouts aligned with smoke-related pathways highlighted in prior experimental work (oxidative stress, inflammatory signaling, and cell-death programs).

5. Conclusion

This study demonstrates that subchronic cigarette smoke exposure induces a multi-domain pattern of hepatic injury in Wistar rats, encompassing steatosis, inflammation, necrosis, and early fibrotic remodeling. Importantly, initiating *P. pellucida* extract after cessation of smoke exposure (200 mg/kg body weight, orally for 4 weeks) significantly attenuated histopathological injury scores and improved overall tissue architecture relative to smoke exposure alone. These findings support *P. pellucida* as a promising post-exposure hepatoprotective candidate and warrant further investigation using dose-response designs, collagen-specific fibrosis staining, and mechanistic biomarkers to clarify pathways and translational relevance.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that there are no financial or personal relationships that could have influenced the work reported in this paper.

Statement of ethical approval

All procedures complied with institutional and national guidelines for animal care and were approved by Institutional Animal Ethics Committee, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya (Approval No. 79/SLE/FK/UWKS/2023).

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