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Prophylactic *Peperomia pellucida* Extract Preserves Myocardial Histomorphology in Secondhand Smoke-Exposed Wistar Rats: A Histopathological Study

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Abstract

Secondhand smoke (SHS) is a persistent involuntary exposure; the World Health Organization estimates that ~1.6 million non-smokers die annually from SHS, and global cardiovascular deaths attributable to SHS reached 598,500 in 2019. We evaluated whether prophylactic *Peperomia pellucida* extract preserves myocardial histomorphology in SHS-exposed rats. An ethanolic aerial-part extract was prepared by 72-h maceration in 96% ethanol. Thirty male Wistar rats (6-8 weeks; 220-280 g) were randomized to Vehicle (ambient air), SHS (one cigarette/rat/day for 4 weeks), or SHS + *P. pellucida* (200 mg/kg/day by oral gavage), initiated 7 days before SHS and continued throughout exposure (n=10/group). At study endpoint, hearts were excised under ketamine-xylazine anesthesia, fixed in 10% neutral buffered formalin for 24 h, paraffin-embedded, sectioned (4-5 µm), and stained with hematoxylin-eosin. Slides were digitized (Aperio CS2) and reviewed in ImageScope. Myocardial injury in ventricular sections was graded on a 0-4 semi-quantitative scale and compared using Kruskal-Wallis with Dunn's post hoc testing. SHS produced prominent disruption of myofiber organization with interstitial expansion and significantly increased injury scores versus Vehicle ($p < 0.0001$). Prophylactic *P. pellucida* reduced injury severity relative to SHS alone ($p = 0.0229$), shifting scores toward milder grades. These findings indicate that prophylactic *P. pellucida* partially preserves myocardial architecture under SHS exposure, supporting follow-up studies that integrate functional endpoints and mechanistic biomarkers.

Keywords: Tobacco Smoke Pollution; *Peperomia*; Myocardium; Plant Extracts; Heart Injuries

1. Introduction

Secondhand smoke (SHS), also termed environmental tobacco smoke, remains a persistent, largely involuntary exposure in homes, workplaces, and public environments [1,2]. Despite substantial progress in smoke-free legislation in many countries, enforcement gaps and household exposure mean that non-smokers continue to inhale a complex mixture of fine particulates and toxic gases generated from sidestream and exhaled mainstream smoke [1]. The World Health Organization (WHO) underscores that there is no safe level of SHS exposure and estimates that tobacco use kills millions annually, including 1.6 million non-smokers who die from exposure to second-hand smoke [3–5].

The cardiovascular burden of SHS is particularly concerning because clinically meaningful harm can occur in people who have never smoked [6]. In the United States, Centers for Disease Control and Prevention (CDC) estimates indicate that SHS exposure among adults who do not smoke causes nearly 34,000 premature deaths from heart disease each year, and increases the risk of coronary heart disease by 25 to 30% [7–9]. Beyond national estimates, global epidemiology continues to highlight SHS as a major cardiovascular risk factor: an analysis of Global Burden of Disease-linked data reported that cardiovascular deaths attributable to SHS increased from 1990 to 2019, reaching 598,500

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deaths in 2019 [3–5]. These figures reinforce the public-health reality that passive exposure is not a minor nuisance but a contributor to preventable cardiovascular morbidity and mortality.

Mechanistically, SHS exerts cardiovascular toxicity through intertwined pathways that culminate in myocardial structural injury. Experimental and translational literature describes how SHS promotes oxidative stress, endothelial dysfunction, platelet activation, autonomic imbalance, and systemic inflammation, processes that can impair coronary microvascular function and increase cardiomyocyte vulnerability [9–12]. Over time or with repeated exposure, such disturbances may translate into histopathological changes including myofiber degeneration, cytoplasmic vacuolization, interstitial edema, inflammatory infiltration, and early remodeling, features that are relevant to the progression from subclinical injury to clinically meaningful cardiac dysfunction [11,13,14].

Primary prevention through comprehensive smoke-free environments remains the most effective strategy to reduce SHS-related harm [1,8]. Nonetheless, exposure persists in real-world settings, and women may be disproportionately affected in household contexts where smoking prevalence is higher among men and smoke-free rules are inconsistently applied. This gap between policy ideals and lived exposure has driven interest in adjunct approaches that might blunt oxidative and inflammatory injury cascades when avoidance is incomplete, without detracting from the primacy of exposure elimination.

Peperomia pellucida is a medicinal plant with growing pharmacological interest, with reports describing a phytochemical profile rich in polyphenols and flavonoid-related constituents and biological activities aligned with redox and inflammatory modulation [15,16]. While such properties do not automatically translate into cardioprotection, they provide a rationale to test whether prophylactic supplementation could preserve myocardial microarchitecture in toxicant-driven injury models where oxidative stress and inflammation are central. Therefore, this study aimed to evaluate whether prophylactic (pre-exposure) administration of *P. pellucida* extract preserves myocardial histomorphology and reduces histopathological evidence of myocardial injury in Wistar rats subjected to secondhand smoke exposure, thereby providing tissue-level evidence that complements the well-established epidemiologic association between SHS and cardiovascular disease.

2. Material and method

2.1. Preparation of *Peperomia pellucida* Extract

The aerial parts (leaves and young stems) of *P. pellucida* were harvested and the species identity was confirmed by a qualified botanist from Materia Medica Herbal Laboratory, Batu, East Java, Indonesia. A representative specimen was prepared and deposited in the same institution (No. 000.9.3/2684/102.20/2023), enabling independent verification of the plant material. After collection, the plant material was rinsed to remove surface impurities, then shade-dried at ambient temperature until a constant weight was reached. The dried material was ground to obtain a coarse powder. Extraction was performed by maceration using 96% ethanol as the solvent for 72 h at room temperature, with intermittent mixing to facilitate solvent penetration. The extract was separated by filtration, and the plant residue was re-extracted under identical conditions to improve recovery. The combined filtrates were then evaporated under reduced pressure (rotary evaporation) to remove ethanol and yield a concentrated crude extract, which was subsequently dried to constant weight.

The final extract was stored in light-protected, airtight containers at 4 °C (short-term) until use. For dosing, the extract was freshly prepared on the day of administration by dissolving it in distilled water at 200 mg/kg body weight (BW), with thorough mixing to ensure uniformity prior to delivery [17,18].

2.2. Study Design, Animals, and Ethics

This experimental study was designed to evaluate whether *P. pellucida* extract preserves myocardial histomorphology in a secondhand cigarette smoke exposure model, with hematoxylin and eosin (H&E)-based cardiac histopathology defined a priori as the primary endpoint. Thirty male Wistar rats (6-8 weeks old; 220-280 g) were obtained from an accredited breeding facility and acclimatized prior to experimentation. Animals were housed under standard laboratory conditions (controlled temperature and humidity, 12 h light/dark cycle) with *ad libitum* access to standard chow and water.

Rats were randomly allocated into three groups (n = 10 per group): (1) Vehicle control, receiving vehicle only and ambient air exposure; (2) SHS, exposed to secondhand cigarette smoke daily for 4 weeks; and (3) SHS + *P. pellucida* (200 mg/kg), receiving *P. pellucida* extract at 200 mg/kg BW by oral gavage once daily. In the treatment group, extract

administration was initiated 7 days prior to the first smoke exposure (prophylactic phase) and continued throughout the 4-week exposure period.

Secondhand smoke exposure was conducted for 4 consecutive weeks, once daily, using a standardized exposure protocol in a designated exposure chamber. Each rat was exposed to smoke generated from one cigarette per rat per day, delivered under controlled conditions to ensure consistent exposure across sessions. Animals in the non-exposed control group were handled similarly but exposed to ambient air [19].

All procedures complied with institutional and national guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Ethics Committee, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia (Approval No. 80/SLE/FK/UWKS/2023). Animal welfare was monitored throughout the study by daily clinical observation, and predefined humane endpoints were applied when necessary to minimize suffering.

2.3. Heart Collection, Fixation, and Hematoxylin-Eosin Staining

At the study endpoint, animals were anesthetized with a ketamine-xylazine mixture administered intraperitoneally until a surgical plane of anesthesia was achieved. Once adequate anesthesia was confirmed (absence of pedal withdrawal reflex), the thoracic cavity was opened and the heart was rapidly excised. The tissue was gently cleared of adherent connective tissue and briefly rinsed in cold phosphate-buffered saline (PBS) to remove residual blood.

For histological consistency, the heart was processed to obtain a standardized myocardial section. In this study, specimens were prepared as a transverse (short-axis) slice at the mid-ventricular level, which provides a reproducible representation of myocardial architecture across animals. The representative slice was immediately immersed in 10% neutral buffered formalin for 24 h at room temperature.

Following fixation, samples underwent routine paraffin histology. Briefly, tissues were dehydrated through graded ethanol, cleared in xylene, and embedded in paraffin. Sections of 4-5 μm thickness were cut using a rotary microtome, mounted on glass slides, deparaffinized, and rehydrated. Slides were stained with H&E using standard protocols, then dehydrated, cleared, and coverslipped with a permanent mounting medium. All stained slides were digitized directly as whole-slide images using an Aperio CS2 slide scanner (Leica Biosystems Imaging, Inc., Vista, CA, USA) and reviewed using Aperio ImageScope (Leica Biosystems Imaging, Inc., Vista, CA, USA) for documentation and subsequent histopathological assessment.

For histopathological grading, myocardial injury was evaluated on H&E sections that included both the right and left ventricles using a semi-quantitative 5-point scale (0-4). Scores were assigned as follows: 0, no detectable injury; 1, minimal injury characterized by scattered/isolated myocyte damage; 2, a single discrete focal area of myocardial injury; 3, multiple (≥ 2) separate foci of injury; and 4, diffuse myocardial damage involving more than 50% of the examined myocardium [20].

3. Results

Representative H&E sections from the Vehicle group showed preserved myocardial architecture, with orderly, continuous cardiomyocyte bundles and no overt histological evidence of injury (Fig. 1A). In contrast, hearts from the secondhand smoke (SHS) group exhibited clear structural disruption, characterized by myofiber disorganization with widened interstitial spaces and scattered areas consistent with myocyte injury (Fig. 1B). Treatment with *P. pellucida* in SHS-exposed rats was associated with an apparent improvement in tissue organization; myocardial bundles appeared more continuous with fewer and less extensive areas of disruption compared with SHS alone, although mild changes remained detectable in some regions (Fig. 1C).

Semi-quantitative grading (0-4 scale) corroborated these histological observations (Fig. 1D). The SHS group demonstrated a marked increase in injury severity compared with Vehicle ($p < 0.0001$, Dunn's post hoc). Administration of *P. pellucida* significantly reduced the myocardial injury score relative to SHS alone ($p = 0.0229$, Dunn's post hoc), indicating partial attenuation of SHS-associated cardiac histopathological damage. Across animals, scores clustered near 0 in the Vehicle group, shifted predominantly to 3-4 in the SHS group, and were lower (commonly 1-2) in the SHS + *P. pellucida* group (Fig. 1D).

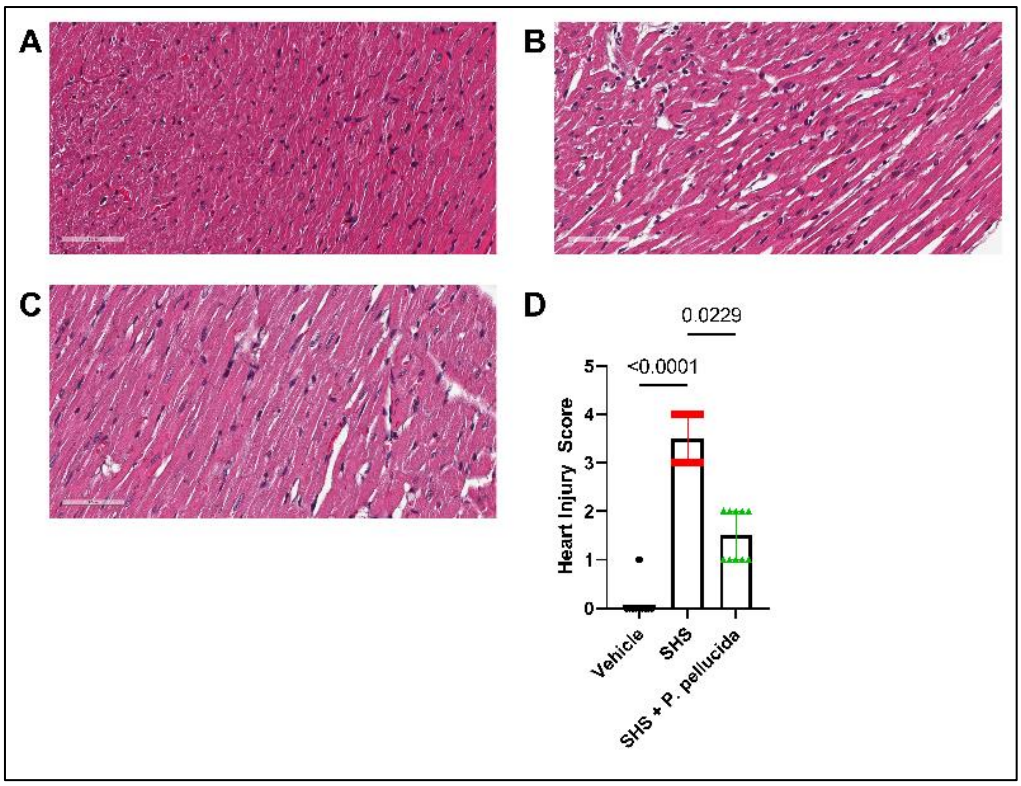

Figure 1 *Peperomia pellucida* mitigates secondhand smoke-associated myocardial histopathological injury. Representative hematoxylin & eosin (H&E)-stained myocardial sections from (A) Vehicle, showing preserved myocardial architecture; (B) SHS, demonstrating disrupted myofiber organization with widened interstitial spaces and features consistent with myocyte injury; and (C) SHS + *P. pellucida*, showing partial preservation of myocardial structure relative to SHS alone. (D) Semi-quantitative myocardial injury scores (0-4) presented as median (IQR) with overlaid individual data points. Group comparisons were analyzed using Kruskal-Wallis followed by Dunn's multiple-comparisons test; *p*-values are indicated (Vehicle vs SHS, $p < 0.0001$; SHS vs SHS + *P. pellucida*, $p = 0.0229$). Scale bars: 60 µm

4. Discussion

This study provides histopathological evidence that secondhand smoke (SHS) exposure is associated with appreciable myocardial injury in Wistar rats and that *P. pellucida* treatment partially mitigates these structural alterations, as reflected by both representative H&E features and a semi-quantitative injury score. Although our endpoint was limited to routine histology, the direction and magnitude of change are biologically plausible and align with the concept that smoke exposure can precipitate early myocardial injury before overt clinical dysfunction becomes evident.

The injurious myocardial pattern observed after SHS exposure is consistent with the broader cardio-toxic profile of tobacco smoke reported in experimental and clinical literature [12–14,21]. Comprehensive reviews of SHS note that even brief exposure can provoke oxidative stress-related injury, including oxidative DNA damage in the myocardium, alongside inflammatory activation that can amplify tissue damage [22]. Beyond acute oxidative effects, repeated exposure has been linked to remodeling phenotypes. For example, Wistar rats exposed to cigarette smoke in a controlled regimen developed cardiac fibrosis in a dose-dependent fashion, supporting the notion that smoke can drive structural remodeling at the tissue level [11,12]. In aging-related models, SHS has similarly been shown to enhance adverse ventricular remodeling and fibrotic pathways, underscoring that myocardial structure can be a sensitive readout of smoke-associated injury [11]. Our findings add to this line of evidence by demonstrating that, in our conditions, SHS produced a marked upward shift in injury scores, while treatment shifted the distribution toward milder grades.

From a mechanistic standpoint, several converging pathways could explain the myocardial changes induced by SHS. Tobacco smoke exposure is known to impair cardiovascular health through endothelial dysfunction, inflammatory signaling, and oxidative stress, which together compromise perfusion, promote leukocyte-endothelium interactions, and increase vulnerability of cardiomyocytes to injury [14]. These processes can manifest histologically as myofiber

disarray, interstitial expansion/edema, and focal cellular injury, features that were captured by our scoring rubric. Several studies also emphasizes that SHS can exert disproportionately large cardiovascular effects relative to dose, reinforcing the clinical relevance of passive exposure as a risk factor [2,5,7,8].

The histological improvement associated with *P. pellucida* is related a broad spectrum of bioactives (including polyphenols and flavonoids) and has been repeatedly characterized as having antioxidant and anti-inflammatory potential across experimental systems [17,23,24]. Recent work further supports immunomodulatory effects, with *P. pellucida* extracts influencing inflammatory mediator profiles *in vivo*, consistent with down-tuning pathways that are commonly activated during smoke-related injury [18,19]. In addition, mechanistic studies and reviews have highlighted signaling nodes such as NF-κB and related inflammatory pathways as targets for *P. pellucida*-derived constituents [25]. While our study did not quantify oxidative stress markers or cytokines, the observed reduction in injury scores is compatible with a model in which *P. pellucida* attenuates SHS-triggered redox imbalance and inflammatory amplification, thereby limiting downstream cardiomyocyte injury and interstitial derangement.

Our results also align with the emerging (though still limited) cardiovascular-adjacent evidence for *P. pellucida*. For example, an experimental report evaluating *P. pellucida* ethanolic extract in a cardiac injury context (doxorubicin-induced cardiotoxicity) described cardioprotective trends across electrical and inflammatory/biomarker indices, supporting the idea that this plant can influence pathways relevant to myocardial injury [26]. Although the trigger in that model differs from SHS, both insults converge on oxidative and inflammatory stress responses, which may explain why *P. pellucida* shows signal across distinct cardiac injury paradigms. Taken together, these studies strengthen biological plausibility for our histopathological findings, while also emphasizing the need to define dose-response relationships and active constituents more precisely.

Several limitations should be acknowledged. First, our outcome was restricted to H&E histopathology and semi-quantitative scoring. This approach is valuable for structural assessment, but it cannot distinguish specific mechanisms (e.g., oxidative stress vs microvascular dysfunction) and does not directly quantify fibrosis, apoptosis, or cardiomyocyte ultrastructural changes. Second, the ordinal scoring system, while practical and widely used, is inherently observer-dependent; rigorous blinding, inter-rater agreement reporting, and standardized field sampling are important to minimize bias and should be clearly documented (or expanded in future work). Third, without functional endpoints (e.g., echocardiography, hemodynamics) or biochemical readouts (e.g., MDA/SOD/GSH, inflammatory cytokines), the extent to which histological improvement translates into preserved cardiac function remains uncertain. Finally, more granular exposure characterization (e.g., chamber concentration metrics and/or cotinine verification) would strengthen causal inference for SHS dose-injury relationships.

Despite these constraints, the present findings support a coherent interpretation: SHS exposure is sufficient to induce measurable myocardial structural injury, and prophylactic *P. pellucida* treatment reduces the severity of these lesions on routine histology. Future studies should (i) incorporate functional cardiac assessment, (ii) pair H&E with collagen-specific staining (e.g., Masson's trichrome) and apoptosis/oxidative stress assays, and (iii) consider extract standardization (marker-guided phytochemical profiling) to improve reproducibility and translational value. Within a broader public-health context in which SHS remains a clinically relevant cardiovascular risk, these data provide a rationale for deeper mechanistic evaluation of *P. pellucida* as a candidate adjunct to mitigate tobacco smoke pollution-associated myocardial injury.

5. Conclusion

In this rat model, secondhand smoke exposure produced clear myocardial histopathological injury, reflected by disruption of myocardial architecture and a marked increase in semi-quantitative injury scores. Prophylactic *P. pellucida* administration significantly attenuated these structural alterations, shifting injury severity toward milder grades. Although the present work is limited to H&E-based assessment and does not establish mechanistic pathways or functional benefit, the findings support the histomorphological cardioprotective potential of *P. pellucida* against secondhand smoke-associated myocardial damage and provide a rationale for follow-up studies integrating functional cardiac evaluation, fibrosis-specific staining, and oxidative/inflammatory biomarkers to clarify translational relevance.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

All procedures complied with institutional and national guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Ethics Committee, Faculty of Medicine, Universitas Wijaya Kusuma Surabaya, Surabaya, Indonesia (Approval No. 80/SLE/FK/UWKS/2023).

References

[1] Nurhasana R, Ratih SP, Djaja K, Hartono RK, Dartanto T. Passive Smokers' Support for Stronger Tobacco Control in Indonesia. Int J Environ Res Public Health 2020;17:1942. https://doi.org/10.3390/ijerph17061942.

[2] Tsai J, Homa DM, Gentzke AS, Mahoney M, Sharapova SR, Sosnoff CS, et al. Exposure to Secondhand Smoke Among Nonsmokers — United States, 1988–2014. MMWR Morb Mortal Wkly Rep 2018;67:1342–6. https://doi.org/10.15585/MMWR.MM6748A3.

[3] Xiang S, Chen Z, Dai Z, Wang F. Global burden of lower respiratory infections attributable to secondhand smoke among children under 5 years of age, 2010–2019: a systematic analysis of the global burden of disease study 2019. BMC Public Health 2023;23:1920. https://doi.org/10.1186/s12889-023-16848-5.

[4] Zhai C, Hu D, Yu G, Hu W, Zong Q, Yan Z, et al. Global, regional, and national deaths, disability-adjusted life years, years lived with disability, and years of life lost for the global disease burden attributable to second-hand smoke, 1990–2019: A systematic analysis for the Global Burden of Disease Study. Science of The Total Environment 2023;862:160677. https://doi.org/10.1016/j.scitotenv.2022.160677.

[5] Flor LS, Anderson JA, Ahmad N, Aravkin A, Carr S, Dai X, et al. Health effects associated with exposure to secondhand smoke: a Burden of Proof study. Nat Med 2024;30:149–67. https://doi.org/10.1038/s41591-023-02743-4.

[6] Brody DJ, Faust E, Tsai J. Secondhand Smoke Exposure Among Nonsmoking Adults: United States, 2015-2018. NCHS Data Brief 2021:1–8.

[7] Okekunle AP, Asowata JO, Adedokun B, Akpa OM. Secondhand smoke exposure and dyslipidemia among non-smoking adults in the United States. Indoor Air 2022;32:e12914.

[8] Arfaeinia H, Ghaemi M, Jahantigh A, Soleimani F, Hashemi H. Secondhand and thirdhand smoke: a review on chemical contents, exposure routes, and protective strategies. Environmental Science and Pollution Research 2023;30:78017–29. https://doi.org/10.1007/s11356-023-28128-1.

[9] Zhang D, Liu Y, Cheng C, Wang Y, Xue Y, Li W, et al. Dose-related effect of secondhand smoke on cardiovascular disease in nonsmokers: Systematic review and meta-analysis. Int J Hyg Environ Health 2020;228:113546. https://doi.org/10.1016/j.ijheh.2020.113546.

[10] Pan S, Karey E, Nieves-Cintron M, Chen Y-J, Hwang SH, Hammock BD, et al. Effects of chronic secondhand smoke exposure on cardiovascular regulation and the role of soluble epoxide hydrolase in mice. Front Physiol 2023;14:1185744.

[11] Wu J-P, Chang-Lee SN, Day CH, Ho T-J, Viswanadha VP, Chung L-C, et al. Secondhand Smoke Exposure Enhances Cardiac Fibrosis Effects on the Aging Rat Hearts. Acta Cardiol Sin 2016;32:594–603. https://doi.org/10.6515/acs20150824c.

[12] Aska AA Al, Soetedjo FA, Kristijanto JAF. Efek Protektif Ekstrak *Peperomia pellucida* terhadap Fibrosis Jantung yang Diinduksi Pajanan Asap Rokok: Suatu Studi Pre-Klinis. Jurnal Sehat Indonesia (JUSINDO) 2025;7:586–94. https://doi.org/10.59141/jsi.v7i2.299.

[13] Wang K, Wang Y, Zhao R, Gong L, Wang L, He Q, et al. Relationship between childhood secondhand smoke exposure and the occurrence of hyperlipidaemia and coronary heart disease among Chinese non-smoking women: a cross-sectional study. BMJ Open 2021;11:e048590. https://doi.org/10.1136/bmjopen-2020-048590.

[14] El-Mahdy MA, Abdelghany TM, Hemann C, Ewees MG, Mahgoup EM, Eid MS, et al. Chronic cigarette smoke exposure triggers a vicious cycle of leukocyte and endothelial-mediated oxidant stress that results in vascular dysfunction. American Journal of Physiology-Heart and Circulatory Physiology 2020;319:H51–65. https://doi.org/10.1152/ajpheart.00657.2019.

[15] Gomes PWP, Barretto H, Reis JDE, Muribeca A, Veloso A, Albuquerque C, et al. Chemical Composition of Leaves, Stem, and Roots of *Peperomia pellucida* (L.) Kunth. Molecules 2022;27:1847. https://doi.org/10.3390/molecules27061847.

[16] Alves NSF, Setzer WN, da Silva JKR. The chemistry and biological activities of *Peperomia pellucida* (Piperaceae): A critical review. J Ethnopharmacol 2019;232:90–102. https://doi.org/10.1016/j.jep.2018.12.021.

[17] Putra IBKAD, Pratiwi NPA, Idrus MF, Alwi RH, Kristijanto JAF, Soetedjo FA. *Peperomia pellucida* Extract Mitigates Cigarette Smoke-Induced Hepatic Histopathological Injury in Wistar Rats: A Post-Exposure Treatment Study. Magna Scientia Advanced Research and Reviews 2026;16:028–35. https://doi.org/10.30574/msarr.2026.16.1.0007.

[18] Soetedjo FA, Kristijanto JA, Agusaputra H, Kusumaningtyas MJ. *Peperomia pellucida* Extract Ameliorates Secondhand Smoke Exposure-Induced Lung Fibrogenesis via Regulation of Matrix Metalloproteinase, Inflammatory, and Fibrotic Cytokines: A Pre-Clinical Study. Pharmaceutical Sciences Asia Pharm Sci Asia 2024;51:223–32. https://doi.org/10.29090/psa.2024.03.24.AP0565.

[19] Kristijanto JAF, Zahiroh VN, Triadi A, Khamidah N, Soetedjo FA. Protective Effects of *Peperomia pellucida* Extract Against Secondhand Smoke-Induced Pulmonary Fibrosis via Antioxidant and Anti-inflammatory Pathways. Tropical Journal of Natural Product Research 2025;9. https://doi.org/10.26538/tjnpr/v9i9.50.

[20] Seo E-H, Song G-Y, Namgung JH, Oh C-S, Lee SH, Kim S-H. Receptor for activated C kinase 1 in rats with ischemia-reperfusion injury: intravenous versus inhalation anaesthetic agents. Int J Med Sci 2018;15:352–8. https://doi.org/10.7150/ijms.22591.

[21] Dianat M, Radan M, Badavi M, Mard SA, Bayati V, Ahmadizadeh M. Crocin attenuates cigarette smoke-induced lung injury and cardiac dysfunction by anti-oxidative effects: the role of Nrf2 antioxidant system in preventing oxidative stress. Respir Res 2018;19:58. https://doi.org/10.1186/s12931-018-0766-3.

[22] Kitamura Y, Mise N, Mori Y, Suzuki Y, Ohashi T, Tada-Oikawa S, et al. Proteomic identification of the proteins related to cigarette smoke-induced cardiac hypertrophy in spontaneously hypertensive rats. Sci Rep 2020;10:18825. https://doi.org/10.1038/s41598-020-75429-3.

[23] Firmansyah Idrus M, Falerio Kristijanto JA, Retno Arimbi M, Wardhani MK, Purbowati R, Syafawi SP N, et al. Total *Peperomia pellucida* Extract-Mediated Reversal of Renal Structural Damage Following Cessation of Cigarette Smoke Exposure in Wistar Rats. Asian Journal of Healthy and Science 2026;5:1–13. https://doi.org/10.58631/ajhs.v5i1.276.

[24] Tuan CT, Men TT. *Peperomia pellucida*'s Ingredients, Antioxidant Properties, and Safe Usage as Food and Herbal Medicine. J Microbiol Biotechnol 2024;34:2321–30. https://doi.org/10.4014/jmb.2406.06025.

[25] Ho KL, Yong PH, Wang CW, Lim SH, Kuppusamy UR, Arumugam B, et al. In vitro anti-inflammatory activity and molecular docking of *Peperomia pellucida* (L.) Kunth extract via the NF-κB and PPAR-γ signalling in human retinal pigment epithelial cells. Bioorg Chem 2024;153:107969. https://doi.org/10.1016/j.bioorg.2024.107969.

[26] Archibong EA, Beshel JA, Okon IA, Ikum GA, Anaba SC, Owu DU. Cardioprotective Effect of *Peperomia pellucida* against Doxorubicin-Induced Cardiotoxicity in Wistar Rats via Modulation of Electrocardiographic and Cardiac Biomarkers. J Pharmacopuncture 2024;27:297–307. https://doi.org/10.3831/KPI.2024.27.4.297