Amelioration of Cigarette Smoke-Induced Hepatic Injury by Green Tea (*Camellia sinensis*) Extract: Evidence from SGOT and SGPT Biomarkers in a Murine Model

Putra Indrajaya[1], Mudawamah[2], Umi Kalsum[2], Adinda Rizky Trisakti[3], Aldin Akbar Rahmatullah[4]*

[1]Master Program of Animal Husbandry, Universitas Islam Malang, Malang, Indonesia, [2]Faculty of Animal Sciences, Universitas Islam Malang, Malang, Indonesia, [3]Professional Program of Veterinary Medicine, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, Indonesia, [4]Veterinarian in AAR Vet Clinic, Banjarbaru, South Kalimantan, Indonesia.

Corresponding author: aldin.akbar01@yahoo.com

ABSTRACT

This study investigated the hepatoprotective effects of green tea extract (GTE) against cigarette smoke-induced liver damage in mice. Twenty-five male mice (*Mus musculus*) were divided into five groups: negative control (C-), positive control exposed to cigarette smoke (C+), and three experimental groups exposed to cigarette smoke and treated with different doses of GTE: 20 mg/kg BW (T1), 40 mg/kg BW (T2), and 60 mg/kg BW (T3). Following 36 days of treatment, serum SGOT and SGPT levels were measured as biomarkers of hepatocellular injury. Results showed significant elevation of both enzymes in the C+ group (SGOT: 50.46 ± 2.49 U/L; SGPT: 19.48 ± 1.47 U/L) compared to the C- group (SGOT: 35.10 ± 2.49 U/L; SGPT: 10.22 ± 1.68 U/L), indicating cigarette smoke-induced hepatotoxicity. GTE administration demonstrated dose-dependent hepatoprotection, with the highest dose (T3) showing the most substantial effect (SGOT: 38.26 ± 1.25 U/L; SGPT: 11.01 ± 1.05 U/L). Statistical analysis revealed significant differences between groups ($p<0.05$). The hepatoprotective mechanisms of GTE likely involve its potent antioxidant properties, enhancement of endogenous antioxidant systems, anti-inflammatory effects, modulation of xenobiotic metabolism, and mitochondrial protection. These findings suggest that green tea extract may serve as a promising natural hepatoprotective agent against cigarette smoke-induced liver injury, with potential applications in preventive healthcare strategies.

Keywords: green tea extract, hepatotoxicity, SGOT, SGPT, tobacco use

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INTRODUCTION

Cigarette smoking, affecting approximately 1.3 billion people globally, contributes to over 8 million deaths annually from tobacco-related diseases (Sakthisankaran *et al.*, 2024). While its impact on respiratory and cardiovascular systems is well-documented, its effects on hepatic function are less explored. As the primary organ for xenobiotic metabolism, the liver is susceptible to cigarette smoke's >7,000 chemicals, including 70 carcinogens and oxidative compounds (Sinha and Haider, 2024). These promote liver pathologies such as non-alcoholic fatty liver disease (NAFLD), fibrosis, and hepatocellular carcinoma (Marti-Aguado *et al.*, 2022).

Cigarette smoke induces hepatotoxicity primarily through oxidative stress, with reactive oxygen species (ROS) generated during hepatic metabolism of polycyclic aromatic hydrocarbons (PAHs) and nitrosamines by cytochrome P450 enzymes (Abu-Bakar *et al.*, 2022). This results in lipid

peroxidation, protein modification, DNA damage, and hepatocellular injury, evidenced by elevated serum liver enzymes, notably serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) (Banerjee *et al.*, 2023). These enzymes, sensitive indicators of hepatocyte damage, reflect cell membrane disruption and are widely used to assess liver injury (Tamber *et al.*, 2023).

Given smoking's prevalence, identifying hepatoprotective agents is critical. Natural antioxidants, particularly green tea (*Camellia sinensis*) extract (GTE), are promising due to their polyphenolic content, especially epigallocatechin-3-gallate (EGCG), comprising 30–40% of GTE solids (Natarajan *et al.*, 2019). EGCG exhibits potent antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial-protective properties by scavenging free radicals, chelating metal ions, and enhancing endogenous antioxidant defenses (Grzesik *et al.*, 2018; Mokra *et al.*, 2022). While GTE's benefits are reported in alcoholic liver disease, drug-induced hepatotoxicity, and metabolic disorders (Tang *et al.*, 2021; Winiarska-Mieczan *et al.*, 2024; Dinh *et al.*, 2019), its role in mitigating cigarette smoke-induced liver damage, including optimal dosing, remains underexplored.

This study investigates GTE's dose-dependent hepatoprotective effects against cigarette smoke-induced liver damage in mice, focusing on serum SGOT and SGPT levels as biomarkers. Using a controlled experimental model, we aim to determine whether GTE can attenuate enzyme elevations caused by smoke exposure, offering insights into its potential as a therapeutic intervention for smoking-related hepatotoxicity.

METHODS

Preparation of Green Tea Extract (GTE)

Green tea leaves (*Camellia sinensis*) were obtained from the Wonosari tea garden in Malang Regency, East Java, Indonesia. The extraction was performed using the maceration method. Briefly, 1000 g of green tea leaf powder was immersed in 8 L of 96% ethanol for 72 hours. The resulting macerate was subsequently concentrated using a rotary evaporator (50°C, 45 rpm) for 5 hours, followed by freeze-drying according to the protocol described by Khoirunnisa *et al.* (2019). The lyophilized extract was then reconstituted in 1% Na-CMC solution to obtain the required dosage concentrations for administration.

Experimental Design

Twenty-five healthy male mice (*Mus musculus*), aged 12 weeks and weighing 20-25 grams, with no previous experimental exposure, were utilized in this study. The animals were housed in cages with sawdust bedding and provided with standard pellet feed and drinking water ad libitum throughout the experimental period. Following a one-week acclimatization period, the mice were randomly allocated into five experimental groups (n=5 per group): Group C- (negative control): Received 0.5 mL of 1% Na-CMC without cigarette smoke exposure, Group K+ (positive control): Exposed to cigarette smoke and administered 0.5 mL of 1% Na-CMC, Group P1: Exposed to cigarette smoke and treated with GTE (20 mg/kg BW), Group P2: Exposed to cigarette smoke and treated with GTE (40 mg/kg BW), and Group P3: Exposed to cigarette smoke and treated with GTE (60 mg/kg BW).

The experimental interventions were conducted over a period of 36 days. Green tea extract was administered daily

via oral gavage (0.5 mL/mouse/day). For cigarette smoke exposure, mice in groups K+, P1, P2, and P3 were placed in a specialized exposure chamber (31 × 19 × 22 cm) equipped with smoke inlet and outlet ports. Each exposure session lasted 20 minutes, during which the animals were exposed to smoke generated from a single clove cigarette containing 2.2 mg nicotine (Fadhilah *et al.*, 2023).

Sample Collection and Biochemical Analysis

On day 37, all mice were euthanized by cervical dislocation under anesthesia. Blood samples were collected via cardiac puncture from the left ventricle and transferred into EDTA-containing tubes and anticoagulant-free tubes. The samples were allowed to stand at room temperature for 30 minutes before being centrifuged at 5000 rpm for 15 minutes to obtain serum.

SGOT and SGPT levels were determined using a spectrophotometric method. For SGPT analysis, clean tubes were prepared for blank, control, and samples. The blank tube was directly analyzed using a microlab 300 spectrophotometer, followed by the control tube containing 1000 µL of SGPT working reagent. For sample analysis, 100 µL of serum was combined with 1000 µL of SGPT working reagent in the sample tube and analyzed using the microlab 300 spectrophotometer. The same procedure was followed for SGOT analysis using the appropriate working reagent. All measurements were recorded and subjected to statistical analysis (Rahmatullah, 2024).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). All data were assessed for normality using the One-Sample Kolmogorov-Smirnov test and homogeneity of variance using Levene's test. Results are presented as mean ± standard deviation (SD). Differences in SGOT and SGPT levels between experimental groups were analyzed using one-way analysis of variance (ANOVA) followed by Duncan's post hoc test for multiple comparisons.

RESULT AND DISCUSSION

The effects of green tea extract (GTE) administration on SGOT and SGPT enzyme activities in mice exposed to cigarette smoke are presented in Table 1 and Figure 1.

The results showed that exposure to cigarette smoke significantly increased both SGOT and SGPT enzyme activities in the positive control group (C+) compared to the negative control group (C−) that was not exposed to cigarette smoke. The mean SGOT activity in the positive control group (50.46 ± 2.29 U/L) was approximately 43.8% higher than in the negative control group (35.10 ± 2.49 U/L). Similarly, SGPT activity in the positive control group (19.48 ± 1.47 U/L) was approximately 90.6% higher than in the negative control group (10.22 ± 1.68 U/L).

Administration of green tea extract demonstrated a dose-dependent protective effect against cigarette smoke-induced elevation of liver enzymes. The lowest dose of GTE (20 mg/kg BW) in the T1 group showed a modest reduction in both SGOT (45.39 ± 1.57 U/L) and SGPT (16.28 ± 1.75 U/L) activities compared to the positive control group, representing approximately 10.0% and 16.4% decreases, respectively.

The medium dose of GTE (40 mg/kg BW) in the T2 group exhibited a more pronounced effect, with SGOT and SGPT activities of 41.15 ± 2.44 U/L and 13.72 ± 1.03 U/L, respectively. This represents approximately 18.5% and

29.6% reductions in SGOT and SGPT activities compared to the positive control group.

The highest dose of GTE (60 mg/kg BW) in the T3 group demonstrated the most substantial protective effect, with SGOT and SGPT activities of 38.26 ± 1.25 U/L and 11.01 ± 1.05 U/L, respectively. These values represent reductions of approximately 24.2% and 43.5% in SGOT and SGPT activities compared to the positive control group, approaching the levels observed in the negative control group. Statistical analysis revealed significant differences ($p<0.05$) in both SGOT and SGPT activities between the treatment groups, confirming the dose-dependent hepatoprotective effect of green tea extract against cigarette smoke-induced liver damage in mice.

Table 1. SGOT and SGPT enzyme activities in mice (*Mus musculus*) exposed to cigarette smoke and treated with different doses of green tea extract (Mean ± SD)

Treatment Group	SGOT enzyme activity (U/L) (Mean ± SD)	SGPT enzyme activity (U/L) (Mean ± SD)
C- (Negative Control)	$35.10^{a} \pm 2.49$	$10.22^{a} \pm 1.68$
C+ (Positive Control)	$50.46^{e} \pm 2.29$	$19.48^{d} \pm 1.47$
T1 (GTE 20 mg/kg BW)	$45.39^{d} \pm 1.57$	$16.28^{c} \pm 1.75$
T2 (GTE 40 mg/kg BW)	$41.15^{c} \pm 2.44$	$13.72^{b} \pm 1.03$
T3 (GTE 60 mg/kg BW)	$38.26^{b} \pm 1.25$	$11.01^{a} \pm 1.05$

Note: Different superscript (a,b,c,d,e) showed significant differences ($p<0.05$).

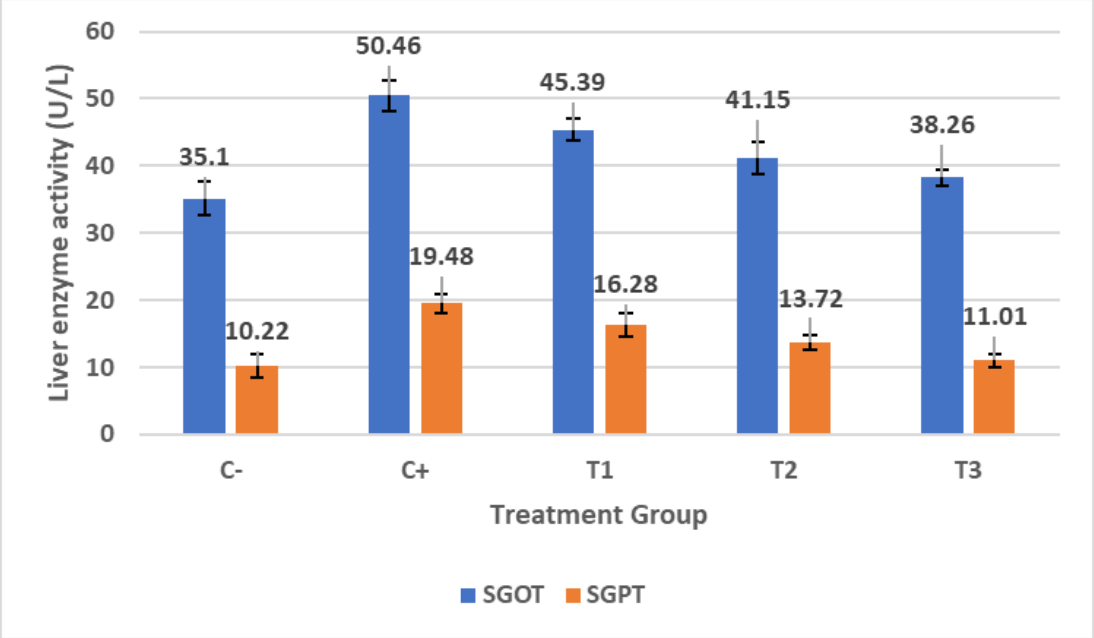

Figure 1. SGOT and SGPT enzyme activities in mice (*Mus musculus*) exposed to cigarette smoke and treated with different doses of green tea extract.

This study investigated the hepatoprotective effects of green tea extract (GTE) against cigarette smoke-induced liver damage in mice, as evidenced by changes in serum SGOT and SGPT levels. Our findings demonstrated that cigarette smoke exposure significantly elevated both SGOT and SGPT levels, indicating hepatocellular injury, while GTE administration mitigated these effects in a dose-dependent manner. The significant elevation of serum transaminases (SGOT and SGPT) in the positive control group (C+) compared to the negative control group (C-) confirms the hepatotoxic effects of cigarette smoke.

Cigarette smoke contains over 7,000 chemicals, including numerous oxidants and free radicals that can induce oxidative stress in the liver (Seo *et al.*, 2023). At the molecular level, this process is primarily mediated through multiple pathways. The polycyclic aromatic hydrocarbons (PAHs) and nitrosamines present in cigarette smoke are metabolized in hepatocytes by cytochrome P450 enzymes, particularly CYP1A1, CYP1A2, and CYP2E1, generating reactive oxygen species (ROS) as byproducts (Bukowska *et al.*, 2023). These ROS, including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•), can directly damage cellular components through oxidation of proteins, lipids, and DNA (Madkour, 2019).

Furthermore, cigarette smoke components activate Kupffer cells, the resident macrophages in the liver, triggering the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) (Nowak and Pawliczak, 2022). These cytokines perpetuate inflammatory responses and exacerbate oxidative stress through the activation of NADPH oxidase and inducible nitric oxide synthase (iNOS), further increasing ROS and reactive nitrogen species (RNS) production (Giménez *et al.*, 2021). The resulting oxidative stress causes lipid peroxidation of hepatocyte cell membranes, disrupting membrane integrity and leading to the leakage of cytosolic enzymes, including SGOT and SGPT, into the bloodstream (Yuniarti *et al.*, 2021). Additionally, sustained oxidative stress can trigger mitochondrial dysfunction by impairing the electron transport chain and depleting mitochondrial glutathione, ultimately leading to the activation of apoptotic pathways via cytochrome c release and caspase activation (Napolitano *et al.*, 2021).

The dose-dependent reduction in SGOT and SGPT levels observed in mice treated with GTE (T1, T2, and T3 groups) suggests significant hepatoprotection against cigarette smoke-induced damage. These findings align with studies on GTE's protective effects. Tang *et al.* (2021) reported reduced liver enzymes in NAFLD patients with GTE supplementation, attributing it to EGCG's antioxidant and anti-inflammatory actions. Similarly, Winiarska-Mieczan *et al.* (2024) found GTE mitigated drug-induced hepatotoxicity in rats, consistent with our dose-dependent results. However, unlike Yang *et al.* (2022), who noted enhanced SOD activity with EGCG, our study focused on enzyme leakage, suggesting further investigation into antioxidant enzyme expression.

This protective effect can be attributed to several molecular mechanisms. Green tea is rich in catechins, particularly epigallocatechin-3-gallate (EGCG), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and epicatechin (EC). These polyphenolic

compounds possess potent antioxidant properties due to their phenolic hydroxyl groups, which can donate hydrogen atoms to neutralize free radicals (Mokra *et al.*, 2022). EGCG, the most abundant catechin in green tea, can directly scavenge ROS including superoxide, hydroxyl, and peroxyl radicals, as well as peroxynitrite, thereby preventing oxidative damage to cellular macromolecules (Yang *et al.*, 2022). At the molecular level, these catechins can chelate transition metal ions such as iron (Fe^{2+}) and copper (Cu^{2+}), preventing their participation in Fenton reactions that generate highly reactive hydroxyl radicals (Grzesik *et al.*, 2018). This metal-chelating activity is particularly important in the liver, where iron overload can exacerbate oxidative stress and hepatocellular injury.

Beyond direct free radical scavenging, GTE enhances the body's intrinsic antioxidant defense mechanisms. The catechins in GTE, particularly EGCG, activate nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that regulates the expression of antioxidant response elements (ARE) in the genome (Talebi *et al.*, 2021). Upon activation, Nrf2 translocates from the cytoplasm to the nucleus and binds to ARE, promoting the expression of numerous antioxidant and detoxifying enzymes, including superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase 1 (NQO1), and heme oxygenase-1 (HO-1). The upregulation of these enzymes significantly enhances the hepatocytes' capacity to neutralize ROS generated during cigarette smoke metabolism, thereby maintaining redox homeostasis and preventing oxidative damage (Tripathi *et al.*, 2024).

The observed hepatoprotective effect of GTE is also attributable to its anti-inflammatory properties. Cigarette smoke exposure activates nuclear factor-kappa B (NF-κB) signaling in hepatocytes and Kupffer cells, leading to the transcription of pro-inflammatory cytokines and chemokines (Zhao *et al.*, 2020). EGCG and other catechins can inhibit this pathway by preventing the phosphorylation and degradation of inhibitor of kappa B (IκB), thereby preventing NF-κB translocation to the nucleus (Natarajan *et al.*, 2019). Additionally, green tea catechins can suppress the activation of mitogen-activated protein kinases (MAPKs), including p38, JNK, and ERK, which are involved in inflammatory signaling cascades. The inhibition of these pathways reduces the production of pro-inflammatory mediators such as cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), further attenuating the inflammatory response (Mokra *et al.*, 2022).

GTE can modulate the expression and activity of cytochrome P450 enzymes involved in the metabolism of cigarette smoke components. Specifically, EGCG has been shown to inhibit CYP1A1 and CYP1A2, which are responsible for the bioactivation of PAHs and nitrosamines to their reactive metabolites (Zeng *et al.*, 2022). This inhibition reduces the generation of reactive intermediates that can damage cellular macromolecules. Simultaneously, green tea catechins can induce phase II detoxifying enzymes, such as UDP-glucuronosyltransferases (UGTs) and sulfotransferases (SULTs), which conjugate reactive metabolites with glucuronic acid and sulfate, respectively, enhancing their water solubility and facilitating their excretion (Chen *et al.*, 2014).

Mitochondrial dysfunction is a key feature of cigarette smoke-induced

hepatotoxicity. Green tea catechins, particularly EGCG, can protect mitochondrial integrity by preventing the depolarization of mitochondrial membrane potential, inhibiting the mitochondrial permeability transition pore (mPTP) opening, reducing cytochrome c release from mitochondria, preserving mitochondrial respiratory chain complexes activity, and enhancing mitochondrial biogenesis through the activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α). These actions collectively prevent mitochondria-mediated apoptotic cell death and maintain cellular energy homeostasis (Chen *et al.*, 2016).

Our results demonstrate a clear dose-response relationship, with the highest dose of GTE (60 mg/kg BW) in the T3 group showing the most pronounced hepatoprotective effect. The SGOT and SGPT levels in this group approached those of the negative control group, suggesting near-complete protection against cigarette smoke-induced liver injury. This dose-dependent effect is consistent with the pharmacokinetics of green tea catechins, which exhibit concentration-dependent absorption and bioavailability (Scholl *et al.*, 2018). Higher doses of GTE provide greater amounts of catechins that can reach the liver through the portal circulation, exerting more potent antioxidant, anti-inflammatory, and hepatoprotective effects. However, it is important to note that excessively high doses of green tea extract may potentially cause hepatotoxicity, particularly when consumed on an empty stomach or by individuals with genetic polymorphisms affecting catechin metabolism (Hu *et al.*, 2018). Therefore, determining the optimal therapeutic window for GTE administration is crucial for maximizing its hepatoprotective benefits while minimizing potential adverse effects.

The findings of this study have important implications for individuals exposed to cigarette smoke, either actively or passively. The hepatoprotective effects of green tea extract suggest that regular consumption of green tea may mitigate liver damage associated with smoking. This is particularly relevant considering that cigarette smoking is a significant risk factor for various liver diseases, including non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and hepatocellular carcinoma (Jung *et al.*, 2019; Rutledge and Asgharpour, 2020). Furthermore, the dose-dependent nature of the hepatoprotective effect provides valuable insights for potential therapeutic applications. The effective dose range identified in this study (20-60 mg/kg BW) can inform the development of nutraceutical formulations tailored for liver protection in individuals exposed to cigarette smoke.

CONCLUSION

This study demonstrates that green tea extract exhibits significant hepatoprotective effects against cigarette smoke-induced liver damage in a dose-dependent manner. The molecular mechanisms underlying this protection include direct antioxidant activity, enhancement of endogenous antioxidant systems, anti-inflammatory effects, modulation of xenobiotic metabolism, and mitochondrial protection. These findings support the potential use of green tea as a natural hepatoprotective agent for individuals exposed to cigarette smoke. Future research should explore the long-term safety and efficacy of green tea extract in chronic exposure models, investigate its effects on other liver injury biomarkers (e.g., alkaline phosphatase, bilirubin),

and evaluate its synergistic potential with other antioxidants. Additionally, clinical studies are needed to validate these findings in human populations and determine optimal dosing regimens for therapeutic applications.

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Author Contribution

Adinda Rizky Trisakti: Conceptualization, Methodology. Aldin Akbar Rahmatullah: Data curation, Writing-Original draft preparation. Putra Indrajaya, Mudawamah, Umi Kalsum: Visualization, Investigation, Writing-Reviewing and Editing.

Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval

This study was conducted with prior approval from the Animal Care and Use Committee of Universitas Airlangga, Surabaya, Indonesia (Approval No. 324/HRECC.FORM/IV/2020).

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