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Protective Effects of *Salacca zalacca* Peel Extract on Oxidative and Inflammatory Liver Injury Biomarkers in CCl_4-Induced Rats

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Abstract

Salacca zalacca peel extract (SPE) contains phenolic and flavonoid compounds with reported antioxidant and anti-inflammatory properties, but *in vivo* evidence from liver injury models remains limited. This study evaluated the effects of SPE on biomarkers in CCl_4-induced liver injury in Wistar rats by measuring serum alanine aminotransferase (SGPT), TNF-α, and superoxide dismutase (SOD). Thirty rats were divided into 5 groups: Healthy controls, 2% CCl_4-treated controls (C-), 3.6 mg/kg NAC-treated controls (C+), and CCl_4-induced rats treated with low (400 mg/kg BW/day) and high (600 mg/kg BW/day) doses of SPE for 14 days. SPE was administered orally following CCl_4 induction. SGPT levels were measured by spectrophotometry, and TNF-α and SOD levels were analyzed using ELISA. Compared to CCl_4 controls, SPE groups showed significantly reduced SGPT and TNF-α levels and elevated SOD activity ($p < 0.005$), indicating improved markers of hepatocellular injury, inflammation, and antioxidant status. The high-dose SPE group exhibited the greatest effect. In conclusion, SPE administration demonstrated antioxidant and anti-inflammatory benefits by lowering SGPT and TNF-α while increasing SOD levels.

Keywords: *Salacca zalacca* peel extract, CCl_4, SGPT, TNF-α, SOD, Hepatoprotection

Introduction

The liver is essential for metabolism and detoxification, with high susceptibility to oxidative stress and inflammation caused by toxins and drugs [1]. Previous studies have shown that various liver injuries are often due to infection, alcohol, or chemicals, serving as major health challenges. Among experimental models, carbon tetrachloride (CCl_4) is widely used to investigate acute liver injury [2,3]. Metabolism of CCl_4 by CYP2E1 produces free radicals and ROS, causing oxidative stress, cellular damage, and activating NF-κB along with high TNF-α levels [4,5]. It also raises serum alanine aminotransferase (SGPT), TNF-α, and lowers superoxide dismutase (SOD) activity, serving as a useful tool for testing hepatoprotective agents [6,7]. Although N-acetylcysteine (NAC) has been widely used as a synthetic hepatoprotective to replenish glutathione and scavenge ROS, the application is associated with inconsistent results, low bioavailability, a short half-life, and side effects [8]. These challenges have increased research interest in plant-derived antioxidants, including flavonoids, which have been widely reported to attenuate oxidative processes in various experimental settings [3,9,10].

Snake fruit (*Salacca zalacca*) peel, a by-product rich in flavonoids and phenolic acids [11,12], contains compounds such as quercetin [13], ferulic acid [14], chlorogenic acid [15], rutin [16], and catechins [17]. These have shown antioxidant and anti-inflammatory properties in previous research, protecting cellular and animal models of oxidative stress. Specific studies highlight roles for quercetin and chlorogenic acid in modulating oxidative and inflammatory responses. Ethanolic extracts of the peel exhibit strong antioxidant activity, and both *in vivo* and *in vitro* studies report its

protective effects in neurotoxicity and metabolic stress, including reduced oxidative markers and inflammatory mediators. Thus, the phytochemical profile of *S. zalacca* peel warrants further study in oxidative and inflammatory conditions, such as CCl_4-induced liver injury [12,18,19]; Gallic acid Peel [20], Caffeic acid, Ferulic acid, Chlorogenic acid, Quercetin, Rosmarinic acid, Gallic acid Peel [20], Caffeic acid, Ferulic acid, Chlorogenic acid, Quercetin, Rosmarinic acid.

Despite the high content of flavonoids and phenolic acids, *in vivo* studies on the effects of *S. zalacca* peel extract, particularly in toxin-induced liver injury models, remain limited. Most available studies have focused on its antioxidant capacity or evaluated isolated compounds rather than whole-extract effects in CCl_4-induced injury [21-23]. There are limited data on the effect on biomarkers such as SGPT, SOD, and TNF-α [15]. Therefore, this study aimed to evaluate the effects of SPE extract on these biomarkers in Wistar rats with CCl_4-induced acute liver injury, providing *in vivo* evidence for its hepatoprotective potential [24,25].

Materials and methods

Ethical statement

All animal procedures complied with relevant ethical guidelines and were approved by the Bioethics Commission of Universitas Sultan Agung Semarang (Ethical Approval No. 153/III/2025). Animals were euthanized by CO_2 inhalation after blood collection [26-28]. A separate control group was used, as recovery from CCl_4-induced injury is unreliable within the study timeframe, rendering a within-subject design unsuitable [29].

Animal handling and experiment design

For the animal model, male Wistar rats (*Rattus norvegicus*), aged 2 to 3 months and weighing between 180 and 200 g, were obtained from the Universitas Gadjah Mada breeding unit. Animals were acclimatized for 7 days under standard housing conditions with ad libitum access to food and water. Thirty rats were randomly assigned to 5 groups (n = 6): P1 (Healthy control): standard diet and water; P2 (negative control): 2% CCl_4 at 0.2 mL/10 g BW orally for 14 days; P3 (positive control): CCl_4 followed 3 h later by oral NAC (3.6 mg/kg BW/day); P4: CCl_4 followed 3 h later by SPE 400 mg/kg BW/day; P5: CCl_4 followed 3 h later by SPE 600 mg/kg BW/day. The 3-hour interval was selected based on previous protocols, allowing sufficient time for CCl_4 absorption while enabling evaluation of post-insult intervention [30,31].

Chemicals and reagents

Analytical-grade NAC, CCl_4, and ethanol (96%) were obtained from Merck (Germany). ELISA kits for TNF-α, SOD, and SGPT were obtained from MyBioSource® (Wuhan, China). High-concentration ethanol (96%) was used as an extraction solvent because previous phytochemical studies report its suitability for efficiently extracting phenolic and flavonoid constituents from tropical plant materials such as *S. zalacca* peel [32,33].

Preparation of *Salacca zalacca* peel extract

Fresh *S. zalacca* var. pondoh peels were collected from Nglumut, Magelang, and authenticated at Universitas Islam Sultan Agung. Peels were sorted, cut, and shade-dried in a temperature-regulated drying cabinet (Memmert, Germany) at 50 - 60 °C under indirect heat to prevent degradation of thermo-sensitive compounds [34,35]. The temperature was controlled with a digital thermostat throughout the process. Dried peels were ground into powder, and 600 g was macerated in 96% ethanol (1:10 w/v) for 4 days at room temperature with intermittent agitation. The mixture was filtered and re-macerated twice under identical conditions to maximize extraction [36,37]. Combined filtrates were concentrated at 45 °C under reduced pressure using a rotary evaporator and stored at 2 - 8 °C. Extraction yield (%) was calculated as:

$$\text{Yield (\%)} = \frac{\text{Weight of crude extract}}{\text{Weight of dry sample}} \times 100$$

Dosage determination

The dosage of SPE (400 and 600 mg/kg BW/day) was selected based on previous *in vivo* studies employing similar dose ranges in antioxidant investigations. A 3.6 mg/kg BW/day NAC dose (200×0.018) was derived from the standard 200 mg human dose using body surface area conversion, to reflect a clinically relevant dose rather than high experimental dosing typically used in hepatoprotection models [38,39]. The CCl_4 dose (2% solution, 0.2 mL/10

g BW) was chosen based on established protocols that reliably induce acute liver injury in rats [9].

Preparation of serum from collected blood

Retro-orbital blood was collected from rats using a modified method. On day 15, approximately 3 mL of blood was collected from the retro-orbital plexus under chloroform inhalation anesthesia by a trained laboratory technician. This method was selected to obtain sufficient serum volume for all biochemical assays [39-41]. Blood samples were centrifuged at 2,000 rpm for 10 min, and the separated serum was aliquoted and stored at −80 °C until analysis.

Activity of serum alanine aminotransferase (ALT/SGPT)

Serum ALT/SGPT levels were measured using the spectrophotometric method [42]. The samples obtained were brought to room temperature and mixed for homogeneity. Reagent tablets were dissolved in buffer (1:10), then 50 µL serum was combined with 500 µL reagent, and the sample was incubated for 1 min. Absorbance at 340 nm was measured at 1-minute intervals for a total of 3 min using a Thermo Fisher spectrophotometer. The measurement of enzyme activity (U/L) was performed by observing the reduction in absorbance.

Activity of tumor necrosis factor-alpha (TNF-α)

The activity of TNF-α was assessed using an ELISA assay [43]. Samples were brought to room temperature and gently mixed to ensure uniformity before analysis. Subsequently, TNF-α was measured with MyBioSource® ELISA kits (MBS2600843) per the manufacturer's guidelines. Samples were analyzed at 450 nm, and the results are in pg/mL (ratio scale).

Activity of superoxide dismutase (SOD)

The activity of SOD was assessed using an ELISA assay [44]. Samples were brought to room temperature, resuspended, and analyzed using MyBioSource® ELISA kits (MBS2600843, Wuhan, China) per manufacturer instructions. Samples were analyzed at 450 nm, and the results were expressed as percent inhibition.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Normality and homogeneity were assessed using the Shapiro-Wilk and Levene's tests, respectively. One-way ANOVA with LSD post hoc was used for homogeneous data, while Tamhane's was used for non-homogeneous data [44,45]. Statistical significance was set at $p < 0.05$. Analyses were performed using SPSS version 26.0.

Results and Discussion

Body weight changes during SPE treatment in CCl_4-induced rats

Body weight was monitored weekly (W0 - W3) (**Table 1**). All groups began with similar baseline weights (175 - 178.6 g). Over 3 weeks, every group gained weight, but to varying degrees: healthy controls (P1) gained the most (+24.2 g), while the CCl_4-treated groups (P2) showed the smallest increase (+14.1 g). NAC-treated groups (P3) and both SPE groups (P4: +20.0 g, P5: +24.1 g) showed intermediate gains. Notably, the highest SPE dose (P5) had a final weight trajectory comparable to healthy controls.

Table 1 Weekly body weight (g) of rats across experimental groups from week 0 to week 3.

Group (n = 6)	Mean ± SD (g)	W0 (g)	W1 (g)	W2 (g)	W3 (g)
P1	190.53 ± 8.95	178.6	186.6	194.1	202.8
P2	183.80 ± 5.25	175.5	183.5	186.6	189.6
P3	185.15 ± 7.36	175	182.5	188	195.1
P4	188.53 ± 7.33	178.3	186	191.5	198.3
P5	188.30 ± 8.92	176.5	184.3	191.8	200.6

Note: P1: Healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced+SZE 400 mg/kg BW/day); P5: CCl_4-induced+SZE 600 mg/kg BW/day). W: Weeks; W0 = Week 0 (baseline); W1 = Week 1; W2 = Week 2; W3 = Week 3.

Body weight is a key indicator of overall health and systemic effects in hepatotoxicity studies. CCl_4 exposure typically suppresses weight gain by impairing appetite, nutrient absorption, and metabolism through oxidative stress and liver injury. In this study, the CCl_4-treated groups (P2) showed the lowest weight gain, confirming previous findings [46]. NAC-treated groups (P3) and both SPE groups (P4, P5) experienced improved weight gain compared to P2. By week 3, P5 nearly matched the healthy control (P1), indicating that SPE may stabilize physiological function during CCl_4 exposure [47]. Benefits similar to those observed here have been reported for other polyphenol-rich extracts, such as pomegranate peel, grape seed [48], and Citrus flavonoids [49]. The outcomes shown in **Figure 1** are attributed to improved biochemical health and reduced stress, although this study did not investigate metabolic mechanisms. Overall, *S. zalacca* peel extract reduced CCl_4-induced weight loss, supporting its hepatoprotective potential. Additional research on food intake, metabolism, and tissue health is recommended for a fuller understanding.

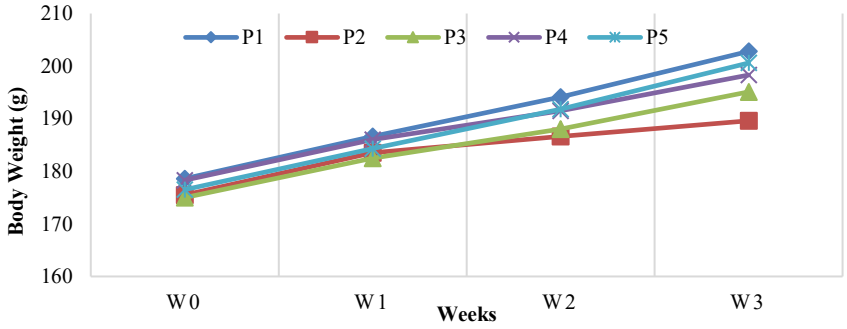

Figure 1 Body Weight Trends Demonstrating Physiological Recovery in SPE-Treated Rats Compared with CCl_4 Controls. P1: Healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). W: Weeks; W0 = Week 0 (baseline); W1 = Week 1; W2 = Week 2; W3 = Week 3.

Effect of SPE on SGPT levels in CCl_4-induced wistar rats

The CCl_4-treated groups (P2) had the highest mean SGPT, indicating liver injury, while the healthy control (P1) had the lowest. SPE at 400 mg/kg (P4) and 600 mg/kg (P5) reduced SGPT significantly vs. the negative control ($p < 0.001$). Since SGPT data were normally distributed but not homogeneous, a one-way ANOVA (**Table 2**) and Tamhane post hoc test (**Table 3**) were performed. The CCl_4-treated groups (P2) had a significantly higher mean SGPT (43.37 ± 0.5902) than other groups ($p < 0.001$), while P3, P4, and P5 had lower

values (29.37 ± 1.98; 29.05 ± 0.56; 23.46 ± 0.79). Significant differences were found among most groups: P2 > P1 ($p < 0.001$); P4 differed from P1, P2, and P5 (all $p < 0.001$) but not P3; and P5 differed from all but P3. P4 and P3 did not differ, and both SPE doses improved SGPT versus controls. The results are displayed in **Figure 2**.

SPE produced a clear reduction in SGPT levels in CCl_4-induced rats compared to untreated controls, indicating improved biochemical markers linked to hepatocellular stress [50]. Although no histological analysis was performed, the decrease in SGPT suggests a lessened biochemical disturbance after extract treatment. This effect is consistent with reports showing that polyphenol-rich plant materials can modulate oxidative processes in liver injury models [42,43]. The largest reduction was seen at 600 mg/kg, likely indicating a dose-related effect and justifying further study. Similar dose-dependent reductions in SGPT and SGOT have been observed with apple, potato, and pomegranate peel extracts in CCl_4-treated rats [51], where polyphenols enhance cellular stability and antioxidant capacity [52-54]. Improvements in other oxidative markers, such as SOD, CAT, and GSH, are also reported in similar models [55]. Elevated SGPT levels in the CCl_4 group match established patterns of acute hepatic stress. CCl_4 undergoes CYP2E1-dependent metabolism, producing reactive intermediates that trigger lipid peroxidation and membrane damage [44,56], processes associated with increased circulating transaminases in liver injury models, though these were not directly measured in this study. SGPT is widely acknowledged as a sensitive marker for hepatocellular leakage under oxidative stress, and its elevation in the untreated group is consistent with expectations. Both SPE doses lowered SGPT values relative to the CCl_4-only group.

Table 2 Results of descriptive analysis, normality test, homogeneity test, and 1-way ANOVA for the SGPT variable.

Group (n = 6)	Mean ± SD (U/L)	Saphiro-Wilk test (*p*)	Levene's test (*p*)	1-way ANOVA test *(p)*
P1	19.09 ± 0.50	0.46[a]	< 0.001[*]	< 0.001[*]
P2	43.37 ± 0.59	0.41[a]		
P3	29.37 ± 1.98	0.26[a]		
P4	29.05 ± 0.56	0.42[a]		
P5	23.46 ± 0.79	0.50[a]		

Note: P1: Healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). SGPT: Serum Glutamic Pyruvate Transaminase; [a] = $p > 0.05$; [*] = $p < 0.05$.

Table 3 Results of Tamhane's post hoc test for SGPT variables.

Group (n = 6)	P2	P3	P4	P5
P1	< 0.001[*]	< 0.001[*]	< 0.001[*]	< 0.001[*]
P2		< 0.001[*]	< 0.001[*]	< 0.001[*]
P3	< 0.001[*]		1.000[a]	0.003[*]
P4	< 0.001[*]	1.000[a]		< 0.001[*]

Note: P1: healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). SGPT = serum glutamic pyruvate transaminase; [a] = $p > 0.05$; [*] = $p < 0.05$.

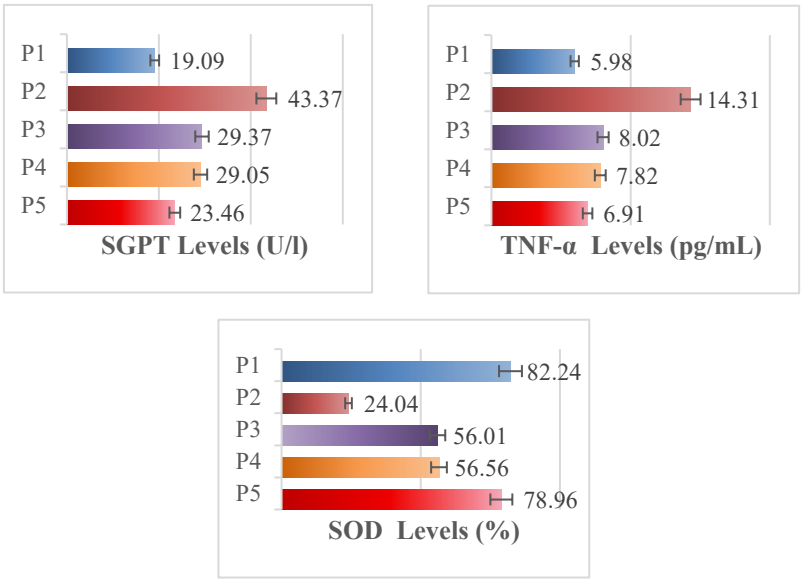

Figure 2 Graph of mean SGPT, TNF-α, and SOD levels among groups: Healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg B W/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). SGPT: Serum glutamic pyruvate transaminase; TNF-α = tumor necrosis factor-alpha; SOD = superoxide dismutase.

With the 600 mg/kg dose matching the effect of NAC [57,58]. While mechanisms behind these improvements remain to be clarified, the biochemical trends align with existing evidence that phytochemical-rich extracts affect oxidative responses. The included schematic summarizes in **Figure 3**, the most commonly cited mechanisms related to context [59,60].

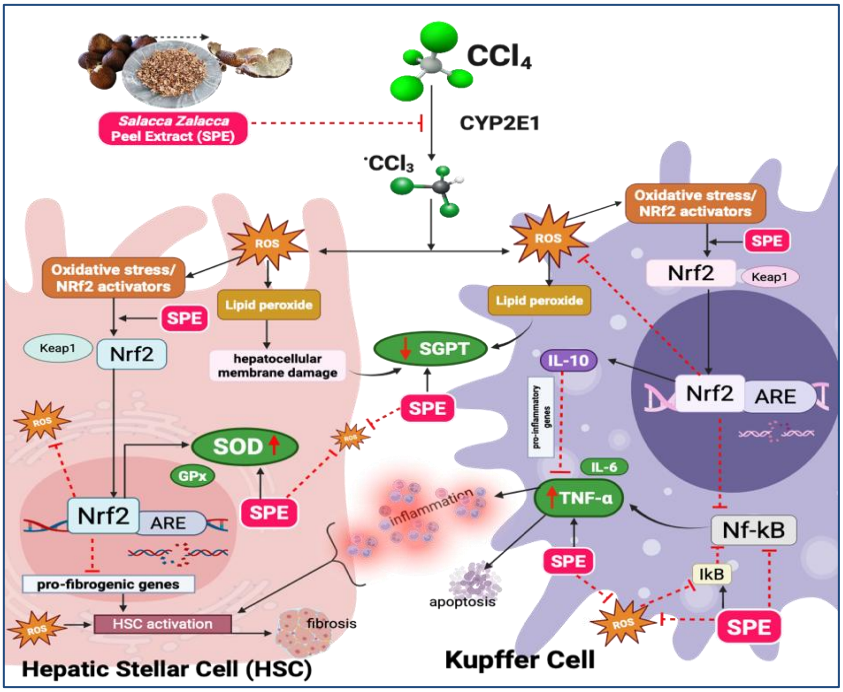

Figure 3 Hepatoprotective mechanism of SPE: NRF2-mediated regulation of kupffer cells and hepatic stellate cells in CCl_4-induced acute liver injury [59,60].

Effect of SPE on TNF-α levels in CCl_4-induced wistar rats

TNF-α levels were significantly higher in the negative control group exposed to CCl_4 (P2; 14.31 ± 0.23) than in the healthy group (P1; 5.98 ± 0.15). SPE treatment at 400 and 600 mg/kg reduced TNF-α to P4 (7.81 ± 0.36) and P5 (6.90 ± 0.14), respectively ($p < 0.001$). One-Way ANOVA (**Table 4**) and LSD Post Hoc tests (**Table 5**) showed significant group differences, with P5 showing the greatest reduction. P2 was higher than all other groups, and both P4 and P5 showed improvements over controls, especially at 600 mg/kg. Results are shown in **Figure 2**.

SPE treatment significantly reduced TNF-α levels in CCl_4-induced rats, reflecting improved biochemical markers of inflammatory stress. While this study did not assess the underlying inflammatory pathways or cellular mechanisms, the observed reduction mirrors findings from many studies where polyphenol-rich plant extracts modulate cytokine levels in oxidative liver injury models. Extracts with nootkatone [29], cyanidin [9], kaempferol [3], and various fruit peels (apple [51], blueberry, cranberry [47], spirulina [61]) have consistently demonstrated dose-dependent decreases in TNF-α, IL-6, and IL-1β in CCl_4-induced hepatotoxicity, often alongside improved liver histology and reduced inflammatory cell infiltration. The elevated TNF-α seen in the untreated CCl_4 group aligns with established patterns of hepatocellular stress and inflammation. Although this study did not explore mechanisms like NF-κB activity, IκB turnover, Kupffer cell activation, or fibrotic signaling, the reduction in TNF-α after SPE administration suggests a beneficial modulation of this inflammatory biomarker [56]. Literature often attributes such reductions to effects on NF-κB or Nrf2/HO-1 pathways by polyphenolics (**Figure 3)** [60,62]. In particular, both doses of SPE, especially 600 mg/kg, significantly decreased TNF-α relative to CCl_4 controls. While several bioactive compounds in SPE may contribute to these effects, specific mechanisms remain to be elucidated. Thus, the TNF-α reduction noted here should be seen as consistent with polyphenol-rich extracts in oxidative injury settings [63,64]. Further research using molecular and histological analysis is needed to clarify the responsible pathways.

Table 4 Results of descriptive analysis, normality test, homogeneity, and 1-way ANOVA for the TNF-α variable.

Group (n = 6)	Mean ± SD (pg/mL)	Saphiro-Wilk test (*p*)	Levene's test (*p*)	1-way ANOVA test (*p*)
P1	5.98 ± 0.15	0.83[a]	0.018[*]	< 0.001[*]
P2	14.31 ± 0.23	0.78[a]		
P3	8.02 ± 0.22	0.96[a]		
P4	7.81 ± 0.36	0.36[a]		
P5	6.90 ± 0.14	0.97[a]		

Note: P1: healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). TNF-α = tumor necrosis factor-alpha; [a] = $p > 0.05$; [*] = $p < 0.05$.

Table 5 Results of the LSD post hoc test for the TNF-α variable.

Group (n = 6)	P2	P3	P4	P5
P1	< 0.001[*]	< 0.001[*]	< 0.001[*]	0.027[*]
P2		< 0.001[*]	< 0.001[*]	< 0.001[*]
P3	< 0.001[*]		0.156[a]	< 0.001[*]

Group (n = 6)	P2	P3	P4	P5
P4	< 0.001*	0.156[a]		< 0.001*
P5	< 0.001*	< 0.001*	< 0.001*	

Note: P1: healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). TNF-α = tumor necrosis factor-alpha; [a] = $p > 0.05$; * = $p < 0.05$.

Effect of SPE on SOD levels in CCl_4-induced Wistar rats

The negative control group (P2; 24.04 ± 3.54) showed a significant reduction in SOD levels compared to the healthy control (P1; 82.24 ± 3.79), confirming oxidative stress. Treatment with SPE at 400 mg/kg BW (P4; 56.56 ± 3.06) and 600 mg/kg BW (P5; 78.96 ± 4.07) significantly increased SOD activity ($p < 0.001$). At 600 mg/kg BW, SOD levels returned close to normal and matched or exceeded levels in the NAC group (P3). ANOVA (**Table 6**) and LSD Post Hoc tests (**Table 7**) confirmed significant differences between groups ($p < 0.001$). P2 had the lowest SOD levels; P3, P4, and P5 were significantly higher. P4 was comparable to P3, differing from P1, P2, and P5, while P5 was distinct from all groups. Overall, 400 mg/kg BW SPE was similar to the positive control, and both doses significantly improved SOD activity compared to controls, as presented in **Figure 2**.

CCl_4 exposure significantly decreased SOD levels in the negative control group, underscoring the oxidative stress typical of this experimental model. SPE administration resulted in a dose-dependent increase in SOD activity, with the most pronounced effect observed in the 600 mg/kg group. Although this study did not assess antioxidant gene expression, redox signaling, or fibrosis-related pathways, the biochemical changes here are consistent with reports on various polyphenol-rich extracts [65], including grape seed [48], pomegranate [57], *Vitis vinifera* leaves [66], propolis [67], Shoumei tea [68], *Sugarcane molasses* [52], and *Fimbristylis miliacea*, which elevate SOD, CAT, and GSH levels in CCl_4 models, especially at higher doses and sometimes on par with NAC. These improvements are often accompanied by reduced MDA and healthier liver histology, though underlying molecular mechanisms are not always investigated [69]. Many studies increased SOD activity in relation to modulation of antioxidant systems such as the Nrf2-Keap1-ARE pathway [60] (**Figure 3)**. Therefore, the current findings should be seen as evidence of biochemical recovery. SOD activity recovery in both SPE-treated groups, matching NAC at 400 mg/kg and surpassing it at 600 mg/kg, demonstrates a dose-dependent benefit for oxidative stress parameters. SPE improved SGPT, TNF-α, and SOD, highlighting its positive effects on biochemical markers of hepatocellular stress, inflammation, and antioxidant status.

Table 6 Results of descriptive analysis, normality test, homogeneity, and **1**-way ANOVA for the SOD variable.

Group (n = 6)	Mean ± SD (%)	Saphiro-Wilk test (*p*)	Levene's test (*p*)	1-way ANOVA test (*p*)
P1	82.24 ± 3.79	0.80[a]	0.986[a]	< 0.001*
P2	24.04 ± 3.54	0.96[a]		
P3	56.01 ± 4.07	0.79[a]		
P4	56.56 ± 3.06	0.96[a]		
P5	78.96 ± 4.07	0.79[a]		

Note: P1: healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). SOD = superoxide dismutase; [a] = $p > 0.05$; * = $p < 0.05$.

Table 7 Results of the LSD post hoc test for the SOD variable.

Group (n = 6)	P2	P3	P4	P5
P1	< 0.001*	< 0.001*	< 0.001*	0.140[a]
P2		< 0.001*	< 0.001*	< 0.001*
P3	< 0.001*		0.802[a]	< 0.001*
P4	< 0.001*	0.802[a]		< 0.001*

Note: P1: healthy control; P2: CCl_4-treated control (C-); P3: NAC-treated control (C+); P4: CCl_4-induced + SZE 400 mg/kg BW/day); P5: CCl_4-induced + SZE 600 mg/kg BW/day). SOD = superoxide dismutase; [a] = $p > 0.05$; * = $p < 0.05$.

SPE demonstrates antioxidant and anti-inflammatory effects by reducing SGPT and TNF-α levels and enhancing hepatic SOD levels. The present findings indicate biochemical improvement in SGPT, TNF-α, and SOD levels following SPE administration. However, without histopathological examination, structural recovery of hepatic tissues cannot be conclusively established. This represents a key limitation of the study and warrants future confirmation using H&E staining and fibrosis grading. Additionally, the assessment of SPE in this study was limited to a few liver injury biomarkers (SGPT, TNF-α, and SOD), which restricted a comprehensive evaluation of acute liver injury, antioxidant responses, and inflammatory processes. Furthermore, the absence of detailed histological evaluation and phytochemical profiling prevented the identification of the specific ethanolic content of SPE, highlighting the need for future studies to clarify its bioactive components and mechanisms.

Conclusions

In conclusion, ethanolic *S. zalacca* peel extract (SPE) demonstrated favorable modulation of biomarkers associated with liver injury in CCl_4-induced rats. Administration of 400 and 600 mg/kg BW was accompanied by reductions in SGPT and TNF-α levels and increases in SOD activity, with the higher dose showing the most pronounced improvement. Although this study did not include histological or molecular analyses, the overall biochemical pattern aligns with previous reports suggesting that polyphenol-rich plant materials may contribute to hepatic protection under oxidative stress conditions. SPE shows potential as a hepatoprotective agent in toxin-induced liver stress. However, further research involving tissue studies, mechanistic analysis, and phytochemical profiling is needed to confirm its effects and explain the mechanisms.

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Declaration of Generative AI in Scientific Writing

The authors acknowledge the use of generative AI tools (e.g., QuillBot and ChatGPT by OpenAI) in the preparation of this manuscript, specifically for language editing and grammar correction. No content generation, data analysis, or interpretation was performed by AI. The authors take full responsibility for the content, scientific integrity, and conclusions presented in this work.

CRediT Author Statement

Danis Pertiwi: Conceptualization, Methodology, Supervision, Validation, Funding acquisition, Writing - original draft, and Writing - Reviewing; **Matisatun Nisa:** Data curation, Writing - Original draft preparation, Methodology, Investigation, and Validation; **Laili Fitria Zulfa:** Data curation, Formal analysis, Visualization, Software, Validation, Writing - original draft, Writing - Reviewing and Editing.

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