

Hepatoprotective Activity of Sunkist Orange Peel Nanoparticles Assessed through Hepatic Function and Morphology Using an Alloxan-Induced Wistar Rat Model of Diabetes Mellitus

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ABSTRACT

The chronic metabolic disturbances associated with diabetes mellitus (DM) may cause liver injury through hyperglycemia, excess production of ROS (reactive oxygen species) and ensuing oxidative stress. Sunkist orange rind (*Citrus sinensis* (L.) Osbeck) provides flavonoids alongside phenolic compounds with antioxidant activity and potential hepatoprotective effects. This investigation tested the potential hepatoprotective effects of Sunkist orange peel extract nanoparticles by assessing hepatic function and morphology using a Wistar rat model with experimentally induced DM. A laboratory experiment used control groups and measurements obtained only after treatment. Animals were assigned to six groups, comprising a healthy reference group, a diabetic group serving as the untreated control, a metformin-treated positive control, and three groups receiving the nanoparticle extract, administered at 100, 200, or 300 mg per kilogram of body weight (BW). Outcomes included total bilirubin concentrations, aspartate aminotransferase (SGOT or AST) activity, alanine aminotransferase (SGPT or ALT) activity, hepatic morphology scores, and representative histological findings. Significant between-group differences were observed in ALT activity ($F(5,12) = 25.859$; $p < 0.001$), AST activity ($F(5,12) = 24.191$; $p < 0.001$), total bilirubin ($p < 0.001$), and liver morphology scores ($H(5) = 24.331$; $p < 0.001$). The two lower dose levels (100 and 200 mg per kilogram of body weight) produced the most consistent biochemical improvement, with mean ALT values approximately 58.4% and 58.6% lower, respectively, and mean AST values approximately 53.8% lower than those in the untreated diabetic control. Treatment with 300 mg/kg BW yielded significant morphological improvement, although its effect on AST was less pronounced than that of the 100 and 200 mg per kilogram of body weight doses. No linear association between dose and response was observed. Sunkist orange peel extract nanoparticles show potential hepatoprotective activity in diabetic Wistar rats, particularly at 100–200 mg/kg BW for biochemical outcomes.

Keywords: diabetes mellitus, *citrus sinensis* peel extract, granular nanoparticles, hepatoprotection, bilirubin, liver morphology

INTRODUCTION

Persistent metabolic dysfunction characterizes diabetes mellitus (DM), a disease caused by inadequate secretion of insulin, insulin action defects, or both abnormalities, resulting in chronically elevated blood glucose. Its complications may be acute or chronic. Chronic complications include microvascular and macrovascular damage, while the accompanying metabolic disturbances may also affect nonvascular organs, including the liver. Uncontrolled hyperglycemia can intensify oxidative stress and inflammatory responses, as well as ROS (reactive oxygen species) production, with these processes contributing to tissue damage [1], [2].

Epidemiological data indicate that DM is a growing global health problem. Changes in lifestyle and

increasing obesity contribute to its rising prevalence. In Indonesia, DM is also an important cause of mortality, and its disease burden has increased over recent decades [3], [4].

The liver has major roles in carbohydrate, lipid, and protein metabolism, as well as detoxification and bilirubin excretion. In DM, chronic hyperglycemia can increase fatty acid oxidation and ROS production. ROS accumulation leads to lipid peroxidation, mitochondrial dysfunction, and activation of inflammatory mediators that may damage hepatocytes. These processes are associated with elevated ALT and AST levels and may contribute to hepatic disorders linked to disrupted metabolism; one such condition is nonalcoholic fatty liver disease (NAFLD) [5], [6].

The rind of Sunkist oranges from *Citrus sinensis* (L.) Osbeck is known to contain biologically active constituents, including the flavonoids hesperidin, narirutin, and nobiletin, as well as phenolic compounds and pectin. These compounds exert antioxidant effects alongside anti-inflammatory actions that may shield cellular membranes against oxidant-mediated injury. Hesperidin has also been reported to protect liver tissue by improving liver enzyme levels, oxidative stress, inflammation, and histological findings [7]–[9].

Nanoparticle technology can serve as a delivery system for bioactive compounds because it may improve their stability, solubility, dispersion, and bioavailability. Studies of orange peel extracts have demonstrated antioxidant activity and biological effects that support their potential use as hepatoprotective agents [10], [11]. However, evidence concerning how Sunkist orange peel extract nanoparticles affect liver function and morphology in diabetic rat models remains limited. This study therefore evaluated their effects on ALT, AST, total bilirubin, and liver morphology in a Wistar rat model of DM.

RESEARCH METHODS

A laboratory experiment compared treated and control groups using measurements taken only at the end of the intervention. The study was conducted at Cendikia Laboratory and the Faculty of Medicine and Dentistry, Universitas Prima Indonesia, Medan, from January to March 2026. The experimental animals were Wistar males (*Rattus norvegicus*) that were 2–3 months of age, with body weights of 250–300 grams. The sample size specified in the study design was calculated using Federer's formula, yielding 24 rats divided among six groups, each comprising four rats. These animals underwent a seven-day acclimatization period. Five groups received alloxan monohydrate at 120 mg per kilogram of body weight, injected intraperitoneally, whereas the healthy control animals did not undergo induction. For the positive control, animals received oral metformin at the dosage of 9 mg for each 200 g of body weight. The treatment groups received Sunkist orange rind nanoparticle granule extract, delivered at 100, 200, or 300 mg per kilogram of body weight by gavage through an oral feeding tube. Treatments were administered after induction according to the study design.

Extract preparation began with washing, drying, grinding, and sieving Sunkist orange peel using a 14-mesh screen. The dried plant material subsequently underwent maceration in 96% ethanol over four days.

Following extraction, the filtrate underwent filtration; the solvent was then removed with a rotary evaporation apparatus operated at 50 °C, 60 rpm, and a pressure of 100 mbar over two hours. This preparation was further concentrated by heating in a water bath to obtain a viscous concentrate, which was subsequently formulated as nanoparticle granules. On day 21, blood samples were obtained via the retro-orbital plexus after anesthesia with ether. The collected samples were placed in tubes without anticoagulant and processed by centrifugation for 10 minutes at 3,000 rpm to separate the serum. ALT (SGPT) and AST (SGOT) were measured spectrophotometrically using the Reitman–Frankel method at 505 nm. The total bilirubin concentration was determined by the Jendrassik–Grof procedure at 546 nm.

Liver morphology was assessed macroscopically based on changes in color, shape, consistency, texture, and signs of injury, with scores of 0–3 assigned according to the degree of change. Liver histological specimens were prepared by fixation with neutral buffered formalin at a concentration of 10%, dehydration, clearing, paraffin embedding, sectioning to a thickness of approximately 4–5 µm, followed by hematoxylin–eosin staining. Several fields were examined at 400× magnification according to the study protocol. Hepatocyte injury was classified as normal, hydropic degeneration, or necrosis. Data were analyzed using IBM SPSS. Normality was evaluated by applying Shapiro–Wilk testing, whereas variance homogeneity was examined using Levene's procedure. ALT and AST data that met parametric assumptions underwent a one-factor analysis of variance (ANOVA) before application of the Tukey honestly significant difference (HSD) procedure used for subsequent group comparisons. Bilirubin and morphology scores that did not meet parametric assumptions were analyzed by Kruskal–Wallis testing, followed by Bonferroni-adjusted pairwise comparisons. Statistical significance required a p-value < 0.05.

RESULT AND DISCUSSION

Liver Biochemical Parameters

One-way ANOVA showed significant between-group differences in ALT, AST, and bilirubin levels ($p < 0.001$). The untreated diabetic control had the highest values for all parameters. Metformin and extract administration were associated with lower ALT, AST, and bilirubin levels. Descriptively, the results for the 100- and 200-mg/kg BW extract treatments appeared closest to values in the healthy reference group.

Table 1. ALT, AST, and total bilirubin levels by group

Group	ALT (U/L)	AST (U/L)	Total bilirubin (mg/dL)
Healthy control	83.33 ± 13.43 ^{b,c,d,e,f}	117.00 ± 23.52 ^{b,c,d,e,f}	0.130 ± 0.010 ^{b,c,d,e,f}
Untreated diabetic control	164.33 ± 8.02 ^{a,c,d,e,f}	245.33 ± 17.90 ^{a,c,d,e,f}	0.483 ± 0.025 ^{a,c,d,e,f}
Metformin-treated positive control	69.33 ± 16.50 ^{a,b,d,e,f}	112.67 ± 28.50 ^{a,b,d,e,f}	0.163 ± 0.021 ^{a,b,d,e,f}
Extract 100 mg/kg BW	68.33 ± 15.28 ^{a,b,c,e,f}	113.33 ± 14.47 ^{a,b,c,e,f}	0.163 ± 0.006 ^{a,b,c,e,f}
Extract 200 mg/kg BW	68.00 ± 9.64 ^{a,b,c,d,f}	113.33 ± 17.04 ^{a,b,c,d,f}	0.193 ± 0.015 ^{a,b,c,d,f}
Extract 300 mg/kg BW	91.00 ± 11.14 ^{a,b,c,d,e}	178.33 ± 6.81 ^{a,b,c,d,e}	0.203 ± 0.059 ^{a,b,c,d,e}
Overall p	< 0.001	< 0.001	< 0.001

Note: Post hoc analyses were performed to evaluate between-group differences. Group codes are a, healthy control; b, untreated diabetic control; c, metformin-treated reference group; d, peel extract administered at a dose of 100 mg per kilogram of body weight; e, peel extract administered at a dose of 200 mg per kilogram of body weight; and f, peel extract given at the dosage corresponding to 300 mg per kilogram of body weight.

These findings were obtained using one-way ANOVA with Tukey HSD comparisons performed afterward. Within the extract groups, both the 100- and 200-mg/kg BW treatments produced the same average AST level of 113.33 U/L, whereas administration at 300 mg/kg BW was associated with a higher value of 178.33 ± 6.81 U/L. Thus, the 100 and 200 mg/kg BW doses yielded lower mean AST levels than the 300 mg/kg BW dose. The greatest bilirubin concentration occurred in the untreated diabetic group (0.483 ± 0.025 mg/dL), and the lowest was observed in the control group comprising healthy rats (0.130 ± 0.010 mg/dL). Among the extract groups, mean bilirubin increased from 0.163 ± 0.006 mg/dL at 100 mg per kilogram of body weight to 0.193 ± 0.015 mg/dL with the 200 mg per kilogram of

body weight dose and 0.203 ± 0.059 mg/dL with the 300 mg per kilogram of body weight dose. The dose of 100 mg per kilogram of body weight therefore produced the lowest mean bilirubin level among the extract groups, which was numerically identical to that of the metformin-treated positive control.

Liver Morphology Scores

Liver morphology was assessed to determine the degree of morphological change in each treatment group. Because the scores were ordinal, they underwent Kruskal–Wallis testing, with Mann–Whitney tests used for the subsequent pairwise comparisons to identify between-group differences.

Table 2. Distribution of liver morphology scores by group

Group	Mean score ± SD	p-value
Healthy control	0.00 ± 0.00	< 0.001
Untreated diabetic control	2.80 ± 0.45	
Metformin-treated positive control	0.80 ± 0.45 ^b	
Extract 100 mg/kg BW	1.80 ± 0.45	
Extract 200 mg/kg BW	1.20 ± 0.45	
Extract 300 mg/kg BW	0.80 ± 0.44 ^b	

Note: Post hoc analyses were performed to evaluate between-group differences. Group codes are a, healthy control; b, untreated diabetic control; c, metformin-treated reference group; d, peel extract administered at a dose of 100 mg per kilogram of body weight; e, peel extract administered at a dose of 200 mg per kilogram of body weight; and f, peel extract given at the dosage corresponding to 300 mg per kilogram of body weight.

The Kruskal–Wallis test showed significant between-group differences in liver morphology scores ($H(5) = 24.331$; $p < 0.001$). After Bonferroni correction, the untreated diabetic control differed significantly from the healthy control, the metformin-treated reference group and the 300 mg/kg BW peel extract-treated cohort. The healthy reference group also differed significantly from the extract group receiving 100 mg/kg BW. No other pairwise comparisons were statistically significant after correction. Descriptively, the decrease in mean scores from the 100 to 300 mg/kg BW dose levels indicated a trend toward improved liver morphology. At 300 mg/kg BW, the extract-treated animals had an identical mean score to that of the metformin recipients, namely 0.80.

Liver Histology

Histological sections were examined at 400× magnification. According to the available assessment sheet, group A, the healthy control, received a score of 1, whereas groups B–F received scores of 2. These scores represented group-level findings rather than individual scores for each rat. Liver histopathology at 400× magnification showed descriptive variation in tissue appearance among the treatment groups. In the available representative specimens, the healthy control (A) had a histological score of 1, while the untreated diabetic control (B), the metformin-treated positive control (C), and the extract groups receiving a dose of 100 mg per kilogram of body weight in group D, a dose of 200 mg per kilogram of body weight in group E, and a dose of 300 mg per kilogram of body weight in group F each had a score of 2. Microscopic liver findings for all study groups appear in Figure 1. As presented in Table

3, the representative histological score was lower in the healthy control than in the other groups. Raising the extract dose across the range from 100 to 300 mg per kilogram of body weight was not associated with a change in the histological score, as all extract groups

retained a score of 2. The same score was observed in the untreated diabetic and metformin-treated control groups. These descriptive findings therefore did not demonstrate a consistent improvement in liver histopathology with increasing extract doses.

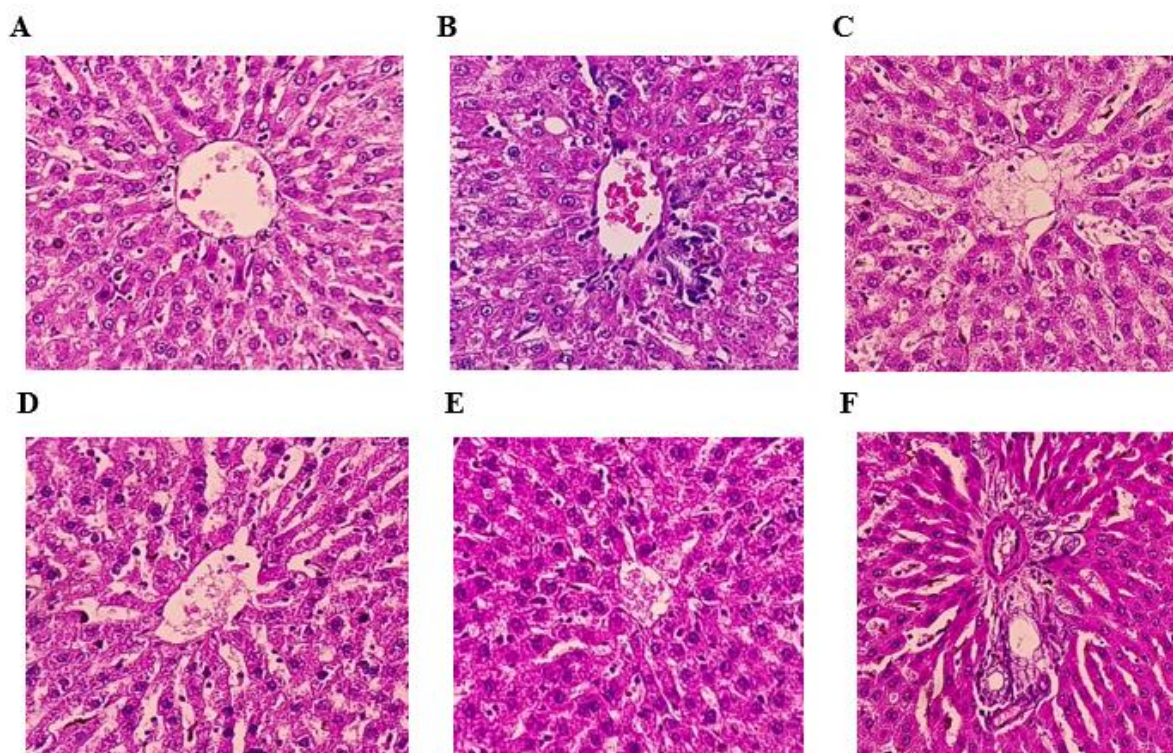


Figure 1. Liver histopathology with hematoxylin and eosin staining at 400× magnification. Panels A–F correspond to the specimen codes used in the study documentation.

Table 3. Representative histological scores by group

Group	Representative histological score
Healthy control (A)	1
Untreated diabetic control (B)	2
Metformin-treated positive control (C)	2
Peel extract 100 mg/kg BW (D)	2
Peel extract 200 mg/kg BW (E)	2
Peel extract 300 mg/kg BW (F)	2

The healthy control received a score of 1, whereas the untreated diabetic group and all treatment groups received scores of 2 in the representative assessments. As only one score was available for each group, these data are descriptive and cannot be treated as individual biological replicates. Representative histological differences should be interpreted alongside the biochemical data and individual morphology scores.

The untreated diabetic group had the greatest ALT and AST activities among the study groups. The finding supports impaired hepatocyte integrity in diabetes. Chronic hyperglycemia can increase ROS generation, lipid peroxidation, mitochondrial dysfunction, and inflammatory responses. Damage to hepatocyte membranes facilitates the release of transaminases into the circulation, resulting in elevated ALT and AST levels [5], [12]. Metformin and Sunkist orange peel extract nanoparticles administered at 100, 200, and 300 mg per kilogram of body weight produced

significantly lower ALT levels than those in the untreated diabetic control. AST levels were also lower in all treatment groups. Relative to the untreated diabetic control, mean ALT levels were approximately 58.4%, 58.6%, and 44.6% lower with dosages corresponding to 100, 200, and 300 mg per kilogram of body weight, respectively. The corresponding differences in mean AST were approximately 53.8%, 53.8%, and 27.3%. These findings indicate hepatoprotective activity, although a linear dose–response relationship was not observed.

Citrus sinensis peel contains flavonoids and phenolic compounds that may attenuate oxidative stress as well as inflammatory responses. Hesperidin and related flavonoids can neutralize free radicals and help preserve cell membrane integrity. Experimental studies in models of liver injury have also reported that *Citrus sinensis* peel extracts and their flavonoid constituents can reduce markers of hepatocellular injury and

improve tissue appearance [9], [13], [14]. The effects of nanoparticles may be related to improved stability and dispersion of bioactive compounds. Nanoparticle systems can support the delivery of active compounds and improve bioavailability, although the magnitude of these effects depends on particle size, carrier materials, surface charge, and formulation characteristics. In this study, nanoparticle characterization (zeta potential, encapsulation efficiency, particle size, and polydispersity index) data were not available in the analyzed results; consequently, the specific contribution of the nanoparticle formulation could not be established. Total bilirubin also showed an overall difference among groups. The untreated diabetic control had the highest level, whereas metformin and all extract groups had lower levels. Elevated bilirubin in liver injury may reflect impaired bilirubin uptake, conjugation, or excretion. Lower bilirubin levels in the treatment groups may be associated with reduced oxidative stress and improved hepatocyte function. However, these findings require cautious interpretation because complete post hoc analyses for bilirubin were unavailable. Liver morphology scores indicated the most severe injury in the untreated diabetic control. The metformin and 300 mg/kg BW extract groups had the same median score of 1 and the same mean rank, while the 200 mg/kg BW group also had a median score of 1. The Kruskal–Wallis test showed significant differences. These findings support structural improvement following treatment, although the morphological response did not fully correspond to the biochemical response.

Administration at a dose of 300 mg per kilogram of body weight did not lower AST as much as the 100- and 200-mg/kg BW treatments, indicating that a higher dosage does not necessarily produce a greater effect. Biological variation among rats, the small sample size, differences in absorption, and formulation characteristics may have contributed to this finding. The 100–200 mg/kg BW doses therefore appear more promising for transaminase outcomes, whereas the 300 mg/kg BW dose produced better morphological findings. Representative histological assessments yielded a score of 1 for the healthy control and scores of 2 for groups B–F. The discrepancy between representative histological scores and individual morphology scores may reflect the availability of only one representative tissue image for each group. A single group-level score cannot capture variation among rats or replace individual histopathological assessment. Representative histological findings should therefore be regarded as supporting visual evidence. Although the study objectives referred to hepatocyte counts, the available data consisted of injury or histopathology scores rather than individual hepatocyte counts per field. Methodologically, hepatocyte counts should be reported as the mean number of cells per field, whereas scores of 1–3 indicate the degree of tissue injury. Accordingly, the available data do not permit a definitive conclusion regarding hepatocyte counts.

CONCLUSION

Sunkist orange rind extract formulated as nanoparticles (*C. sinensis* (L.) Osbeck) demonstrated potential hepatoprotective activity in a Wistar rat model of diabetes mellitus. Comparisons across the groups identified statistically significant differences in total bilirubin, AST, ALT, and liver morphology scores. The two lower dose levels (100 and 200 mg per kilogram of body weight) produced the most consistent biochemical improvement, whereas administration at a dose of 300 mg per kilogram of body weight yielded significant morphological improvement. The response to increasing doses was not linear. Representative histological findings cannot be used as quantitative evidence of hepatocyte counts because only one score was available for each group.

Future studies should use consistent sample sizes across all outcomes, in accordance with the sample size calculation. Histopathological scoring should be performed for each rat across multiple fields by an assessor blinded to treatment allocation. If hepatocyte counts remain a study objective, hepatocytes should be counted quantitatively per field. Bilirubin analysis should also include appropriate nonparametric post hoc comparisons. Further research should assess dose–response relationships, dose safety, and nanoparticle characteristics, including zeta potential, particle size, encapsulation efficiency, polydispersity index, stability, and patterns of compound release.

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