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ORIGINAL ARTICLE

Nutrition, Metabolism, and Prevention of NCDs | Functional and Novel Foods

Preventive and Corrective Effects of *Citrus sinensis* Peel Supplementation on Metabolic Dysregulation, Oxidative Stress, and Histopathological Alterations in High-Fat Diet-Induced Obese Rats

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ABSTRACT

Background: Obesity is a complex metabolic disorder frequently associated with insulin resistance, dyslipidemia, and oxidative stress.

Aims: This study investigated the preventive and corrective effects of sweet orange (*Citrus sinensis*) peel (CSP) supplementation in a high-fat diet (HFD)-induced model of obesity in Wistar rats.

Material and Methods: Five experimental groups were established: a control group (C–), a CSP-treated control group (C+), an obese group (Ob+), a preventive obese group (Ob-P: 12 weeks of HFD combined with 10% CSP), and a curative obese group (Ob-C; 8 weeks of HFD followed by 4 weeks of CSP supplementation). Plasma concentrations of glucose, triglycerides (TG), cholesterol, and the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were quantified. Oxidative stress biomarkers, including superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), peroxynitrite (ONOO-), malondialdehyde (MDA), and protein carbonyls (PC), were assessed in erythrocyte lysates and in tissue homogenates (liver, adipose tissue, and pancreas). A comprehensive histological examination of these three tissues was also performed.

Results: HFD administration induced a significant increase in body weight and a marked elevation in fasting glucose, insulin, and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). The obese rats also exhibited pronounced dyslipidemia. CSP supplementation effectively normalized the metabolic parameters (glucose, HOMA-IR, TG, high-density lipoprotein cholesterol (HDL-C) and the atherogenic index). With regard to redox balance, the HFD caused a notable decrease in antioxidant enzyme activities (SOD, CAT activities, and GSH levels) and a significant elevation in oxidative stress markers (MDA, $ONOO^-$, and PC) in the blood, liver, adipose tissue, and pancreas. CSP treatment significantly restored redox status.

Conclusions: CSP exerted significant anti-obesity, antioxidant, and hepatoprotective effects. These findings highlight the potential of CSP as a functional food ingredient for mitigating obesity-associated metabolic and oxidative disturbances and support further investigation of CSP as a promising dietary strategy.

Keywords: *Citrus Sinensis* (Sweet Orange Peel); Obesity; High-Fat Diet; Insulin Resistance (HOMA-IR); Oxidative Stress; Antioxidants; Functional Food; Wistar Rats.

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1 INTRODUCTION

Obesity constitutes a major global socio-economic challenge. The World Health Organization (WHO) projected that, by 2025, approximately 167 million people will suffer from health complications related to overweight and obesity (Novelli *et al.* 2023). This "silent pandemic" has increased an alarming increase in prevalence and is strongly associated with the onset of numerous metabolic disorders and co-morbidities, including type 2 diabetes, dyslipidemia, cardiovascular diseases, and certain cancers (Morys *et al.*, 2021). Additionally, dyslipoproteinemia and oxidative stress play central roles in the development and progression of obesity (Safaei *et al.*, 2021). The rapid rise in obesity rates can be attributed to various social and environmental factors, such as inadequate health policies, poor dietary habits, and sedentary lifestyles (Annesi, 2022). Addressing this global crisis requires innovative and effective therapeutic strategies, with particular emphasis on dietary interventions. In this

regard, the exploration of the phytochemical properties of natural food sources presents promising therapeutic potential, possibly with fewer of the adverse effects commonly associated with traditional pharmacological treatments (Dini & Mancusi 2023).

Although current pharmacological treatments for obesity, including glucagon-like peptide-1 (GLP-1) receptor agonists and further approved anti-obesity medications, can achieve clinically meaningful weight loss and improve obesity-related complications; however, their use may be limited by adverse effects, treatment discontinuation, and the need for long-term therapy (Pedersen *et al.*, 2025; Shi *et al.*, 2024). In real-world clinical practice, financial and insurance-related barriers also represent significant reasons for discontinuation of novel therapies such as semaglutide and tirzepatide (Gasoyan *et al.*, 2025). These limitations justify continued investigation of accessible, naturally derived bioactive compounds as potential complementary approaches for managing obesity and its associated metabolic and oxidative disturbances. Among such sources, orange (*Citrus sinensis*) peel has recently garnered attention due to its rich content of bioactive compounds (Farahmandfar *et al.*, 2020). This by-product contains fibers, vitamins, minerals, and phenolic compounds, which have been reported to promote weight loss, exert hypoglycemic and hypolipidemic effects, and exhibit antioxidant and anti-inflammatory properties, thereby targeting the metabolic disturbances associated with obesity (Singh *et al.*, 2020).

Previous experimental studies have provided evidence supporting the anti-obesity potential of orange and citrus peels, although they have focused on different preparations, experimental designs, and outcome measures. Batubara *et al.* (2023) investigated a *C. sinensis* peel extract from Berastagi sweet orange in male Wistar rats fed a high-fat, high-fructose diet. They primarily evaluated body weight, the Lee obesity index, body fat percentage, and visceral fat, and reported beneficial effects of the extract on several anthropometric indicators of obesity. Similarly, Huang *et al.* (2022) demonstrated that fermented citrus peel supplementation alleviated obesity induced by a high-fat diet (HFD) in Sprague-Dawley rats, reducing body weight, visceral fat, body fat percentage, triglycerides, total cholesterol, LDL-cholesterol, malondialdehyde (MDA) levels, and hepatic lipid accumulation. That study also investigated selected molecular markers involved in lipid metabolism, including acetyl-CoA carboxylase, fatty acid synthase, and hormone-sensitive lipase.

However, no study has yet examined the preventive and corrective effects of non-fermented *C. sinensis* peel (CSP) supplementation within a unified experimental design, nor provided an integrated assessment of the systemic and tissue-specific redox disturbances associated with obesity. In particular, the extent to which dietary orange peel can concurrently influence glucose homeostasis, insulin resistance, lipid metabolism, atherogenic risk, antioxidant defenses, and oxidative damage in key metabolically relevant tissues remains insufficiently elucidated. Furthermore, comparing supplementation initiated during the development of obesity with supplementation introduced after obesity has been established may provide valuable insights into the distinct preventive and corrective capacities of CSP.

Accordingly, the present study investigated the preventive and corrective effects of CSP supplementation in an HFD-induced model of obesity in Wistar rats. An integrated assessment of metabolic homeostasis was performed by evaluating blood glucose, insulin resistance estimated using the homeostatic model assessment of insulin resistance (HOMA-IR), triglycerides, high-density lipoprotein cholesterol (HDL-C), and atherogenic risk indices. Systemic and tissue redox status was further characterized through a comprehensive panel of antioxidant and oxidative damage biomarkers, including superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), peroxynitrite ($ONOO^-$), MDA, and protein carbonyls (PC), assessed in erythrocytes, liver, adipose tissue, and pancreas. Histological analyses of these metabolically relevant tissues were additionally performed to determine whether the biochemical responses to CSP supplementation were accompanied by corresponding tissue-level changes.

A distinctive feature of the present study is the direct comparison of preventive and corrective CSP supplementation within the same experimental framework. This design allows assessment of whether CSP supplementation can not only attenuate the development of HFD-induced metabolic and oxidative disturbances when administered during the development of obesity, and whether it can ameliorate established alterations when introduced after obesity has been induced. By integrating metabolic, redox, and histological endpoints across multiple tissues, this study provides a more comprehensive characterization of the biological effects of non-fermented *C. sinensis* peel and contributes to the evaluation of its potential as a sustainable functional-food ingredient for mitigating obesity-associated metabolic and oxidative disturbances.

2 Material and Methods

2.1 Plant Material

Oranges of the "Thomson Navel" variety were harvested in the El Fhoul region of Tlemcen, northwestern Algeria. The fruits were thoroughly washed and manually peeled. The peels were dried in the dark, finely ground into powder, and stored at 4 °C until utilization.

2.2 Animals

Twenty-five male Wistar rats (4 weeks old; 90 ± 10 g), were obtained from the Pasteur Institute in Algiers, Algeria. All procedures were approved by the Tlemcen University Ethics Committee (Approval No. D00L01UN130120220002) and conducted in accordance with INSERM's institutional guidelines and the French National Charter on the Ethics of Animal Experimentation (CNREEA, 2014) and Directive 2010/63/EU". The rats were allocated to five experimental groups (n = 5 per group) and housed under controlled conditions (temperature, 25 °C; relative humidity, 60 ± 5%; 12-h light/dark cycle). The dietary regimens, summarized in Table 1, were applied over a 12-week experimental period as follows:

- The control group (C–) received a standard diet (330 kJ/100 g) providing 25% of energy as protein, 65% as carbohydrate and 10% as lipid (ONAB; Algeria).
- The treated control group (C+) received the standard diet supplemented with CSP at 3 g/rat/day for 12 weeks.
- The obese group (Ob+) received an HFD containing 20% corn oil for 12 weeks, according to the protocol described by Huang *et al.* (2009).
- The preventive group (Ob-P) received the HFD supplemented with 10% CSP throughout the 12-week experimental period.
- The corrective group (Ob-C) received the HFD alone for the first 8 weeks and the HFD supplemented with 10% CSP for the remaining 4 weeks. Body weight was measured weekly throughout the study.

Table 1. Summary of the Five Experimental Groups

Group	Diet / treatment
C–	Standard diet (12 weeks)
C+	Standard diet + CSP (12 weeks)
Ob+	HFD containing 20% corn oil (12 weeks)
Ob-P (Prevention)	HFD containing 20% corn oil + 10% CSP (12 weeks)
Ob-C (Correction)	HFD containing 20% corn oil (8 weeks), followed by CSP supplementation (4 weeks)

2.3 Sacrifice and Sample Collection

Following overnight fasting, the animals were anesthetized by intraperitoneal injection of ketamine/midazolam (100/5 mg/kg), in accordance with institutional animal-care procedures and accepted principles for the anesthesia and humane treatment of laboratory animals (National Research Council, 2011). Blood samples were collected from the abdominal aorta into two separate tubes, one containing heparin as an anticoagulant and the other without. Serum was employed to prepare lipoprotein fractions, and plasma was used for biochemical analysis. After plasma removal, erythrocytes were washed with isotonic phosphate-buffered saline (PBS), lysed with ice-cold distilled water, stored at 4°C for 15 minutes, and then centrifuged at 2000 g for 15 minutes to remove cell debris. Subsequently, the abdominal adipose tissue, liver, and pancreas were harvested, washed with ice-cold 0.1 mol/L PBS, and an aliquot of each tissue was weighed. The tissue samples were homogenized with 10 volumes of ice-cold 10 mmol/L PBS (pH 7.4) containing 1.15% KCl using an Ultra-Turrax homogenizer (Bioblock Scientific, Illkirch, France) and centrifuged at 6000 g for 15 minutes at 4°C. The resulting supernatant was stored for the analysis of oxidant/antioxidant biomarkers.

2.4 Determination of Biochemical Parameters

Plasma glucose, triglycerides, cholesterol, and the transaminases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured using colorimetric enzymatic kits (Spinreact, Santa Coloma, Spain). Serum lipoprotein fractions were separated by precipitation followed by centrifugation. Cholesterol and triglyceride concentrations in each fraction—high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL)—were quantified through a colorimetric enzymatic kit (Sigma-Aldrich, St. Louis, MO).

2.5 Oxidant/Antioxidant Status Determination

Biomarkers were assessed in both erythrocyte lysates and in tissue homogenates (liver, adipose tissue, and pancreas). SOD (EC 1.15.1.1) activity was measured based on its ability to inhibit pyrogallol autoxidation, with one unit of activity defined as the amount causing 50% inhibition of pyrogallol oxidation (Marklund 1985). Absorbance was recorded at 405 nm every 5 min for 1 h, using 1/20 dilutions of tissue homogenates and 1/5 dilutions of hemolysates. CAT (EC 1.11.1.6) activity was determined spectrophotometrically by monitoring hydrogen peroxide decomposition at 240 nm in the presence of erythrocyte lysate or tissue homogenate (Aebi, 1974). GSH levels were assessed colorimetrically, based on the reduction of 5,5'-dithiobis- (2-nitrobenzoic) acid by GSH to form the yellow chromophore 2-nitro-5-thiobenzoic acid, employing a Sigma-Aldrich kit (St. Louis, MO, USA). Peroxynitrite (ONOO-) levels were determined spectrophotometrically by measuring the nitration of phenol induced by peroxynitrite (Beckman *et al.*, 1992; Vanuffelen *et al.*, 1998). MDA, a marker of lipid peroxidation, was measured through its reaction with thiobarbituric acid (Draper & Hadley, 1990). Finally, carbonylated proteins, an indicator of protein oxidation, were evaluated by derivatizing protein carbonyl groups with 2,4-dinitrophenylhydrazine to form stable dinitrophenylhydrazone adducts, which were quantified utilizing the Sigma-Aldrich kit.

2.6 Histology

Following euthanasia and sacrifice, the liver was carefully excised, cut into small fragments, and promptly fixed in 10% formalin for 48 hours. The tissues were then dehydrated through a series of increasing ethanol concentrations (75% to 100%), cleared in xylene, and embedded in paraffin. Sections of 4 µm thickness were cut using a microtome (Histoline, Italy) and stained with hematoxylin and eosin (H&E). The stained slides were examined and photographed under a light microscope (Zeiss Primo Star, Germany).

2.7 Statistical Analysis

Data are presented as means ± standard deviation (SD). After verifying the normality of the distribution through the Shapiro-Wilk test, means among the five experimental groups (C-, C+, Ob+, Ob-P, Ob-C) were compared through two-way analysis of variance (ANOVA), followed by Tukey's post hoc test. Statistical significance was set at $p < 0.05$, and analyses were performed with GraphPad Prism 8.0.1 software. To explore the relationships between weight gain and key parameters of obesity-related metabolic dysfunction, and redox biomarkers, multivariate analysis was performed employing a free online platform for data visualization and graphing (Tang *et al.*, 2023).

3 Results

3.1 Effects of CSP on Body Weight, Weight Gain, and Organ Weights

Body weight, weight gain, and organ weights (liver, adipose tissue, and pancreas) of the experimental rats are presented in Figure 1. Following 12 weeks of treatment, both body weight and weight gain were significantly higher in the obese rats (Ob+) than in control group (C-). Supplementation with *Citrus sinensis* peel (CSP) significantly reduced body weight and weight gain in both the preventive (Ob-P) and corrective (Ob-C) groups compared to their respective controls. Moreover, liver and adipose tissue weights were significantly reduced in both Ob-P and Ob-C rats than in Ob+ rats ($p < 0.05$).

3.2 Effects of CSP on Biochemical Parameters

The biochemical parameters of the studied rats are summarized in Table 2. The systemic metabolic impact of HFD and the protective or corrective efficacy of CSP supplementation were evaluated across plasma glycemic, lipid, and hepatic biomarkers. One-way ANOVA revealed statistically significant variations among all experimental groups for every parameter evaluated ($p < 0.0001$).

Glucose homeostasis. Induction of obesity by the HFD (Ob+) resulted in severe metabolic impairment, characterized by a marked elevation in fasting plasma glucose (162.00 ±

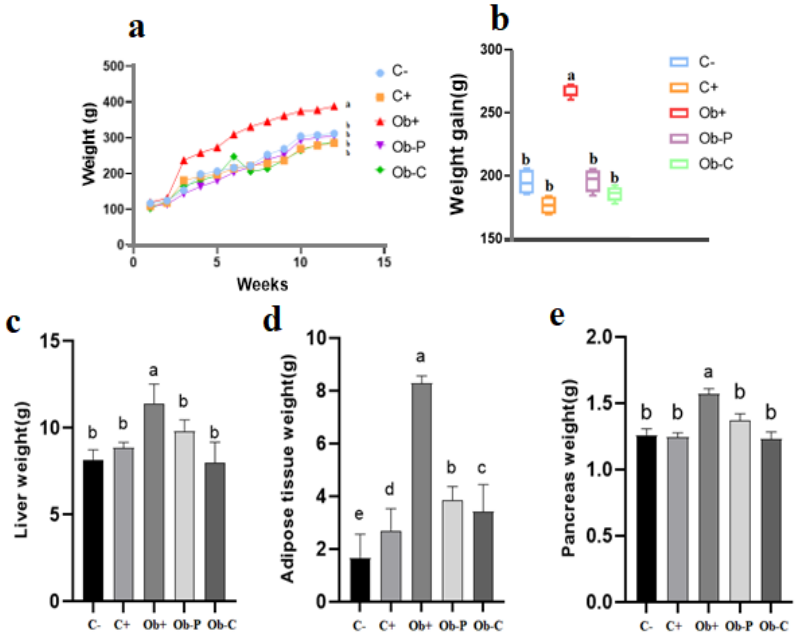


Figure 1. Body Weight, Weight Gain, and Tissue Weight in Rats

Values are presented as means ± S.D. C-: control rats; C+: control rats treated with orange peel; Ob+: obese rats fed a high-fat diet (HFD, 20% corn oil); Ob-P: obese rats fed HFD (20% corn oil) supplemented with 10% CSP for 12 weeks; Ob-C: obese rats fed HFD (20% corn oil) for 8 weeks followed by CSP supplementation (10%) for the remaining 4 weeks. Data were analyzed by two-way ANOVA followed by Tukey post hoc tests. Means with different letters (a, b, c, d, e) are significantly different ($p < 0.05$)

Table 2. Effects of *Citrus Sinensis* Peel on Plasma Biochemical Parameters in Experimental Groups

Parameter	C–	C+	Ob+	Ob-P	Ob-C	*p-value*
Glucose (mg/dL)	78.82 ± 1.81	72.90 ± 1.94	162.00 ± 2.10***	86.36 ± 2.92***	87.61 ± 4.72***	< 0.0001
Insulin (µIU/mL)	6.56 ± 0.19	6.07 ± 0.21*	8.02 ± 0.31***	7.09 ± 0.17***	7.27 ± 0.16**	< 0.0001
HOMA-IR	0.60 ± 0.03	0.51 ± 0.01	1.50 ± 0.08***	0.70 ± 0.04***	0.73 ± 0.04***	< 0.0001
Triglycerides (mg/dL)	88.31 ± 2.70	76.19 ± 2.81***	139.80 ± 1.87***	97.37 ± 1.51***	90.73 ± 4.53***	< 0.0001
VLDL-TG (mg/dL)	56.58 ± 1.46	46.17 ± 3.05***	94.38 ± 3.34***	62.63 ± 1.56***	59.56 ± 2.50***	< 0.0001
LDL-TG (mg/dL)	20.30 ± 1.66	17.21 ± 1.16	37.29 ± 1.60***	23.79 ± 1.50***	21.65 ± 1.70***	< 0.0001
HDL-TG (mg/dL)	11.43 ± 0.50	12.82 ± 0.66*	8.13 ± 0.61***	10.95 ± 0.32***	9.52 ± 0.55*	< 0.0001
Total cholesterol (mg/dL)	140.02 ± 4.32	116.71 ± 7.77***	171.40 ± 4.81***	140.30 ± 7.24***	140.50 ± 2.62***	< 0.0001
VLDL-C (mg/dL)	39.84 ± 2.07	23.32 ± 3.00***	54.15 ± 1.70***	37.71 ± 3.00***	41.32 ± 2.44***	< 0.0001
LDL-C (mg/dL)	44.84 ± 1.65	34.83 ± 3.13***	76.76 ± 3.66***	50.03 ± 2.39***	51.90 ± 1.40***	< 0.0001
HDL-C (mg/dL)	55.34 ± 1.79	58.57 ± 2.99	40.48 ± 1.88***	52.56 ± 2.62***	47.28 ± 3.00*	< 0.0001
Atherogenic index (TG/HDL-C)	1.60 ± 0.02	1.30 ± 0.05*	3.46 ± 0.18***	1.86 ± 0.12***	1.93 ± 0.20***	< 0.0001
AST (IU/L)	17.96 ± 0.48	16.16 ± 0.62**	36.02 ± 0.53***	17.88 ± 0.75***	18.70 ± 0.55***	< 0.0001
ALT (IU/L)	14.34 ± 0.42	9.46 ± 0.62***	24.65 ± 0.82***	14.47 ± 0.36***	15.75 ± 0.71***	< 0.0001

Notes: C–: control rats fed a standard diet; C+: control rats fed a standard diet supplemented with 10% Citrus sinensis peel (CSP); Ob+: obese rats fed a high-fat diet (HFD, 20% corn oil); Ob-P: obese rats fed HFD supplemented with 10% CSP for 12 weeks; Ob-C: obese rats fed HFD for 8 weeks, followed by HFD supplemented with 10% CSP for the remaining 4 weeks. Values are expressed as mean ± standard deviation (SD). Differences among groups were analyzed by one-way ANOVA followed by Tukey's honestly significant difference (HSD) post hoc test. HOMA-IR: homeostasis model assessment of insulin resistance; TG: triglycerides; VLDL, LDL, HDL: very-low-, low- and high-density lipoproteins; -C: cholesterol fraction; AST: aspartate aminotransferase; ALT: alanine aminotransferase. Atherogenic index = TG/HDL-C. C+ and Ob+ are compared with C–; Ob-P and Ob-C are compared with Ob+. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (Tukey HSD).

2.10 mg/dL) and hyperinsulinemia (8.02 ± 0.31 µIU/mL) relative to lean controls (C–; 78.82 ± 1.81 mg/dL and 6.56 ± 0.19 µIU/mL, respectively; $p < 0.001$). Consequently, the HOMA-IR index in the Ob+ cohort increased 2.5-fold (1.50 ± 0.08 vs. 0.60 ± 0.03; $p < 0.001$), indicating the onset of diet-induced insulin resistance. In contrast, incorporation of 10% CSP significantly mitigated glycemic dysfunction in both treatment protocols. Co-administration of CSP throughout the 12-week regimen (Ob-P) prevented severe hyperglycemia, maintaining fasting glucose at 86.36 ± 2.92 mg/dL ($p < 0.001$ vs. Ob+). Similarly, initiating CSP intervention after 8 weeks of established obesity (Ob-C) reduced glucose levels to 87.61 ± 4.72 mg/dL ($p < 0.001$ vs. Ob+). Both CSP regimens also lowered circulating insulin concentrations (7.09 ± 0.17 µIU/mL for Ob-P, $p < 0.001$; 7.27 ± 0.16 µIU/mL for Ob-C, $p < 0.01$ vs. Ob+) and restored HOMA-IR scores close to control values (0.70 ± 0.04 for Ob-P and 0.73 ± 0.04 for Ob-C; $p < 0.001$ vs. Ob+). In healthy control rats, CSP administration (C+) produced a modest but significant decrease in insulin levels (6.07 ± 0.21 µIU/mL; $p < 0.05$ vs. C–), while maintaining physiological normoglycemia.

Lipid profile. Chronic HFD consumption induced pronounced dyslipidemia in the Ob+ group, characterized by significant increases in plasma triglycerides (139.80 ± 1.87 mg/dL) and total cholesterol (171.40 ± 4.81 mg/dL) compared with normolipidemic C– rats (88.31 ± 2.70 mg/dL and 140.02 ± 4.32 mg/dL, respectively; $p<0.001$). Subfraction analysis demonstrated substantial accumulation of pro-atherogenic lipoproteins, including VLDL-C (54.15 ± 1.70 mg/dL), LDL-C (76.76 ± 3.66 mg/dL), VLDL-TG (94.38 ± 3.34 mg/dL), and LDL-TG (37.29 ± 1.60 mg/dL) ($p < 0.001$ vs. C–). Conversely, anti-atherogenic HDL-cholesterol levels declined significantly in Ob+ rats (40.48 ± 1.88 mg/dL vs. 55.34 ± 1.79 mg/dL in C–; $p < 0.001$), leading to a more than two-fold rise in the atherogenic index (TG/HDL-C: 3.46 ± 0.18 vs. 1.60 ± 0.02; $p < 0.001$). Both preventive (Ob-P) and curative (Ob-C) CSP therapies significantly attenuated diet-induced dyslipidemia. CSP supplementation reduced circulating triglycerides (97.37 ± 1.51 mg/dL for Ob-P and 90.73 ± 4.53 mg/dL for Ob-C; $p < 0.001$ vs. Ob+) and lowered total cholesterol to values comparable to those of C– rats (140.30 ± 7.24 mg/dL and 140.50 ± 2.62 mg/dL, respectively; $p < 0.001$ vs. Ob+). Relative to Ob+, pro-atherogenic LDL-C decreased by 34.8% (Ob-P) and 32.4% (Ob-C), and VLDL-C by 30.4% and 23.7%, respectively ($p < 0.001$). Furthermore, HDL-C concentrations were significantly recovered (52.56 ± 2.62 mg/dL in Ob-P and 47.28 ± 3.00 mg/dL in Ob-C; $p < 0.001$ and $p < 0.05$ vs. Ob+, respectively), resulting in a marked improvement in the atherogenic risk profile (1.86 ± 0.12 for Ob-P and 1.93 ± 0.20 for Ob-C; $p < 0.001$ vs. Ob+). Supplementation of healthy control rats with CSP (C+) also conferred a hypolipidemic effect, significantly decreasing total cholesterol (116.71 ± 7.77 mg/dL) and triglycerides (76.19 ± 2.81 mg/dL) ($p < 0.001$ vs. C–), as well as the atherogenic index (1.30 ± 0.05; $p < 0.05$ vs. C–).

Hepatic enzymes. Transaminase activities indicated HFD-induced hepatic stress in the Ob+ cohort, evidenced by 2.0- and 1.7-fold increases in plasma aspartate aminotransferase (AST; 36.02 ± 0.53 IU/L) and alanine aminotransferase (ALT; 24.65 ± 0.82 IU/L), respectively, compared with lean C– rats (17.96 ± 0.48 IU/L and 14.34 ± 0.42 IU/L; $p < 0.001$). Dietary intervention with CSP alleviated hepatocellular injury. Both Ob-P and Ob-C regimens

reduced AST (17.88 ± 0.75 IU/L and 18.70 ± 0.55 IU/L) and ALT levels (14.47 ± 0.36 IU/L and 15.75 ± 0.71 IU/L) to values comparable to those of C– rats ($p < 0.001$ vs. Ob+). Additionally, C+ animals exhibited lower basal ALT levels (9.46 ± 0.62 IU/L; $p < 0.001$ vs. C–), suggesting an inherent hepatoprotective potential of CSP.

3.3 Effects of CSP on Blood and Tissue Oxidant/Antioxidant Status

Variations in redox biomarkers in erythrocytes, liver, adipose tissue, and pancreas are presented in Figures 2, 3, 4, and 5, respectively. The results revealed a compromised oxidant/antioxidant status in obese rats. Specifically, a decrease in the levels of GSH and the enzymatic activities of CAT and SOD was observed in both erythrocytes and tissues of obese rats (Ob+) compared to the control group (C-). In contrast, CSP supplementation (Ob-P and Ob-C) significantly increased these three parameters in comparison to controls. Moreover, erythrocyte and tissue levels of peroxynitrite ($ONOO^-$), MDA, and CP were significantly elevated in obese rats (Ob+) compared to controls (C-), whereas CSP supplementation significantly reduced these markers of oxidative damage in the Ob-P and Ob-C groups.

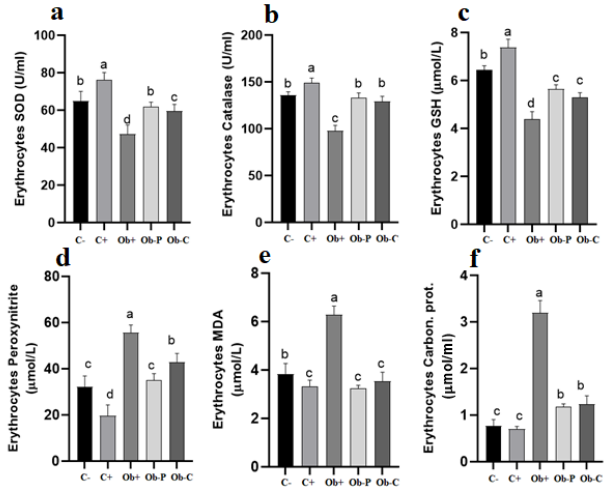


Figure 2. Erythrocyte Oxidative Stress Markers in Rats

Values are presented as means ± S.D. C-: control rats; C+: control rats treated with orange peel; Ob+: obese rats fed a high-fat diet (HFD, 20% corn oil); Ob-P: obese rats fed HFD (20% corn oil) supplemented with 10% CSP for 12 weeks; Ob-C: obese rats fed HFD (20% corn oil) for 8 weeks followed by CSP supplementation (10%) for the remaining 4 weeks. Data were analyzed by two-way ANOVA followed by Tukey post hoc tests. Means with different letters (a, b, c, d) are significantly different ($p < 0.05$)

3.4 Multivariable Analysis

Figure 6 illustrates the linear relationships among the metabolic and oxidative stress parameters. Weight gain exhibited strong positive correlations with glucose, HOMA,

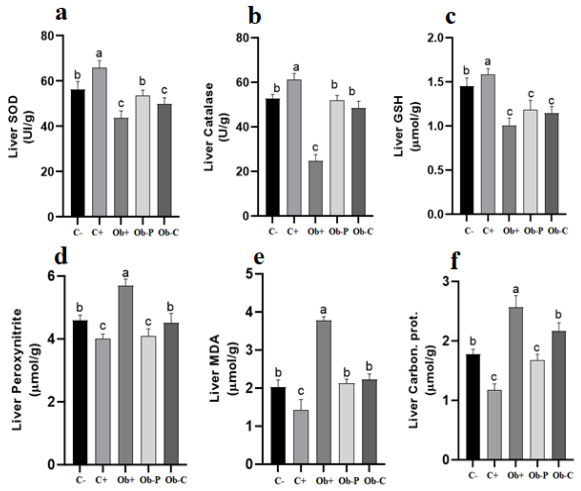


Figure 3. Liver Oxidative Stress Markers in Rats

Values are presented as means ± S.D. C-: control rats; C+: control rats treated with orange peel; Ob+: obese rats fed a high-fat diet (HFD, 20% corn oil); Ob-P: obese rats fed HFD (20% corn oil) supplemented with 10% CSP for 12 weeks; Ob-C: obese rats fed HFD (20% corn oil) for 8 weeks followed by CSP supplementation (10%) for the remaining 4 weeks. Data were analyzed by two-way ANOVA followed by Tukey post hoc tests. Means with different letters (a, b, c, d) are significantly different ($p < 0.05$)

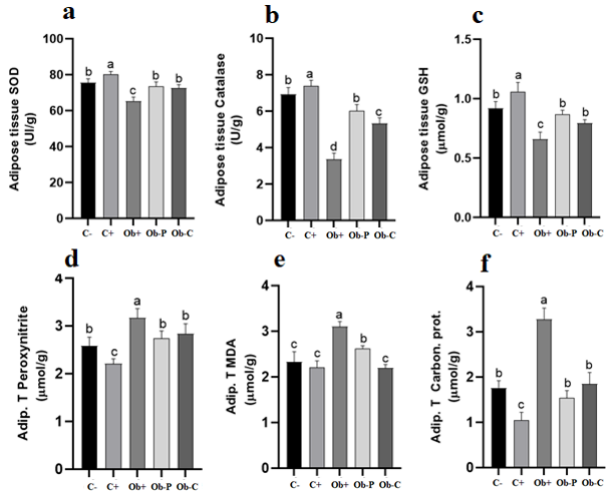


Figure 4. Adipose Tissue Oxidative Stress Markers in Rats

Values are presented as means ± S.D. C-: control rats; C+: control rats treated with orange peel; Ob+: obese rats fed a high-fat diet (HFD, 20% corn oil); Ob-P: obese rats fed HFD (20% corn oil) supplemented with 10% CSP for 12 weeks; Ob-C: obese rats fed HFD (20% corn oil) for 8 weeks followed by CSP supplementation (10%) for the remaining 4 weeks. Data were analyzed by two-way ANOVA followed by Tukey post hoc tests. Means with different letters (a, b, c, d) are significantly different ($p < 0.05$)

TG, MDA, ONOO–, and PC (r = 0.96, 0.95, 0.96, 0.92, 0.78, and 0.93, respectively; all $p < 0.05$). In contrast, weight gain was negatively correlated with HDL-C, SOD, CAT, and GSH (r = –0.76, –0.82, –0.90, and –0.84, respectively; all $p < 0.05$). These associations indicate that greater weight gain

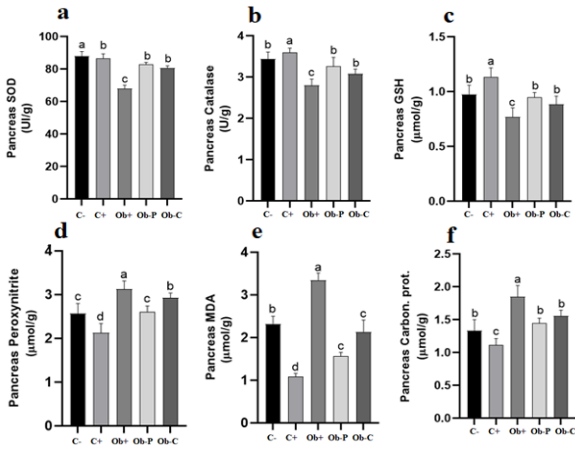


Figure 5. Pancreas Oxidative Stress Markers in Rats

Values are presented as means ± S.D. C-: control rats; C+: control rats treated with orange peel; Ob+: obese rats fed a high-fat diet (HFD, 20% corn oil); Ob-P: obese rats fed HFD (20% corn oil) supplemented with 10% CSP for 12 weeks; Ob-C: obese rats fed HFD (20% corn oil) for 8 weeks followed by CSP supplementation (10%) for the remaining 4 weeks. Data were analyzed by two-way ANOVA followed by Tukey post hoc tests. Means with different letters (a, b, c, d) are significantly different ($p < 0.05$).

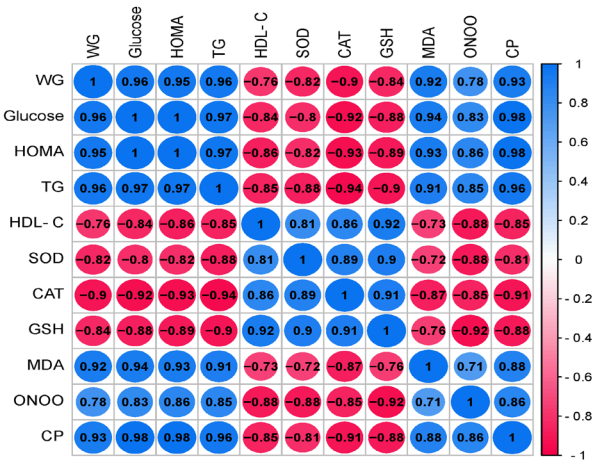


Figure 6. Heatmap of Pearson's Correlation Coefficients Between Biochemical Parameter and Redox Status (Correlations Plot)

was accompanied by impaired glucose and lipid homeostasis and increased oxidative stress, together with reduced antioxidant status.

HDL-C was also strongly and negatively correlated with weight gain, glucose, HOMA, and TG (r = −0.76, −0.84, −0.86, and −0.85, respectively; all $p < 0.05$). In addition, MDA was strongly and positively correlated with TG and HOMA (r = 0.91 and 0.93, respectively; both $p < 0.05$), suggesting an association between lipid disturbances, insulin resistance, and lipid peroxidation. These findings support a close relationship between metabolic dysregulation and oxidative imbalance in the present obesity model.

The perfect correlation observed between glucose and HOMA (r = 1.00) reflects the mathematical construction of the HOMA index, which is derived from fasting glucose and insulin concentrations. Therefore, this correlation was not considered biologically informative and was excluded in the biological interpretation of the correlation matrix.

3.5 Histology

The results of histological analysis are displayed in Figure 7. Liver sections from control rats (C-) exhibited normal lobular architecture, with hepatocytes arranged in trabeculae radiating from the central vein and separated by sinusoids. Liver sections from rats administered orange peel (C+) demonstrated mild to moderate sinusoidal congestion accompanied by slight dilation of the central vein, while the organization of the hepatic cords remained well-preserved. In contrast, liver sections from obese rats (Ob+) revealed swollen, "ballooned" hepatocytes with enlarged, reticulated cytoplasm due to small aggregates of micro vesicular steatosis. Consequently, the sinusoids were compressed by hypertrophic hepatocytes, resulting in loss of normal hepatic architecture and reduced sinusoidal spaces. Liver tissue from obese rats receiving CSP as a protective dietary supplement (Ob-P) displayed a normal lobular structure, with hepatocytes arranged in radial trabeculae emanating from the central vein and the usual interspersed sinusoids. By comparison, liver histology from obese rats receiving the corrective CSP diet (Ob-C) exhibited mild to moderate hepatocyte swelling with micro vesicular steatosis around the central vein, and binucleated hepatocytes were occasionally observed.

4 Discussion

Obesity is increasingly recognized as a major health risk, primarily due to its strong association with chronic diseases, that numerous can be fatal (Bray *et al.*, 2018). In the present study, we examined key characteristics of obesity, including glucose intolerance, insulin resistance, hyperlipidemia, and elevated oxidative stress levels. Citrus peels represent a valuable by-product that can be utilized various applications, ranging from biofuel production (ethanol and methane) to direct utilization as an ingredient in food products. Moreover, their bioactive components, such as polyphenols, essential oils, and dietary fibers, have been associated with beneficial effects on human health, particularly in metabolic diseases, cancer, and oxidative stress (Liu *et al.*, 2021).

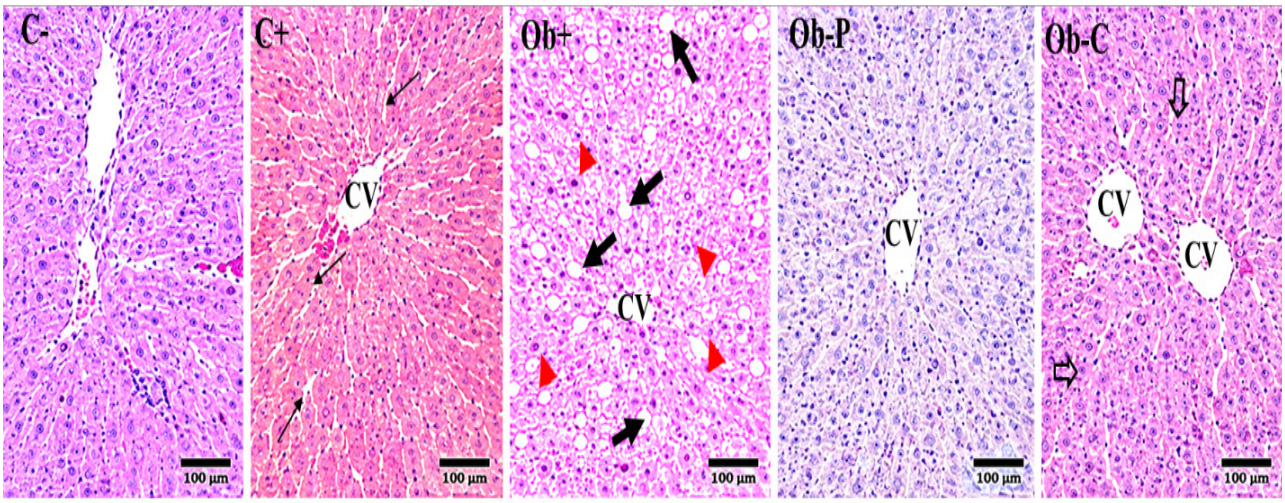


Figure 7. Effect of Orange Peel on Liver Histopathological Changes in the Studied Rats

C-, Liver histology of control rats revealed a normal liver lobule structure. C+Liver sections of rats receiving orange peel showed near normal hepatic structure with mild to moderate congestion of sinusoids (Arrow). Ob+ Liver section of obese rats revealed the presence of swollen, 'ballooned' hepatocytes (Red head arrow) with small cytoplasmic aggregates of micro vesicular steatosis (Bold arrow). Ob-P Liver histology of rats receiving orange peel as a protective diet revealed a normal liver lobule structure. The liver cells are arranged in trabecules that are organized radially from the center-lobular vein (CV) and are disconnected by sinusoids. Ob-C, histology of the liver of obese rats receiving orange peel as a corrective diet showed normal structure with some binucleated hepatocytes (Empty arrow). Scale barre 100 µm, H&E stains 400x.

This *in vivo* study investigated the preventive and corrective effects of orange peel on obesity-related metabolic alterations. High-fat diet (HFD)-induced obesity, selected as the experimental model in this study, is frequently employed in animal models owing to its relevance to human obesity. Body weight and tissue weights (liver, adipose tissue, and pancreas) were higher in the HFD group (Ob+) than in the control group (C–), which can be attributed to the high energy content of the HFD. However, supplementation with CSP, recognized for its high dietary fiber and polyphenol content, significantly mitigated body weight gain and tissue hypertrophy in HFD-fed rats. These findings are consistent with previous studies (Hu *et al.*, 2021), which reported that CSP supplementation helps to manage overweight conditions by increasing energy expenditure, suppressing appetite, and modulating adipogenesis, lipogenesis, gut microbiota, and obesity-related inflammation (Dini & Mancusi, 2023). Notably, comparison of the healthy control groups (C+ vs. C–) also revealed specific metabolic and antioxidant effects of CSP in the absence of obesity. CSP supplementation was associated with changes in serum ALT and cholesterol levels, together with a significant modulation of SOD activity, indicating that its effects were not restricted to the correction of HFD-induced metabolic disturbances. The reduction in ALT observed in the C+ group may suggest a favorable effect of CSP on hepatic biochemical status, whereas the changes in cholesterol indicate an influence on lipid metabolism even under non-obese conditions. The modulation of SOD activity further suggests that CSP may influence endogenous antioxidant defenses independently of obesity-associated oxidative stress. These observations are consistent with the biological activity expected from citrus peel constituents, particularly dietary fiber and polyphenolic compounds, although the mechanisms underlying these effects in healthy animals remain to be established. Importantly, the absence of adverse variations in the other evaluated metabolic parameters supports the need to further investigate the safety and metabolic effects of CSP in non-obese conditions (Ademosun *et al.*, 2021).

Orange peel is composed primarily of dietary fiber (Zhou *et al.*, 2023), which plays a crucial role in weight management. Dietary fiber promotes satiety, thereby reducing calorie intake. Moreover, fibers have been demonstrated to decrease lipid retention and blood glucose levels by decelerating glucose absorption into the bloodstream, which contributes to reduced total calorie consumption (Barber *et al.*, 2020). Furthermore, the fermentation of insoluble fibers by intestinal microbiota produces short-chain fatty acids (SCFAs), which stimulate the release of satiety hormones and positively influence glucose regulation (Dalile *et al.*, 2019). Because food intake was not recorded in the present study, the contribution of reduced energy intake to the observed effects cannot be established.

CSP supplementation also improved blood glucose, insulin, and HOMA-IR in obese rats in obese rats. The hypoglycemic effects of orange peel are largely attributed to its polyphenol content. Several studies have suggested that flavonoids can modulate insulin secretion, enhance insulin sensitivity, and reduce the absorption of carbohydrates in the

gut. These properties are particularly relevant in the context of obesity, assumed the close association between hyperglycemia, insulin resistance, lipoprotein abnormalities, and oxidative dysregulation (Khubber *et al.*, 2023; Golovinskaia & Wang, 2023). Recent studies further support the beneficial metabolic effects of CSP in experimental models of obesity. Mutia *et al.* (2025) reported that administration of Sunkist orange (*C. sinensis* [L.] Osbeck) peel granule extract to obese rats significantly affected body weight, blood glucose, and total cholesterol levels, providing further evidence of the potential of orange peel-derived preparations to modulate obesity-associated metabolic disturbances. These findings are consistent with the current study, in which CSP supplementation reduced body weight and restored glucose, insulin, HOMA, and lipid-related parameters in HFD-induced obese rats. However, differences in the experimental model, formulation, dose, and duration of treatment should be considered when comparing these results (Kumari *et al.*, 2025).

Obesity is closely associated with significant disruptions in lipid and lipoprotein metabolism, including increased levels of triglycerides, total cholesterol, LDL, and VLDL, alongside a decrease in HDL cholesterol. Consistent with Wang *et al.* (2019), the atherogenic index was significantly higher in obese rats than in controls. This dysfunction in lipoprotein metabolism promotes lipid accumulation in peripheral tissues, thereby contributing to a deleterious pro-atherogenic and pro-inflammatory state (Groenen *et al.*, 2021). In the present investigation, CSP supplementation attenuated these lipid alterations, in agreement with AbdEl-Gwaad *et al.*, (2020), who reported that CSP supplementation could mitigate lipoprotein disturbances. Huang *et al.* (2022), reported that an orange peel powder diet significantly reduced expression of the *SREBF1* gene, which regulates hepatic lipogenesis; modulation of this pathway may therefore contribute to the lipid-lowering effects observed here, although gene expression was not assessed in our study. Dietary supplementation with dried orange peel powder significantly reduced plasma triglyceride and total cholesterol levels while increasing HDL-cholesterol levels in obese rats (Gong *et al.*, 2022). These hypolipidemic effects may be associated with the high concentration of bioactive phenolic compounds, particularly flavonoids, present in orange peel. Such compounds have been reported to exert lipid-modulating effects and may contribute to improved lipid metabolism and the attenuation of obesity-associated dyslipidemia. Furthermore, they can modulate the expression and activity of various enzymes involved in lipoprotein metabolism, including lipoprotein lipase, lecithin-cholesterol acyltransferase, and cholesterol ester transfer protein. Additionally, the soluble fibers abundant in orange peel contribute to the regulation of lipoprotein parameters, promote fecal excretion of bile acids and sequester bile acids and cholesterol within the intestine, thereby limiting their reabsorption through the enterohepatic circulation and reducing plasma cholesterol (Singh *et al.*, 2018). Beyond fiber content, orange peel is also rich in calcium (approximately 41.9 mg/100 g of dry matter), which has been demonstrated to exert anti-obesity effects by regulating fat metabolism, notably by stimulating lipolysis and inhibiting lipogenesis, (Ben Hsouna *et al.*, 2023).

Polyphenols from CSP have been reported to decrease triglyceride (TG), total cholesterol, LDL-C, and VLDL-C levels, while increasing HDL-C, thereby reducing dyslipidemia and tissue lipid accumulation in adipose and hepatic tissues (Ahmed *et al.*, 2017; Vajdi & Farhangi, 2021). Additionally, polyphenols play a crucial role in the preferential regulation of the lipogenic process by activating genes involved in fatty acid and triglyceride synthesis, offering natural protection against hepatic steatosis (Li *et al.*, 2011). Obesity constitutes also a major risk factor for liver damage, a risk exacerbated by additional metabolic factors such as hyperlipidemia and insulin resistance (Chalasani *et al.*, 2018). AST and ALT are key indicators of liver health, and elevated levels of these enzymes are frequently associated with obesity-related liver damage (Wu *et al.*, 2021). In the present study, AST and ALT levels were significantly lower in obese rats receiving CSP than in Ob+ rats.

Oxidative stress, a hallmark of obesity, leads to the oxidation of lipids and proteins, DNA modification, and liver damage, resulting in the destruction of cell membranes and the release of liver enzymes (ALT and AST) into the bloodstream. In addition to its hypoglycemic and lipid-lowering effects, orange peel also exhibits notable antioxidant properties. AbdEl-Gwaad *et al.*, (2020) previously reported that these antioxidant effects include a significant decrease in serum nitric oxide levels and restoration of hepatic catalase activity. Such disturbances play a central role in the development of inflammation and the metabolic complications of obesity (Pérez-Torres *et al.*, 2021). Obesity has also been associated with cognitive impairment through various markers of oxidative stress, including SOD, catalase, GSH, ONOO, MDA, and CP (Imessaoudene *et al.*, 2016).

In the present study, SOD, CAT, and GSH levels were significantly lower, and $ONOO^{-}$, MDA, and PC concentrations significantly higher, in the erythrocytes and tissues (liver, adipose tissue, and pancreas) of the Ob+ group. These findings align with results from other studies (Dajnowicz-Brzezik *et al.*, 2022; Hajiluian *et al.*, 2018). CSP supplementation in HFD-fed rats markedly restored redox status, as revealed by significant increases in SOD, CAT, and GSH and significant reduction in ONOO, MDA, and CP. The role of orange peel powder as a dietary supplement for

managing obesity and restoring the oxidative/antioxidant balance has not been extensively explored.

The metabolic benefits of CSP may also extend beyond glucose and lipid homeostasis to the protection of organs affected by obesity-associated oxidative stress. In this regard, Osuji and Chigemezu (2025) demonstrated that ethanolic CSP extract improved several markers of renal function and oxidative status in obese Wistar rats, including reductions in serum urea, creatinine, sodium, and MDA, together with enhanced antioxidant enzyme activity. These observations complement our findings of improved hepatic biochemical parameters and restoration of antioxidant defenses. Collectively, these studies suggest that orange peel may exert a broader protective action against the metabolic and oxidative consequences of obesity, although the specific mechanisms and active constituents remain to be elucidated.

In our previous study using HPLC polyphenol analysis, CSP was found to contain high levels of polyphenols, including quercetin, rutin, caffeine, epicatechin, and gallic acid (Berroukeche *et al.*, 2024), which may partly account for the antioxidant effects observed with this diet. These compounds can directly scavenge reactive oxygen species (ROS), chelate metal ions involved in radical production, and activate signaling pathways that regulate endogenous antioxidant defenses. In addition, *in vitro* assays (such as DPPH, FRAP, etc.) have demonstrated significant antioxidant activity of CSP (Berroukeche *et al.*, 2024). Ke *et al.* (2020) further reported that preventive and corrective administration of citrus peel extract improved glucose tolerance and insulin sensitivity, and lipid profiles, oxidative stress, hepatic steatosis, and inflammatory markers were likewise ameliorated in mouse models of steatosis (Martínez-Noguera *et al.*, 2021).

Beyond these direct effects on lipoprotein parameters and oxidative stress, orange peel appears to exert beneficial indirect actions by modulating other factors closely associated with obesity and its metabolic complications (Golovinskaia & Wang, 2023). Chronic low-grade inflammation, a hallmark of obesity, is recognized as a major aggravating factor for lipoprotein dysregulation and oxidative stress. In fact, bioactive compounds in orange peel, such as flavonoids and coumarins, are recognized to inhibit the activation of various pro-inflammatory signaling pathways, thereby reducing the production of pro-inflammatory cytokines and cell adhesion molecules, thus limiting the recruitment and infiltration of immune cells into peripheral tissues (Leo *et al.*, 2022).

The correlation analysis revealed significant relationships between metabolic and oxidative stress parameters. Weight gain, glucose, HOMA-IR, and TG were strongly and positively correlated, which is consistent with the metabolic syndrome profile, in which weight gain and elevated glucose are commonly accompanied by increased triglycerides and insulin resistance (Lemieux & Després, 2020). Insulin resistance (reflected by glucose and HOMA-IR) was positively correlated with markers of oxidative stress (MDA, ONOO, and CP), suggesting a relationship between metabolic dysfunction and oxidative stress. Regarding triglycerides and HDL-C, a strong inverse correlation was observed, as these are well-established markers of cardiovascular health. Elevated triglycerides are typically correlated with lower HDL-C levels, indicating an adverse lipid profile. In contrast, the negative correlation between HDL-C, markers of oxidative stress, and metabolic dysfunction highlights the protective role of HDL-C against these conditions. The antioxidant markers SOD, CAT, and GSH were positively correlated with one another, reflecting coordinated antioxidant defense mechanisms. Overall, these correlations offer insight into the interrelationships among metabolic markers, oxidative stress, and antioxidant defenses (Masenga *et al.*, 2023) and underscore the importance of addressing both metabolic and oxidative parameters in the management of obesity and its complications (Kosmas *et al.*, 2023). They should nevertheless be interpreted as associations rather than evidence of causality.

Histological analysis provides a reliable method for assessing the effects of orange peel on liver function and integrity in obese rats. Ten precent orange peel supplementation largely prevented the hepatic liver alterations induced by the HFD in the preventive group and partially reversed them in the corrective group, with a marked improvement in the steatotic changes observed in the Ob+ group. The hepatoprotective effects of citrus by-products may be attributed to phytoconstituents, particularly phenolic compounds, including flavanone glycosides such as hesperidin, naringin, narirutin, and neohesperidin (Chen *et al.*, 2013). The protective effects of orange peel in liver function, particularly against damage induced by N-acetyl-p-aminophenol (APAP) administration in rats, were further supported by treatments with naringin and naringenin (Ahmed *et al.*, 2019). Additionally, El-Shazly *et al.* (2017) suggested that the isoflavones present in orange peel might influence liver and adipose tissue lipase enzyme activity. Their study also proposed that these compounds could upregulate LDL receptors and induce the gene expression of various enzymes and proteins involved in lipid metabolism, either directly or indirectly. These findings suggest that orange peel supplementation may ameliorate obesity and related metabolic disorders in mice subjected to a high-fat diet (El-Shazly *et al.*,2017).

Limitations and Perspectives

While the present study provides evidence that *Citrus sinensis* peel (CSP) supplementation can attenuate obesity-

associated metabolic and oxidative disturbances in a preclinical model, several limitations should be acknowledged. The relatively reduced number of animals (n = 5 per group) may limit statistical power and generalizability of the findings and should therefore be considered when interpreting the results. In addition, although the Wistar rat model is widely utilized to investigate diet-induced obesity, extrapolation of these findings to humans remains limited. Further *in vitro* and *in vivo* studies are warranted to elucidate the molecular mechanisms underlying the observed effects, identify the bioactive constituents primarily responsible for these responses, and characterize their bioavailability and metabolism. Future investigations should also examine the specific signaling pathways and molecular targets modulated by CSP, including changes in relevant gene and protein expression in metabolically active tissues. Dose-response studies will be particularly important for establishing the effective dose range, optimal supplementation level, and safety profile of CSP. Moreover, longer-term studies are required to assess the persistence of its metabolic and redox effects and to evaluate potential adverse effects associated with prolonged consumption. Ultimately, well-designed clinical studies will be essential to determine the safety, tolerability, bioavailability, and efficacy of CSP at doses relevant to dietary consumption. Computational approaches may further assist in identifying potential molecular targets.

5 Conclusions

The present study demonstrates that *Citrus sinensis* peel (CSP) supplementation exerts both preventive and corrective effects against high-fat diet (HFD)-induced obesity and its associated metabolic and oxidative disturbances in Wistar rats. Weight gain was positively associated with blood glucose, HOMA-IR, and triglyceride levels, whereas HDL-C was negatively correlated with these parameters. The inverse associations of SOD activity with weight gain and blood glucose further support the relationship between metabolic dysregulation and impaired redox homeostasis.

CSP supplementation attenuated body weight gain and adipose tissue accumulation and improved several markers of glucose and lipid homeostasis, including blood glucose, insulin resistance, triglycerides, and HDL-C. These effects were accompanied by improved antioxidant defenses, reflected by increased SOD, CAT, and GSH levels, together with reduced markers of oxidative damage. CSP also ameliorated the hepatic alterations induced by the HFD, as evidenced by improvements in liver biochemical parameters and histological features. Notably, the comparison of preventive and corrective supplementation within the identical experimental framework provides complementary evidence that CSP can limit the development of obesity-associated metabolic and oxidative alterations and improve those already established.

Taken together, these findings support the potential of non-fermented *C. sinensis* peel as a promising functional-food ingredient and a sustainable source of bioactive compounds for mitigating obesity-related metabolic and oxidative disturbances. However, the translation of these findings to human nutrition requires further investigation. Future studies should clarify the contribution, bioavailability, and mechanisms of action of individual CSP bioactive constituents through complementary *in vitro* and *in vivo* approaches, as well as assess their efficacy under conditions relevant to human consumption. Computational approaches may further contribute to the identification of potential molecular targets and mechanisms of action. Such investigations will be important for determining whether the beneficial effects observed in this experimental model can be reproduced and ultimately translated into practical nutritional strategies.

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Previous submissions: None

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