Chitosan Nanoparticles as Delivery System for *Lactobacillus plantarum*: Lipid and Antioxidant Modulation in Non-Alcoholic Fatty Liver Disease in Rat Model

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***Abstract*—** Non-Alcoholic Fatty Liver Disease (NAFLD) is a major global health concern characterized by hepatic lipid accumulation, dyslipidemia, and oxidative stress. Postbiotic chitosan nanoparticles offer a promising therapeutic strategy. Postbiotics-loaded chitosan nanoparticles represent a compelling therapeutic approach worth exploring. This study investigated the effects of *Lactobacillus plantarum*-Chitosan Nanoparticles (LCN) on serum lipid profiles and antioxidant capacity in a rat model of NAFLD. Thirty-two male Wistar rats were divided into four groups: G1 (negative control, standard diet), G2 (positive control, high-fat diet to induce NAFLD for two months), G3 (NAFLD + *L. plantarum* oral administration), and G4 (NAFLD + LCN oral administration). Serum lipid profile - triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) — were measured alongside oxidative stress markers, including superoxide dismutase (SOD) activity and malondialdehyde (MDA) levels. Nanoformulation treatment in G4 significantly lowered TG, TC, LDL-C, VLDL-C, and MDA relative to G2, while restoring normal levels of HDL-C and SOD activity.. These findings indicate that LCN exerts meaningful hypolipidemic and antioxidant effects in NAFLD rats, pointing to their potential as a novel nutraceutical intervention.

***Keywords* —** Chitosan nanoparticales , *Lactobacillus plantarum* , Oxidative stress , Postbiotics, NAFLD.

INTRODUCTION

The most prevalent chronic liver disease worldwide, Non-Alcoholic Fatty Liver Disease (NAFLD). Cirrhosis, fibrosis, non-alcoholic steatohepatitis (NASH), and simple steatosis are all included in this range of hepatic disorders (1). It is thought to affect 25–30% of people worldwide, and its incidence is increasing in tandem with the obesity and metabolic syndrome epidemics. (2). NAFLD is closely associated with insulin resistance, lipoprotein dyslipidemia and oxidative stress promoting a vicious cycle between these three pathophysiological mechanisms that perpetuates hepatocellular injury (3). NAFLD dyslipidemia consists of increased serum triglycerides, cholesterol, total- and LDL-C VLDL-C but decreased HDL-C which promoting atherogenesis and cardiovascular comorbidities (4). Oxidative stress, driven by mitochondrial dysfunction and reactive oxygen species (ROS) overproduction, further amplifies hepatic inflammation and lipid peroxidation, measurable by elevated malondialdehyde (MDA) and diminished antioxidant enzyme activity, including superoxide dismutase (SOD) (5).

A crucial pathophysiological axis in NAFLD is the gut-liver axis. (6). Gut dysbiosis promotes intestinal barrier dysfunction, bacterial translocation, and hepatic exposure to lipopolysaccharides (LPS), exacerbating liver inflammation (7). *Lactobacillus plantarum*, have demonstrated capacity to modulate the gut microbiota, strengthen intestinal barrier integrity, and attenuate hepatic steatosis through multiple mechanisms including short-chain fatty acid production, bile acid metabolism, and direct antioxidant activity (8). In addition, some strains of *L. plantarum* exert hepatoprotective effects by improving liver enzyme activity and reducing serum TG and total cholesterol (TC) levels (9,10). Postbiotics are defined as inactivated bacteria and/or their components that improve host health by the International Scientific Association of Probiotics and Prebiotics (ISAPP) in 2021 (11). Lactic acid bacteria postbiotic preparations contained a large number of bioactive metabolites, including organic acids and exopolysaccharides (12). probiotics improve insulin resistance and reduce fat gain, possibly for the amelioration of NAFLD (13). Bacterial lysates have also been reported to improve glucose metabolism, reduce body and liver lipid levels, reduce hepatic immune cell infiltration, (14).

As a result of their high bioactive content and high stability (no live bacteria), postbiotics have a lot of promise in the treatment of NAFLD. Despite growing evidence for individual components, limited studies have directly assessed LCN's combined efficacy on both lipid metabolism and antioxidant status in experimental NAFLD models. The present study was designed to evaluate the therapeutic potential of LCN on lipid profile parameters and antioxidant enzyme activity in a high-fat diet-induced NAFLD rat model.

MATERIALS AND MTHODS

Preparation of LCN

Lactobacillus plantarum was cultured in de Man, Rogosa and Sharpe (MRS) broth at 37°C for 24 hours under anaerobic conditions. The bacterial extract was prepared by centrifugation, washing, and sonication. Chitosan nanoparticles were prepared by ionic gelation using tripolyphosphate (TPP) as a cross-linking agent. Briefly, chitosan (molecular weight 50–190 kDa, degree of deacetylation ≥75%) was dissolved in 1% acetic acid (2 mg/mL), and bacterial extract was incorporated under magnetic stirring at room temperature. TPP solution (1 mg/mL) was added dropwise to achieve nanoparticle formation (15,16). The formation of nanoparticles was verified using the following analysis: Fourier Transforms Infrared Spectroscopy Analysis (FTIR) (Shimadzu corporation/Japan), Atomic Force Microscopy (AFM) Analysis (Negara/Russian Federation) , X-ray Diffraction (XRD) Analysis(Shimadzu/ japan) , Scanning Electron Microscope (SEM) (ZEISS/ Germany).

Experimental Design

The study took place from October 2025 to March 2026 at the College of Veterinary Medicine/University of Kerbala and involved 32 adult male Wistar rats aged 8 to 10 weeks with an average weight of (200 - 250 g) . After a 15-day period of acclimatization in metal cages with controlled environmental conditions (temperature of approximately 23±2°C and a 12-hour light/dark cycle for each) and unrestricted access to food and water , the rats were randomly assigned to four groups (n = 8 per group): G1 (negative control, standard diet and water), G2 (positive control, high-fat diet [HFD] , G3 (HFD + oral administration of *L. plantarum* postbiotics, 200 mg/kg/day, and G4 (HFD + oral administration of LCN 20 mg/kg/day) (17, 18). All animal procedures were conducted in accordance with institutional ethical guidelines for the use of laboratory animals. At study termination, blood serum was taken for the laboratory tests.

Biochemical Analysis

The levels of serum biochemical markers associated with NAFLD, including total (TC), (TG) and (HDL) were determined using ELISA and the commercial kits provided by (ELKBiotechnology /USA), while (LDL) and (VLDL) was calculated using the Friedewald equation (19). Antioxidant activity SOD and MDA levels were assessed by ELISA from the same source.

Ethical approval

Each and every experimental technique was authorized by the College of Veterinary Medicine of Kerbala and complied with the ethical approval number (UOK.VET.PH.2025.146).

Statistical Analysis

Data are expressed as mean ± Standard Error of Mean (SEM). One-way ANOVA followed by Tukey's multiple comparisons test was used to determine significant differences among groups using GraphPad Prism software. A p-value < 0.05 was considered statistically significant. Significance levels are indicated as *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$.

RESULT AND DISCUSSION

Effect of *Lactobacillus plantarum*-Chitosan Nanoparticles (LCN) on Lipid Profile

The lipid profile data for all experimental groups are summarized in Table 1. The positive control group (G2) exhibited significantly elevated serum TG (117.5 ± 1.32 mg/dL) (Figure1: A) , TC (155.4 ± 6.91 mg/dL) (Figure1: B) , LDL-C (65.33 ± 3.19 mg/dL) (Figure1: D), and VLDL-C (31.09 ± 1.38 mg/dL) compared to G1 (all $p < 0.01$), confirming successful induction of NAFLD-associated dyslipidemia (Figure1: E). HDL-C was significantly decreased in G2 (21.08 ± 0.58 mg/dL) versus G1 (34.40 ± 2.98 mg/dL, $p < 0.05$) (Figure1.: C).

Treatment with *L. plantarum* postbiotics alone (G3) partially improved the lipid profile: TC was reduced to 127.3 ± 8.01 mg/dL, LDL-C to 58.55 ± 1.96 mg/dL, and VLDL-C to 25.46 ± 1.60 mg/dL compared to G2, though differences from G2 did not always reach statistical significance. HDL-C in G3 (26.90 ± 1.46 mg/dL) showed partial but non-significant improvement over G2.

Table 1. Lipid profile parameters across experimental groups (Mean ± SEM).

Parameter	G1 Mean ± SEM	G2 Mean ± SEM	G3 Mean ± SEM	G4 Mean ± SEM
TG (mg/dL)	82.71 ± 3.46	117.5 ± 1.32	110.9 ± 4.56	95.77 ± 2.99
TC (mg/dL)	86.30 ± 5.03	155.4 ± 6.91	127.3 ± 8.01	103.9 ± 4.39
HDL-C (mg/dL)	34.40 ± 2.98	21.08 ± 0.58	26.90 ± 1.46	33.48 ± 3.31
LDL-C (mg/dL)	30.85 ± 1.65	65.33 ± 3.19	58.55 ± 1.96	41.51 ± 6.20
VLDL-C (mg/dL)	17.26 ± 1.00	31.09 ± 1.38	25.46 ± 1.60	20.77 ± 0.87

G1: Negative control; G2: NAFLD positive control; G3: NAFLD + *L. plantarum*; G4: NAFLD + LCN. Values are Mean ± SEM.

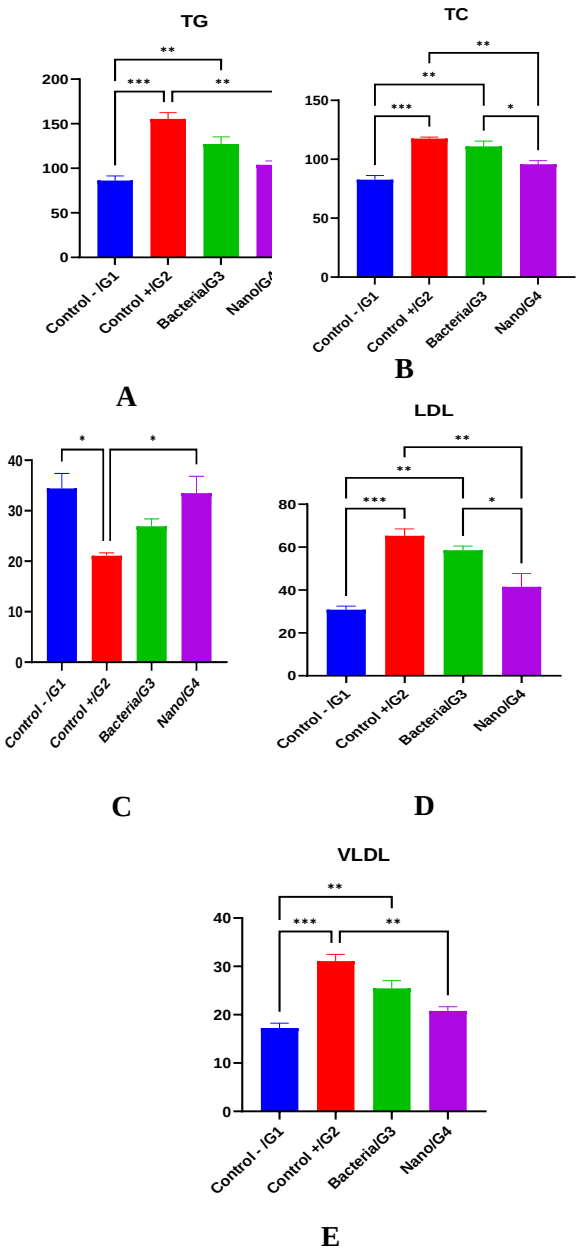


Figure 1 . Effect of *L.plantarum* postbiotics and *Lactobacillus plantarum*-Chitosan Nanoparticles (LCN) on lipid profile , on TG (A), TC (B) HLD (C) LDL (D) and (E) VLDL. *p<0.05, **p<0.01, ***p<0.001**.**

The study showed that treatment with *Lactobacillus plantarum*-chitosan nanoparticles (G4) resulted in the most noticeable improvements. TG was reduced to 95.77 ± 2.99 mg/dL (significantly lower than G2, p = 0.0071, and G3, p = 0.0471), TC to 103.9 ± 4.39 mg/dL (p = 0.0018 vs. G2), LDL-C to 41.51 ± 6.20 mg/dL (p = 0.0083 vs. G2), and VLDL-C to 20.77 ± 0.87 mg/dL (p = 0.0018 vs. G2). HDL-C in G4 (33.48 ± 3.31 mg/dL) was restored to near-normal values (p = 0.0248 vs. G2), with no significant difference from G1 (p = 0.9923). Significantly, the lipid profile was almost entirely normalized, as evidenced by the fact that none of the LCN treatment parameters varied from G1.

The hyperlipidemia of G2 group (high levels of TG, TC, LDL-C, VLDL-C; a low HDL-C) approximates the dyslipidemic phenotype of human NAFLD and confirms the previously described rodent HFD model . This pattern is accomplished by de novo hepatic lipogenesis, impaired fatty acid β-oxidation, and increased VLDL secretion (20).

The outcomes revealed that *L. plantarum* monotherapy (G3) resulting in partial, but statistically significant reductions in TC (p = 0.0073 vs G2) and LDL-C (p = 0.0034 vs G2), in agreement with previous reports. In high-fat diet-fed mice, Huang *et al* (21) showed that *Lactobacillus acidophilus* reduced TC and LDL-C, which was attributed to inhibition of intestinal cholesterol absorption and upregulation of hepatic LDL receptor expression. The bile salt hydrolase (BSH) activity of *Lactobacillus reuteri* deconjugates bile acids, thus decrease their enterohepatic recirculation and diverting cholesterol towards bile acid synthesis (22).

Lactobacillus plantarum-Chitosan Nanoparticles (LCN) (G4) showed near-complete normalization of all the lipid parameters, significantly greater effect than free bacteria for TG (p = 0.0471) and LDL-C (p = 0.0475). This enhancement probably corresponds to the improved gastrointestinal survival due to chitosan encapsulation. Chitosan nanoparticles act as a shield for probiotics against gastric acidity and bile salts, leading to a more efficient delivery of viable cells to the colon (23). Besides that, chitosan itself exhibits intrinsic hypolipidemic properties, with its cationic amine groups binding to negatively charged bile acids and dietary lipids, leading to decreased intestinal fat absorption (24). The enhanced lipid-lowering effect of LCN may be attributed to the synergistic effects of *L. plantarum* metabolic activity and lipid-binding capacity **of** chitosan.

The findings demonstrated particular significance in improvement of HDL-C in G4 (33.48 mg/dL, equivalent to G1). HDL is crucial for reverse cholesterol transport and elevated levels reduced the risk of atherosclerosis. Probiotic-mediated modulation of intestinal microbiota composition with subsequently increases in short-chain fatty acid (SCFA) production has shown to enhance hepatic HDL synthesis (25). In a similar vein Wang et al. (26) reported that encapsulated Lactobacillus preparations increased HDL-C and reduced atherogenic index in NAFLD models.

Effect of *Lactobacillus plantarum*- Chitosan Nanoparticles (LCN) on Antioxidant Activity

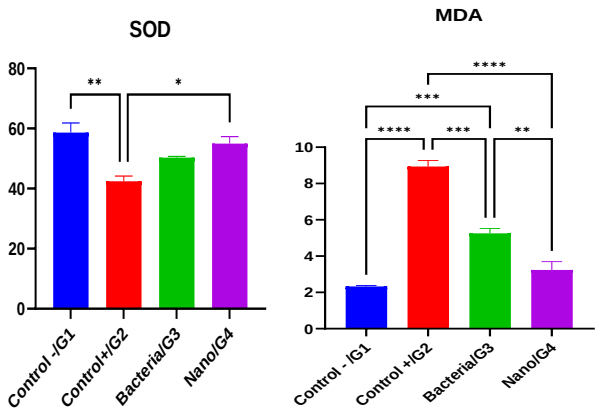
Antioxidant parameters are presented in Table 2. NAFLD induction (G2) significantly reduced serum SOD activity to 42.43 ± 1.72 U/mL compared to G1 (58.66 ± 3.15 U/mL, p = 0.0031), reflecting impaired antioxidant defense (Figure 2: A). MDA levels were markedly elevated in G2 (8.933 ± 0.33 nmol/mL) versus G1 (2.330 ± 0.04 nmol/mL, p < 0.0001), indicating extensive lipid peroxidation (Figure 2: B).

L. plantarum treatment (G3) significantly increased SOD to 50.30 ± 0.41 U/mL (p = 0.0942 vs G2, ns) and reduced MDA to 5.250 ± 0.27 nmol/mL (p = 0.0008 vs G2, ***), demonstrating partial antioxidant restoration. LCN treatment (G4) produced the greatest antioxidant benefit: SOD activity was restored to 54.97 ± 2.31 U/mL (p = 0.0140 vs G2, *), approaching G1 values (p = 0.6351). MDA was profoundly reduced to 3.240 ± 0.45 nmol/mL (p < 0.0001 vs G2), not significantly different from G1 (p = 0.2516). LCN was significantly more effective than postbiotics alone in reducing MDA (p = 0.0086).

Table 2. Oxidative stress parameters across experimental groups (Mean ± SEM)

Parameter	G1 Mean ± SEM	G2 Mean ± SEM	G3 Mean ± SEM	G4 Mean ± SEM
SOD (U/mL)	58.66 ± 3.15	42.43 ± 1.72	50.30 ± 0.41	54.97 ± 2.31
MDA (nmol/mL)	2.330 ± 0.04	8.933 ± 0.33	5.250 ± 0.27	3.240 ± 0.45

G1: Negative control; G2: NAFLD positive control; G3: NAFLD + *L. plantarum*; G4: NAFLD + LCN. Values are Mean ± SEM. SOD: Superoxide dismutase; MDA: Malondialdehyde.



A

Figure 2. Effect of *L.plantarum* postbiotics and *Lactobacillus plantarum*-Chitosan Nanoparticles (LCN) on Oxidative stress parameters SOD (A), MDA (B) *p<0.05, **p<0.01, ***p<0.001.

The current study demonstrates that LCN significantly improves dyslipidemia and restores antioxidant capacity in a high-fat diet-induced NAFLD rat model, and its benefits are more effective than *L. plantarum* postbiotics administration. These findings are in consensus with, and extend, the growing literature of probiotic therapy in metabolic liver disease.

Oxidative stress plays a crucial role in the pathophysiology of NAFLD, as demonstrated by the significant rise in MDA and suppression of SOD in G2. Hepatic lipid accumulation generates excessive ROS through mitochondrial electron transport chain dysfunction and peroxisomal fatty acid oxidation, overwhelming endogenous antioxidant defenses (5). Lipid peroxidation's final product, MDA, is a reliable indicator of oxidative tissue damage (27).

L. plantarum postbiotics (G3) significantly reduced MDA (p = 0.0008 vs G2) and showed a tendency toward SOD restoration, aligning with previous investigations. In obese rats, *L. plantarum* supplementation raised hepatic SOD, catalase, and glutathione peroxidase activities through activation of the Nrf2 antioxidant pathway, according to Kumar *et al*. (28). *L. plantarum* produces antioxidant metabolites including exopolysaccharides, short-chain fatty acids, and hydrogen peroxide-detoxifying enzymes that directly quench reactive oxygen species (ROS) (8).

The highest value antioxidant restoration was found in *Lactobacillus plantarum*-Chitosan Nanoparticles (LCN) (G4), with SOD activity significantly higher than G2 and MDA levels not significantly different from G1. Chitosan may also have antioxidant properties because LCN is more effective than postbiotics at reducing MDA (p = 0.0086). Chitosan and its oligosaccharides are rich in hydroxyl and amino groups, which have the ability to scavenge free radicals (29). Chitosan nanoparticles have been shown to reduce hepatic oxidative stress biomarkers in vivo, independent of probiotic content (30). A powerful mechanistic foundation for the increased MDA reduction is provided by the dual antioxidant mechanism of LCN, which combines direct ROS scavenging by chitosan with probiotic-mediated Nrf2 activation..

Comparing with recent literature, our results are consistent with Zhang *et al*. (31), who found that microencapsulated *Lactobacillus rhamnosus* reduced hepatic MDA by 65% and increased SOD by 40% in NASH mice. Also, these results align with El-Sayed *et al*. (32), who demonstrated that chitosan nanoparticles enhanced the antioxidant potency of encapsulated probiotics versus free-form administration in streptozotocin-induced diabetic rats.

Conclusion

The present study demonstrates the significant and better hypolipidemic and antioxidant effects of *Lactobacillus plantarum*-Chitosan Nanoparticles (LCN) than *L. plantarum* postbiotics in a high-fat diet-induced NAFLD rat model. Namoformulation of postbiotics (LCN) normalized serum TG, TC, LDL-C, VLDL-C and HDL-C to similar levels as healthy controls and significantly reduced MDA and restored SOD activity. The improved efficacy of LCN is probably attributed to synergistic effects of enhanced probiotic gastrointestinal survivability. Inherent lipid binding and antioxidant properties of chitosan and probiotic mediated gut microbiota

modulation. These findings support the development of LCN as a promising nutraceutical adjuvant for the management of NAFLD. Future studies should investigate the underlying molecular mechanisms, assess hepatic histopathology, and conduct dose-optimization and clinical translation studies.

Acknowledgements
N/A

Conflict of Interest
The authors declare no conflict of interest.

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