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The influence of Nata de Papaya supplementation on the lipid profile of rats with high-fat diet induction

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ABSTRACT: Diet-induced dyslipidemia is a major risk factor for cardiovascular disease, driving the search for functional food-based interventions. Nata de Papaya, a fermented bacterial cellulose product, is a rich source of dietary fiber, but its lipid-lowering potential remains unexplored. A high-fat diet (HFD) was used to induce dyslipidemia in a rat model. The rats were subsequently treated for 2 weeks with varying doses of Nata de Papaya (NdP1: 0.54 g, NdP2: 1.08 g, NdP3: 1.62 g), compared against a positive (ezetimibe) and negative control. Serum levels of total cholesterol, triglycerides, and low- (LDL) and high-density lipoproteins (HDL) were measured and statistically analyzed. The HFD successfully induced dyslipidemia. Nata de Papaya supplementation, particularly the high-dose NdP3 group, significantly improved the lipid profile. Reductions in total cholesterol (5.81%), triglycerides (6.78%), and LDL (6.60%) were observed, alongside a significant increase in HDL (7.31%). The efficacy of the NdP3 intervention was statistically equivalent to the positive control drug ($p > 0.05$), demonstrating a clear dose-dependent response. The lipid-lowering effects are attributed to the soluble fiber in Nata de Papaya, which likely acts via bile acid sequestration and enhances LDL clearance. The results posit Nata de Papaya as a potent, natural alternative to pharmaceutical agents for managing dyslipidemia. Further clinical studies are warranted to confirm its efficacy and safety in humans.

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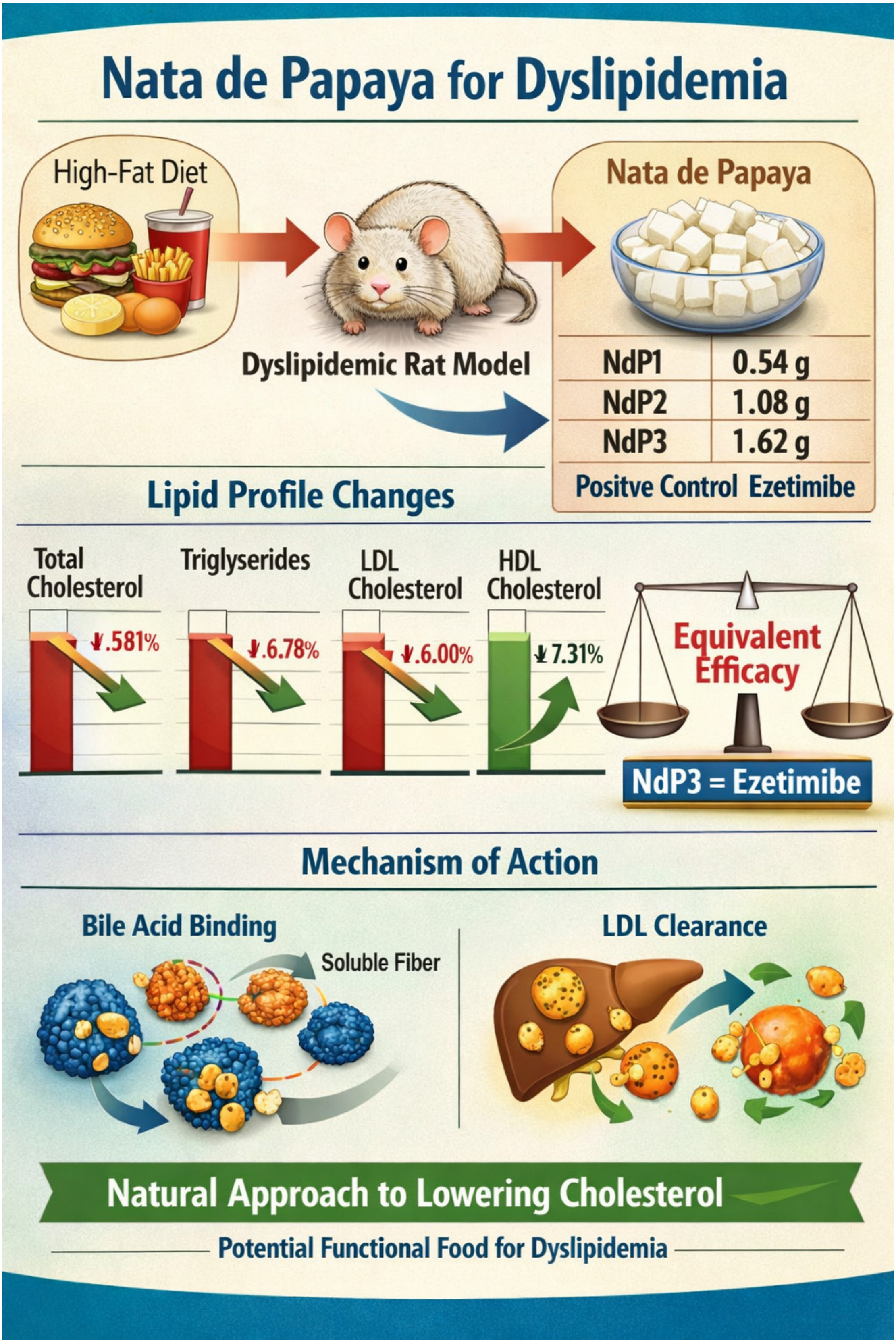
GRAPHICAL ABSTRACT



1. INTRODUCTION

Cardiovascular diseases (CVDs) remain a leading cause of global morbidity and mortality, with dyslipidemia—characterized by elevated triglycerides, low-density lipoprotein (LDL)-cholesterol, and reduced high-density lipoprotein (HDL)-cholesterol— serving as a primary modifiable risk factor (Chan et al., 2021). The modern diet, often high in saturated fats, is a significant contributor to the development of this condition (Zimmerman et al., 2021). To investigate the pathophysiology and potential interventions for diet-induced dyslipidemia, animal models, particularly rats (*Rattus norvegicus*) fed a high-fat diet (HFD), are extensively utilized (Du & Qin, 2023). These models reliably replicate key aspects of human metabolic syndrome, including adverse alterations in the lipid profile, providing a robust platform for preclinical evaluation of functional foods and nutraceuticals (Du & Qin, 2023; Petrovic et al., 2024).

In the search for natural, accessible, and cost-effective therapeutic agents, fermented food products have garnered significant scientific interest for their potential health benefits beyond basic nutrition (Prabhu et al., 2025). Nata de Papaya is a novel fermented gel derived from papaya (*Carica papaya*) juice, produced through the action of the bacterium *Acetobacter xylinum* (Kumarasinghe et al., 2024). Similar to the well-known nata de coco, it is primarily composed of bacterial cellulose. Given that papaya is itself a rich source of dietary fiber and potent antioxidants such as flavonoids and vitamin C, it is hypothesized that Nata de Papaya may possess enhanced bioactive properties (Kumarasinghe et al., 2024). These properties include the ability to modulate lipid metabolism, potentially through mechanisms such as the binding of dietary cholesterol, inhibition of lipid absorption in the gut, and the mitigation of oxidative stress associated with hyperlipidemia (Akanda et al., 2025; Matsuane et al., 2023).

Despite the documented health benefits of its raw ingredient, papaya, and the established probiotic and prebiotic potential of other nata products, scientific literature on the specific bioactivity of Nata de Papaya is notably scarce (Shang et al., 2024). While previous studies characterized its general nutritional composition, a critical gap exists in understanding its physiological impact on metabolic health, particularly concerning lipid regulation (Deng et al., 2024; Yilmaz et al., 2024). Therefore, this study is designed to bridge this gap by systematically evaluating the influence of Nata de Papaya supplementation on the lipid profile of HFD-induced rats. The findings aim to provide preliminary scientific evidence for its potential development as a functional food adjuvant in the management of dyslipidemia.

Based on the provided background, the central research problem addressed in this study is to determine whether supplementation with Nata de Papaya, a fermented papaya product hypothesized to possess bioactive properties from bacterial cellulose and papaya-derived antioxidants, can significantly ameliorate the adverse alterations in the lipid profile induced by an HFD in a rat (*R. norvegicus*) model, thereby evaluating its potential as a novel therapeutic intervention for diet-induced dyslipidemia. Hence, the objectives of this study are to quantitatively analyze the fiber and antioxidant content in Nata de Papaya and, subsequently, to evaluate its effect on the lipid profile of rats (*R. norvegicus*) induced by an HFD.

2. LITERATURE REVIEW

2.1. Pathophysiology of diet-induced dyslipidemia

Diet-induced dyslipidemia, driven by excessive intake of saturated fats and refined carbohydrates, leads to the overproduction of triglyceride-rich very low-density lipoprotein (VLDL) particles in the liver, thereby saturating clearance mechanisms. This triggers a cascade mediated by cholesteryl ester transfer protein (CETP), which exchanges VLDL triglycerides for cholesterol esters from LDL and HDL, remodeling the lipoprotein profile into a highly atherogenic state. The result is the classic dyslipide Xuemic triad: elevated triglycerides, an increase in small, dense LDL particles that readily infiltrate arterial walls to form plaques, and reduced levels of functional HDL cholesterol, collectively accelerating atherosclerosis and significantly increasing cardiovascular disease risk (Xue et al., 2023).

Table 1 presents the complex pathophysiology of diet-induced dyslipidemia using a logical, sequential model, illustrating how dietary excess triggers a harmful metabolic cascade. It begins by clearly identifying the primary dietary drivers—saturated fats and refined carbohydrates—and then maps their direct hepatic consequences: the overproduction of VLDL and the saturation of clearance pathways (Duran & Pradhan, 2021). The table is particularly strong in demonstrating the domino effect, where the central role of Cholesteryl Ester Transfer Protein (CETP) remodels lipoproteins, transforming them into atherogenic particles (Shrestha et al., 2018). Finally, it successfully connects these molecular and cellular events to the definitive clinical outcome—the atherogenic triad of high triglycerides, elevated small, dense LDL, and low HDL—providing a comprehensive overview from initial cause to the significantly increased risk of cardiovascular disease.

2.2. Papaya (*Carica papaya*) as a source of bioactive compounds

Papaya (*C. papaya*) is a tropical fruit renowned not only for its distinctive taste but also for its dense and diverse profile

Table 1
Pathophysiology of diet-induced dyslipidemia.

Stage	Key process/driver	Physiological mechanism	Consequence on lipids & lipoproteins
Dietary Trigger & Hepatic Overproduction	High Saturated/Trans Fat Intake	Liver overproduces Apolipoprotein B-100 and assembles excess Triglyceride (TG)-rich VLDL.	↑↑ VLDL Production
	High Refined Carbohydrate/Sugar Intake	Sugars fuel *de novo lipogenesis*, creating new fatty acids that further boost VLDL production.	Saturation of normal clearance pathways.
Lipid Exchange & Remodeling	Cholesteryl Ester Transfer Protein (CETP) Activity	CETP mediates the exchange of TGs (from VLDL) for Cholesterol Esters (from LDL and HDL).	VLDL becomes cholesterol-enriched. LDL and HDL become triglyceride-enriched.
Formation of Atherogenic Lipoprotein Profile	Enzymatic Modification (Hepatic Lipase)	Triglyceride-enriched LDL and HDL are acted upon by hepatic lipase, which removes the excess TGs.	LDL: Becomes small, dense, and numerous (more atherogenic). HDL: Becomes small, dense, and dysfunctional.
Final Dyslipidemic Triad & Clinical Risk	Altered Clearance & Function	Small, dense LDL is more prone to oxidation and arterial entry. Dysfunctional HDL is rapidly cleared from circulation.	The Atherogenic Triad: 1. ↑ Triglycerides 2. ↑ Small, Dense LDL-C 3. ↓ HDL-C Final Outcome: Accelerated atherosclerosis and significantly increased risk of cardiovascular disease (CVD).

of bioactive compounds that contribute to its nutritional and therapeutic value. It is rich in dietary fiber, both soluble and insoluble, and a powerful array of antioxidants (Ujjan et al., 2025). These antioxidants include vitamin C, a potent water-soluble antioxidant, and carotenoids such as lycopene and beta-carotene, which are fat-soluble pigments with significant biological activity. Furthermore, papaya contains the unique proteolytic enzyme papain, which aids in digestion. This synergistic combination of fiber and antioxidants forms the foundational rationale for investigating papaya's role in promoting metabolic health, particularly in managing conditions such as dyslipidemia, where both lipid metabolism and oxidative stress are key factors.

The documented health benefits of papaya are largely attributed to its robust antioxidant properties. The compounds vitamin C, lycopene, and beta-carotene function as effective scavengers of reactive oxygen species (ROS), thereby reducing systemic oxidative stress. This action is critically important for cardiovascular health, as the oxidation of LDL cholesterol is a pivotal early step in the pathogenesis of atherosclerosis. By neutralizing the free radicals that drive this oxidation, the antioxidants in papaya help prevent the formation of oxidized LDL, which is more readily taken up by macrophages to form foam cells within the arterial wall. Thus, the antioxidant capacity of papaya contributes directly to an antiatherogenic environment, protecting vascular integrity.

Beyond its antioxidant action, the significant dietary fiber content in papaya plays a crucial and direct role in modulating lipid metabolism, aligning with the mechanisms common to soluble fibers as previously outlined. The viscous soluble fiber in papaya can bind to bile acids in the intestine, preventing their reabsorption and promoting excretion. This process forces the liver to divert hepatic cholesterol toward the synthesis of new bile acids, thereby depleting the liver's cholesterol pool. To compensate, the liver increases the expression of its surface LDL receptors, leading to enhanced clearance of LDL cholesterol from the bloodstream. Consequently, through this well-established pathway of bile acid sequestration and upregulation of LDL receptor activity, the dietary fiber in papaya directly contributes to the lowering of circulating total and LDL cholesterol levels.

2.3. Nata de Papaya: A novel fermented fiber product

Nata de Papaya is a unique functional food produced by fermenting pasteurized, sweetened papaya juice with the bacterium *A. xylinum*. During fermentation, the bacteria consume the fruit sugars and synthesize a floating, gelatinous pellicle composed of a three-dimensional network of bacterial nanocellulose. This process transforms the liquid juice into a solid, translucent, and chewy substance that is essentially pure dietary fiber. While the original water-soluble nutrients in papaya are largely lost in the discarded liquid, the final product is a potent source of this unique bacterial cellulose, whose specific health benefits and potential synergistic effects with retained papaya compounds warrant further investigation.

The nutritional profile of Nata de Papaya is dominated by its high cellulose content, making it a potent source of dietary fiber that can act through multiple mechanisms in the gut. However, a key distinction from the original papaya juice is that water-soluble antioxidants, such as vitamin C, are largely (Leitão et al., 2022) lost during fermentation, remaining in the discarded liquid. This creates a significant research gap, as it is unknown whether its unique bacterial cellulose structure has a specific lipid-modulating effect distinct from plant fibers. Furthermore, a potential synergistic effect is hypothesized: residual fat-soluble antioxidants from the papaya could work in concert with the fiber. The fiber could lower LDL cholesterol, while the antioxidants protect it from oxidation, offering a dual mode of protection against atherosclerosis (Kumarasinghe et al., 2024). This study is therefore justified in investigating whether Nata de Papaya possesses unique functional properties for improving lipid profiles beyond its role as a simple fiber source.

3. METHODOLOGY

This study was an experimental research project utilizing a Completely Randomized Design (CRD). The research design was structured as follows: a positive control group (K+) received ezetimibe, while a negative control group (K-) received aquades (distilled water). Three treatment groups were established: NdP1 received a 0.54 g dose of Nata de Papaya, NdP2 received a 1.08 g dose, and NdP3 received a 1.62 g dose. The lipid profile was measured at three different time points: T1 (before the rats were given an HFD), T2 (after the rats were given an HFD), and T3 (after the rats were administered Nata de Papaya).

The study population consisted of male Wistar rats (*R. norvegicus*) that met the following inclusion and exclusion criteria. The inclusion criteria required rats to be healthy, actively mobile, aged 2–3 months, male, and weighing between 150 and 200 g. The exclusion criteria eliminated female rats, pregnant females, those weighing less than 150 g, individuals with hair loss or anatomical abnormalities, any Wistar rats that became sick or experienced health issues during the adaptation period, and any rats that died during the research.

The samples in this study were 25 male Wistar rats (*R. norvegicus*) obtained from the Makassar College of Pharmacy, aged 2–3 months and weighing 150–200 g. The rats were divided into five groups: a positive control group (K+), a negative control group (K–), Treatment Group 1 (NdP1), Treatment Group 2 (NdP2), and Treatment Group 3 (NdP3).

The equipment used in the production of Nata de Papaya included an autoclave, blender, stove, pot, analytical balance, measuring cup, knife, basin, filter, media bottle, syringe, rubber band, pH paper, and tissue. The materials used in the production consisted of papaya fruit flesh, water, nata starter, food-grade ZA (ammonium sulfate), sugar, and glacial acetic acid. The equipment used for testing Nata de Papaya on rats included the following: cages, spectrophotometer, centrifuge, vacutainer tubes, feeding tube (sonde), micropipette, blue and yellow tips, a blender, syringes, test tubes, test tube rack, vortex mixer, timer, dry cotton, 70% alcohol swabs, and tissue. The materials used in the testing of Nata de Papaya on the rats comprised Nata de Papaya, aquades (distilled water), Glory Diagnostic lipid profile assay reagents, and ezetimibe.

The maceration method was used to test the antioxidant levels of Nata de Papaya. In this method, the sample is soaked in a solvent until it penetrates and softens the cellular structure, allowing the compounds to dissolve easily. A 20 g sample was weighed and extracted with ethanol. The ethanol extract was then filtered, transferred into a 5 mL volumetric flask, and 0.7 mL of DPPH was added. The solution was then made up to the mark using 70% ethanol. Subsequently, it was incubated for 30 min. After incubation, the absorbance was measured at the maximum wavelength using a UV-Vis spectrophotometer. The testing used vitamin C as a standard solution for comparison, following the same procedure.

The high-fat feed was prepared by mixing 300 g of chicken fat and 200 g of duck egg yolk into 100 mL of aquades (distilled water) with the addition of 1 mL of 0.5% Carboxymethyl Cellulose (CMC). The animal fat dosage for humans is 150 mg/day. This value was converted using the formula 0.018×150 g = 2.7g/200g BW/day, for determining the equivalent dosage in rates. Therefore, the administered animal fat dosage for the rats was 3/200 g BW/day. The duck egg yolk dosage was 2/200 g rat BW. The high-fat feed was administered at a volume of 3 mL/200 g rat BW/day.

The dosage of ezetimibe was determined based on its common human dose of 10 mg/day. This was converted to a rat dose using a conversion factor of 0.018 for a human weighing 70 kg to a rat. The dose for a 200 g rat was calculated as 10 mg x 0.018 = 0.18 mg/200g BW, equivalent to 0.9 mg/kg rat BW. The dosages for Nata de Papaya were determined as 0.54, 1.08, and 1.62 g per 200 g rat BW/day. These dosages were based on the recommended daily human fiber requirement of 20–30 g, which was converted to a rat-appropriate dose according to the body weight and adjusted to account for the fiber content present in the Nata de Papaya.

Blood collection from the rats was performed via the orbital sinus using a capillary tube. The rats were first fasted for 10 h and placed under mild anesthesia to reduce movement. The rat was properly restrained, and the tip of the capillary tube was then inserted into the medial canthus. The tube was gently advanced through the conjunctiva into the orbital sinus with slow, rotating motion and downward pressure until blood was observed flowing into the tube. The tube was then tilted, and 2 mL of blood was collected into a Vacutainer tube.

After the adaptation period ended, the test animals were randomly divided into five groups with an equal number of subjects, specifically n = 5 in each group. The high-fat feed was administered in a fresh condition. 3 mL of the feed was injected via oral gavage every day for a period of 14 days.

The lipid profile was tested three times: after the rats completed the adaptation period, after being fed a high-fat diet, and after being administered Nata de Papaya. Total cholesterol levels were tested using the enzymatic colorimetric CHOD-PAP (Cholesterol Oxidase Phenyl Aminophenzone) method, while triglycerides were examined using the GPO-PAP (Glycerol Phosphate Oxidase-phenyl Aminophenazone) principle. Blood was drawn from the orbital sinus blood vessel, with a 2 mL sample collected in a tube and centrifuged for 5 min at 10,000 rpm. From the obtained serum, a 10 μL aliquot was pipetted and mixed with 1000 μL of reagent. After homogenization, the mixture was incubated at room temperature for 10 min and then measured using a UV-Vis spectrophotometer at wavelengths of 500 and 505 nm for total cholesterol and triglycerides, respectively.

The data obtained from the examination of the lipid profile, including cholesterol, triglycerides, HDL, and LDL in male rats, were processed and statistically analyzed to compare the lipid profile data before and after the administration of Nata de Papaya. Data analysis employed ANOVA, preceded by a homogeneity test to determine whether the generated data were homogeneous. This was followed by a post hoc Tukey test to examine the differences in mean values at each time point within the treatment groups, with a significance value of $p < 0.05$.

4. RESULTS

4.1. Characteristics of Nata de Papaya

Nata de Papaya was harvested on Days 14 and 21 of incubation following fermentation by *A. xylinum*. The characteristics of Nata de Papaya, including its color, thickness, texture, and surface appearance, are shown in Table 2. Based on the macroscopic characteristics, Nata de Papaya presents as a visually and texturally distinct food product. Its pure white color and smooth surface give it a clean, uniform, and somewhat gelatinous appearance. The physical dimensions are notable, with a substantial thickness ranging from 1 to 1.5 cm, indicating a robust, sheet-like structure. This combination of color, surface quality, and thickness suggests the properties of a product formed in a controlled environment, allowing for consistent microbial fermentation and mat formation.

The sensory properties of Nata de Papaya, as described, highlight its unique edible qualities. The texture is explicitly characterized as chewy, which is a defining feature of nata products, resulting from the dense cellulose matrix produced by the fermenting bacteria. This firm and resilient texture is complemented by a slightly sour aroma, a common byproduct of the acetic acid fermentation process involved in its production. This subtle tartness does not necessarily indicate spoilage but rather contributes to the product's fresh, fermented profile, which often serves as a base for sweetened syrup or desserts to balance its mild acidity.

4.2. Crude fiber and antioxidant content of Nata de Papaya

This study quantified the crude fiber and antioxidant levels in Nata de Papaya, as these components are believed to mediate their antihyperlipidemic properties. For comparative purposes, fresh papaya juice was also analyzed for the same parameters. Crude fiber content was determined using gravimetric analysis, while antioxidant activity was measured spectrophotometrically. The results of these analyses are presented in Table 3.

Based on the data presented in Table 3, the analysis reveals significant differences in the nutritional profile between papaya juice and its fermented derivative, Nata de Papaya. In terms of crude fiber, both products contain a remarkably similar percentage, with papaya juice at 2.16% and Nata de Papaya at a marginally higher value of 2.19%. This indicates that the fermentation process used to create Nata de Papaya, which is a bacterial cellulose gel, does not substantially diminish or enhance the total fibrous content as measured by the

Table 2
Macroscopic characteristics of Nata de Papaya.

Parameter	Macroscopic results
Color	White
Thickness	1 cm–1.5 cm
Texture	Chewy
Surface	Smooth
Aroma	Slightly sour

Table 3
Crude fiber and antioxidant content.

Type of analysis	Crude fiber (%)	Antioxidant (mg/kg)
Papaya juice	2.16	43.01
Nata de Papaya	2.19	8.42

crude fiber method. This shared characteristic suggests that both food items can contribute to dietary bulk and support digestive health to a comparable degree.

However, a stark contrast is observed in their antioxidant content. Papaya juice demonstrates a significantly higher concentration, measuring 43.01 mg/kg, whereas Nata de Papaya contains a much lower level of 8.42 mg/kg. This dramatic difference, where the juice possesses over five times the antioxidant capacity of Nata, can be attributed to the nature of the fermentation process. Many of the potent antioxidant compounds, such as carotenoids (like lycopene and beta-carotene) and vitamin C, which are abundant in the original papaya fruit, are likely water-soluble and may be lost in the liquid byproduct (the supernatant) during the production of the solid Nata de Papaya cellulose pellicle. Consequently, while Nata de Papaya retains the fibrous structure, it is a poor source of antioxidants compared to the juice from which it is derived.

4.3. Mean body weight of rats

Rat body weight was measured after the adaptation period (Day 7/T1), after high-fat diet feeding (Day 21/T2), and after the treatment period (Day 35/T3). The results, presented in Table 4, showed an increase in body weight following the administration of a high-fat diet. On the other hand, body weight measurements after the treatment period showed a decrease in weight, as shown in Figure 1. The results indicate that higher doses of nata supplementation led to greater reductions in body weight in the rats.

Based on Table 4 and Figure 1, the posttreatment data indicate changes in the rats' body weight. The NdP3 group exhibited the highest weight loss at 17.5%, followed by the positive control group at 10%, NdP2 at 8.33%, and NdP1 at 5.83%. Statistically, there was no significant difference between the positive control group and the Nata de Papaya treatment groups. On the other hand, the negative control group experienced a weight gain of 21.66%, and statistical comparisons revealed a significant difference between the positive and negative control groups.

4.4. Lipid profile levels

Before the main analysis, a homogeneity test was conducted on the serum lipid profile data (total cholesterol, triglycerides, HDL, and LDL) across all treatment groups. The results indicated that the data for serum lipid profile levels in all rat treatment groups were homogeneously distributed and followed a normal distribution both before and after the intervention ($p > 0.05$).

4.4.1. Mean total cholesterol levels

Statistical analysis of the differences in total cholesterol levels before and after treatment was performed using one-way ANOVA and paired sample T-test, as shown in Table 5. All groups exhibited an increase in total cholesterol levels

Table 4
Mean body weight of rats

Treatment group	Variation of time	Mean ± SD	Δ Difference in levels (g)		P *value*
		n=5	T2–T1	T3–T2	
K+	T1	177.40 ± 7.98	28.2	–2.4	0.000
	T2	205.60 ± 6.54			
	T3	203.20 ± 7.32			
K–	T1	190.00 ± 9.08	14.0	5.2	0.003
	T2	204.00 ± 5.83			
	T3	209.20 ± 5.93			
NdP1	T1	182.20 ± 8.52	17.2	–1.4	0.001
	T2	199.40 ± 4.39			
	T3	198.00 ± 4.69			
NdP2	T1	186.60 ± 6.73	16.4	–2.0	0.001
	T2	203.00 ± 4.84			
	T3	201.00 ± 3.39			
NdP3	T1	191.80 ± 5.16	15.0	–4.2	0.001
	T2	206.80 ± 4.86			
	T3	202.60 ± 5.03			

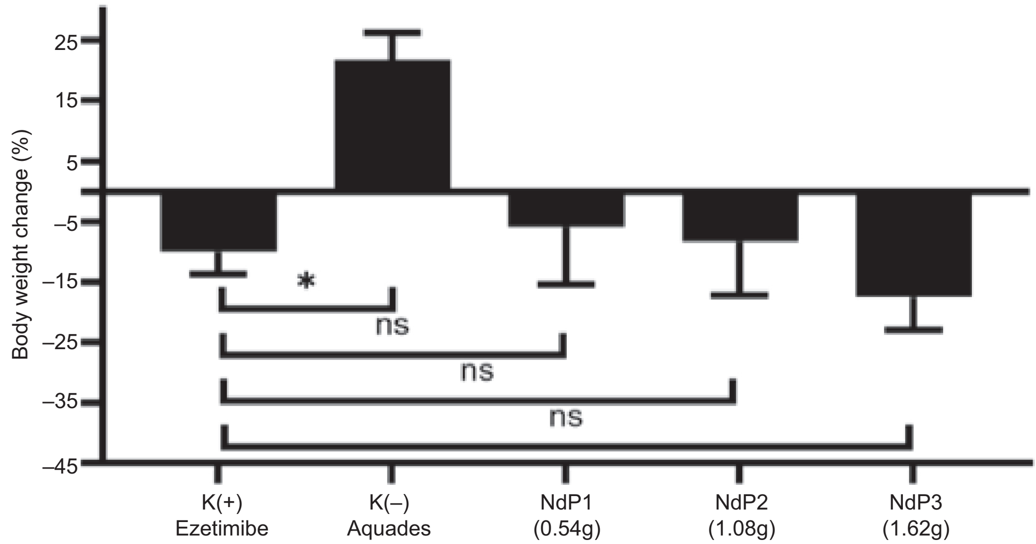


Figure 1. Comparison of body weight change percentage after treatment. A minus sign (–) indicates a decrease. An asterisk (*) denotes significance at $p < 0.05$ using Tukey's post hoc test, and (ns) indicates not significant using Tukey's post hoc test. K (+): positive control ezetimibe (0.18 mg), K (–): negative control aquades, NdP1: Nata de papaya (0.54 g), NdP2: Nata de Papaya (1.08 g), NdP3: Nata de Papaya (1.62 g).

Table 5
Mean total cholesterol levels in rats.

Treatment group	Variation of time	Mean ± SD	Δ Difference in levels (mg/dL)		P *value*
		n=5	T2-T1	T3-T2	
K+	T1	93.88 ± 6.45	11.62	–10.33	0.008
	T2	105.50 ± 5.65			
	T3	95.17 ± 2.86			
K–	T1	105.97 ± 11.99	4.71	1.67	0.555
	T2	110.68 ± 8.95			
	T3	112.35 ± 6.41			
NdP1	T1	88.80 ± 8.83	2.87	–2.58	0.809
	T2	91.64 ± 7.23			
	T3	89.05 ± 6.41			
NdP2	T1	88.65 ± 8.11	7.43		0.283
	T2	96.08 ± 7.52			
	T3	91.41 ± 5.30			
NdP3	T1	91.04 ± 7.13	6.42	–6.52	0.157
	T2	97.46 ± 4.27			
	T3	90.94 ± 5.22			

following the administration of a high-fat diet for 2 weeks, compared to their levels before the diet administration, with the same dosage regimen. Subsequently, a decrease in levels was observed after the administration of the positive control treatment and Nata de Papaya. The total cholesterol levels measured after the 2-week treatment period showed a reduction in the positive control group and all Nata de Papaya treatment groups.

Based on Table 5 and Figure 2, the largest sequential reductions in total cholesterol levels after treatment occurred in the positive control group, followed by NdP3, NdP2, and NdP1, with decreases of 9.20, 5.81, 4.16, and 2.30%, respectively. Statistical results showed no significant difference between the positive control group and the Nata de Papaya treatment groups. On the other hand, the negative control group showed a 1.48% increase in total cholesterol

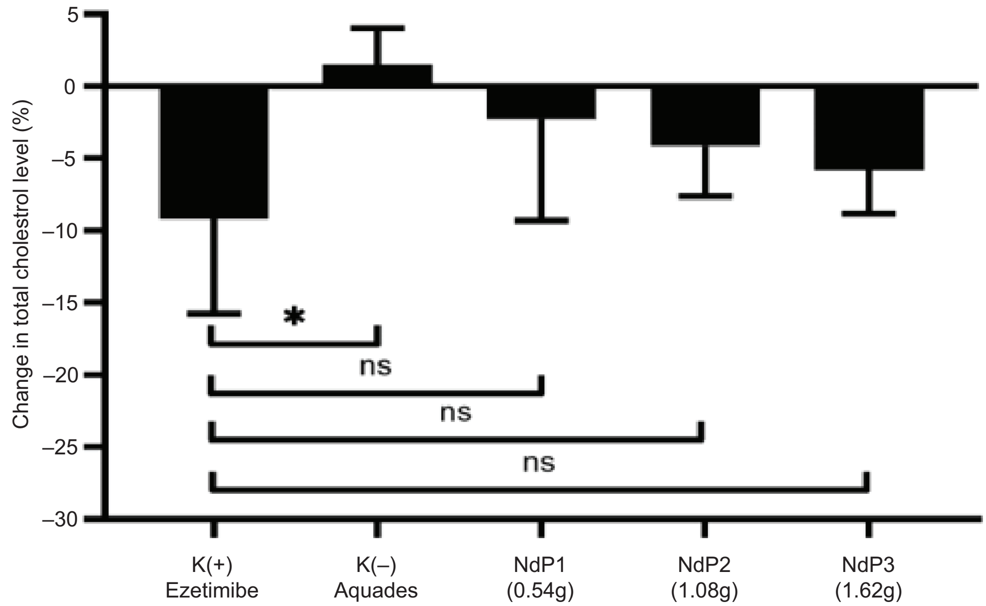


Figure 2. Comparison of total cholesterol percentage change after Treatment. A minus sign (–) indicates a decrease. An asterisk (*) denotes significance at $p < 0.05$ using Tukey's post hoc test, and (ns) indicates not significant using Tukey's post hoc test. K (+): positive control ezetimibe (0.18 mg), K (–): negative control aquades, NdP1: Nata de Papaya (0.54 g), NdP2: Nata de Papaya (1.08 g), NdP3: Nata de Papaya (1.62 g).

levels and was significantly different from the positive control group.

4.4.2. Mean triglyceride levels

Statistical analysis of the differences in rat triglyceride levels before and after treatment was performed using one-way ANOVA and paired sample T-test, as shown in Table 6. The results indicated that all groups exhibited increased levels after administration of a high-fat diet for 2 weeks compared to their pre-diet levels. Subsequently, a significant decrease in levels was observed following administration of the positive control intervention and Nata de Papaya.

Based on Table 6 and Figure 3, the treatment administrations resulted in changes in triglyceride levels. The positive control group showed the highest reduction in triglyceride levels at 7.05%, followed sequentially by the NdP3 group at 6.78%, the NdP2 group at 4.74%, and the NdP1 group at 1.71%. Statistically, there was no significant difference between the positive control group and the Nata de Papaya treatment groups. On the other hand, the negative control group experienced an increase of 0.30%, and statistical comparisons showed a significant difference between the positive and negative control groups.

4.4.3. Mean HDL levels

A comparison of HDL levels can be seen in Table 7. The results indicate that induction with a high-fat diet for 2 weeks decreased HDL levels in all groups, although the decrease was not significant ($p > 0.05$). Following treatment administration, HDL levels increased, with a significant increase ($p < 0.05$) observed in the NdP3 group.

Based on Table 7 and Figure 4, all groups showed an increase in HDL levels. The highest level was observed in the NdP3 group (7.31%), followed by the positive control group (7.10%), NdP2 (2.79%), NdP1 (1.88%), and the negative control group (0.91%). Statistically, there was no significant difference between the positive control group and either the Nata de Papaya treatment groups or the negative control group.

4.4.4. Mean LDL levels

A comparison of LDL levels is shown in Table 8. The results for the LDL parameter showed that high-fat diet feeding increased LDL levels in all treatment groups. Meanwhile, the posttreatment examination results (T3) showed a decrease in LDL levels in all groups except the negative control group (K–), where no change in levels was observed.

Based on Table 8 and Figure 5, the largest sequential reductions in LDL levels after treatment occurred in the positive control group (8.54%), followed by NdP3 (6.60%), NdP2 (2.59%), and NdP1 (2.25%). Statistical results showed no significant difference between the positive control group and the Nata de Papaya treatment groups. Meanwhile, the negative control group showed no change in LDL levels after treatment and was significantly different from the positive control group.

Table 6
Mean triglyceride levels.

Treatment group	Variation of time	Mean ± SD	Δ Difference in levels (mg/dL)		P value
		n=5	T2-T1	T3-T2	
K+	T1	86.30 ± 6.46	8.34	–33.89	0.000
	T2	94.64 ± 3.45			
	T3	60.75 ± 9.58			
K–	T1	89.07 ± 12.04	1.23	1.44	0.944
	T2	90.30 ± 12.61			
	T3	91.75 ± 12.70			
NdP1	T1	56.67 ± 14.17	36.32	–8.24	0.001
	T2	92.99 ± 9.92			
	T3	84.75 ± 8.07			
NdP2	T1	59.44 ± 13.16	26.33	–22.77	0.013
	T2	85.77 ± 10.74			
	T3	63.00 ± 13.82			
NdP3	T1	62.22 ± 18.11	22.11	–32.8	0.008
	T2	84.33 ± 15.07			
	T3	51.75 ± 3.70			

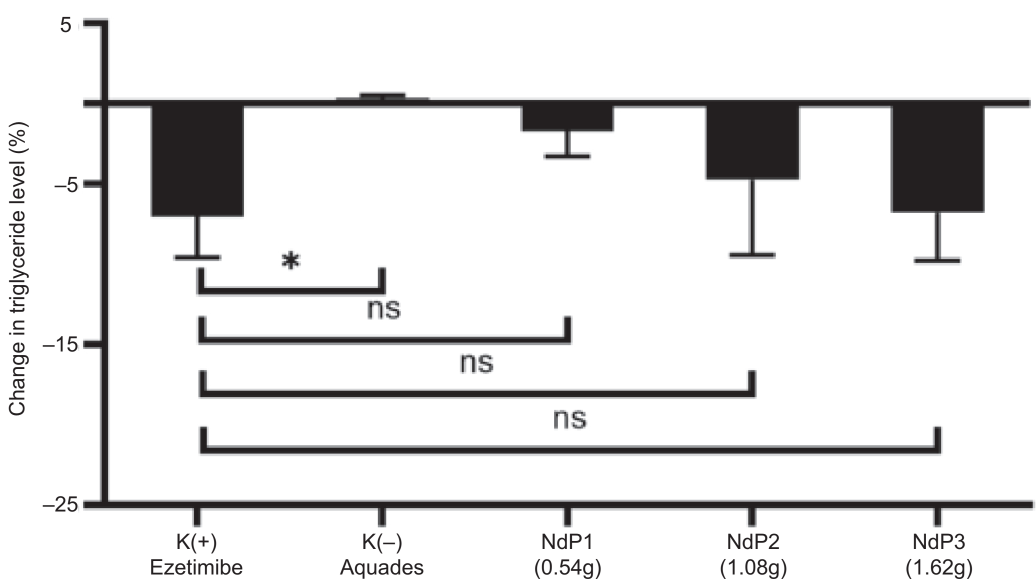


Figure 3. Comparison of triglyceride percentage change after treatment. A minus sign (–) indicates a decrease. An asterisk (*) denotes significance at $p < 0.05$ using Tukey's post hoc test, and (ns) indicates not significant using Tukey's post hoc test. K (+): positive control ezetimibe (0.18 mg), K (–): negative control aquades, NdP1: Nata de Papaya (0.54 g), NdP2: Nata de Papaya (1.08 g), NdP3: Nata de Papaya (1.62 g).

5. DISCUSSION

5.1. Characteristics of Nata de Papaya

The visual and structural characteristics of Nata de Papaya are defined by its production process (Katyal et al., 2025). The product is characteristically white in color, as a result of the pure cellulose matrix formed by the metabolization of sugars by *A. xylinum*. Its thickness, which ranged from 1.0 to 1.5 cm, falls within the quality standards set by the Indonesian National Standards (SNI) and is directly determined by the incubation period; a longer fermentation allows for more

Table 7
Mean HDL levels.

Treatment group	Variation of time	Mean ± SD	Δ Difference in levels (mg/dL)		P value
		n=5	T2-T1	T3-T2	
K+	T1	63.01 ± 11.66	–0.37	10.76	0.192
	T2	62.64 ± 11.72			
	T3	73.40 ± 4.58			
K-	T1	72.41 ± 6.41	–4.47	1.37	0.412
	T2	67.94 ± 4.30			
	T3	69.31 ± 4.75			
NdP1	T1	63.70 ± 6.90	–4.73	2.84	0.531
	T2	58.97 ± 7.80			
	T3	61.81 ± 4.37			
NdP2	T1	65.68 ± 10.17	–3.77	4.22	0.665
	T2	61.91 ± 7.23			
	T3	66.13 ± 5.98			
NdP3	T1	65.68 ± 2.10	–2.89	11.07	0.002
	T2	62.79 ± 3.27			
	T3	73.86 ± 5.68			

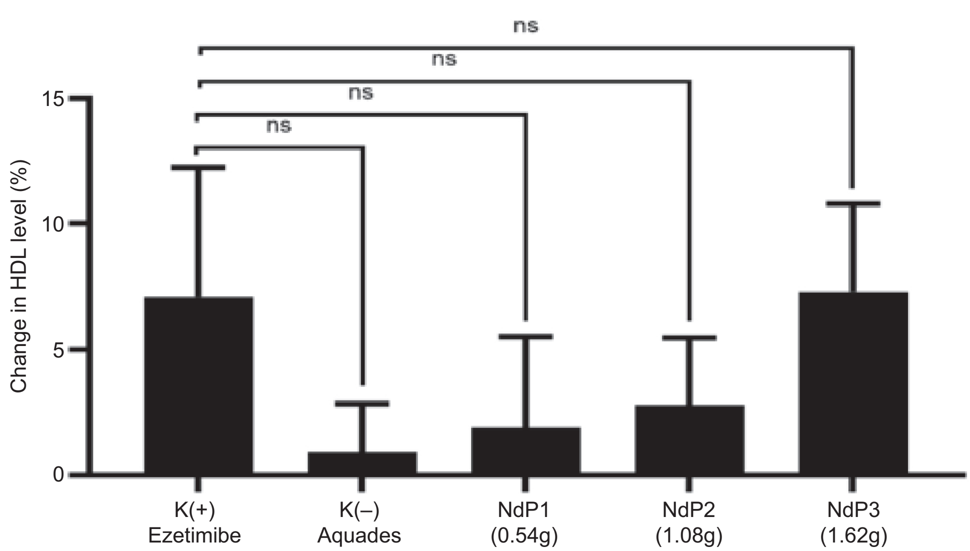


Figure 4. Comparison of HDL percentage change after treatment. A minus sign (–) indicates a decrease. An asterisk (*) denotes significance at $p < 0.05$ using Tukey's post hoc test, and (ns) indicates not significant using Tukey's post hoc test. K (+): positive control ezetimibe (0.18 mg), K (–): negative control aquades, NdP1: Nata de Papaya (0.54 g), NdP2: Nata de Papaya (1.08 g), NdP3: Nata de Papaya (1.62 g).

extensive cellulose synthesis. However, exceeding the optimal incubation time can deplete nutrients and halt production. The texture was notably chewy, a quality influenced by the high fiber content and low water activity within the dense, interwoven cellulose fibrils.

The organoleptic properties, namely the color and aroma, are influenced by both raw materials and fermentation conditions. The whiteness of the final product can be affected by the sugar concentration in the medium and the natural color of the papaya juice, while a thicker nata tends to be more

Table 8
Mean LDL levels.

Treatment group	Variation of time	Mean ± SD	Δ Difference in levels (mg/dL)		P value
		n=5	T2-T1	T3-T2	
K+	T1	13.60 ± 5.75	10.32	–14.31	0.073
	T2	23.92 ± 14.19			
	T3	9.61 ± 3.75			
K–	T1	15.74 ± 5.80	8.94	0	0.055
	T2	24.68 ± 7.28			
	T3	24.68 ± 4.51			
NdP1	T1	13.76 ± 4.71	0.31	–3.78	0.717
	T2	14.07 ± 8.93			
	T3	10.29 ± 9.55			
NdP2	T1	11.07 ± 7.88	5.94	–4.34	0.646
	T2	17.01 ± 12.36			
	T3	12.67 ± 9.88			
NdP3	T1	12.91 ± 6.40	4.89	–11.07	0.009
	T2	17.80 ± 3.92			
	T3	6.72 ± 3.02			

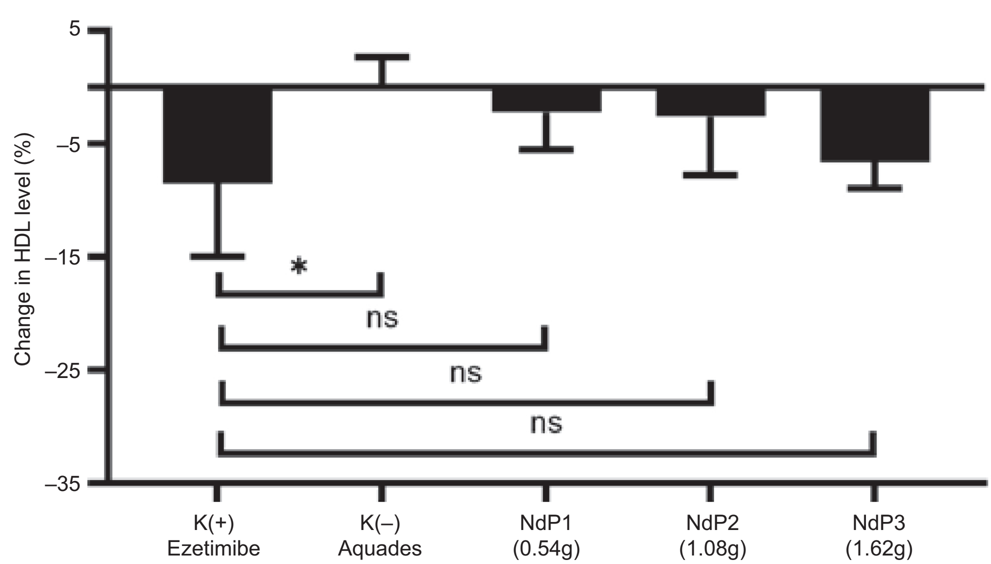


Figure 5. Comparison of percentage change in LDL levels after treatment. A minus sign (–) indicates a decrease. An asterisk (*) indicates significance at $p < 0.05$ using Tukey's post hoc test, and (ns) indicates not significant using Tukey's post hoc test. K (+): positive control ezetimibe (0.18 mg), K (–): negative control aquades, NdP1: Nata de Papaya (0.54 g), NdP2: Nata de Papaya (1.08 g), NdP3: Nata de Papaya (1.62 g).

opaque (Maryati et al., 2024). The slightly sour aroma is a distinctive feature of freshly produced nata. This is a direct byproduct of bacterial fermentation, where sugars are partially converted into acetic acid, lowering the pH of the medium (Yovita et al., 2020).

In addition, the quality of Nata de Papaya is a direct reflection of the fermentation biochemistry. The actions of *A. xylinum* contribute to the formation of a white, chewy cellulose pellicle of standard thickness and the generation of a characteristic sour aroma (Santosa et al., 2020). Understanding the interplay between fermentation factors—such as incubation time, nutrient concentration, and sugar levels—is crucial for consistently producing nata with the desired physical and sensory properties (Mashitoa et al., 2021).

5.2. Fiber and antioxidant levels in Nata de Papaya

Previous analytical studies have established that papaya fruit is a natural source of both dietary fiber and antioxidants. Gravimetric analysis, which uses strong acids and bases to isolate indigestible components, has measured the crude fiber content in papaya pulp at 1.03 and 1.60% in separate studies (Leitão et al., 2022). Similarly, a review of the antioxidant activity of papaya pulp concluded that it has strong to very strong antioxidant potential (Nur et al., 2022). This study builds upon that foundation by processing papaya pulp into a fermented product, Nata de Papaya, and confirming the retention of these bioactive compounds. Analysis revealed that Nata de Papaya contained a slightly higher crude fiber content (2.19%) than its papaya juice counterpart (2.16%). As supported by previous research, this increase is a direct result of the fermentation process (Garcia-Amezquita et al., 2018), where the bacterium *A. xylinum* metabolizes sugar to produce a thick, pure cellulose layer, thereby concentrating the fiber (do Prado et al., 2021).

In contrast to the fiber content, the antioxidant levels in Nata de Papaya were found to be significantly lower than in the original papaya juice. This decrease is a critical observation and is primarily attributed to the heating involved in the production process (Noor & Maizura, 2025). Antioxidant compounds, particularly those found in papaya, are often heat-sensitive and can decompose when exposed to high temperatures. Research indicates that to preserve the maximum antioxidant activity, processing temperatures should not exceed 60 °C, a threshold likely surpassed during the standard production of nata, leading to the observed reduction as supported by previous research (Pérez-Lamela et al., 2021; Vega-Gálvez et al., 2022).

Despite the loss of some antioxidants, the presence of both fiber and residual antioxidants in Nata de Papaya is highly relevant for health. Dietary fiber is well-known for its role in disease prevention and management, particularly in modulating lipid metabolism and supporting digestive health (Wu et al., 2024). Antioxidants are crucial for neutralizing harmful free radicals in the body, thereby reducing oxidative stress, which is a key driver in the development of chronic metabolic diseases and the process of lipid peroxidation. Therefore, the confirmation that Nata de Papaya retains these compounds justifies further investigation into its potential as a functional food for therapeutic applications, such as improving lipid profiles (ElGamal et al., 2023).

5.3. Body weight of rats

A high-fat diet is a well-established risk factor for weight gain and obesity, primarily due to the high energy density of fatty foods, which can lead to hyperphagia and a chronic positive energy balance (Ciesielska & Gajewska, 2023). The type of fat is also critical; saturated fatty acids (SFA) are more readily esterified and stored in adipose tissue, whereas unsaturated fats (PUFA/MUFA) are more often oxidized for energy (Fernández-Felipe et al., 2023). This chronic energy surplus promotes the hypertrophy and hyperplasia of adipocytes, leading to significant fat accumulation both subcutaneously and in ectopic sites. This expansion of adipose tissue disrupts the normal secretion of adipokines, characterized by increased levels of leptin and resistin and reduced levels of adiponectin, further exacerbating metabolic dysfunction (Bastías-Pérez et al., 2020). Consequently, as demonstrated here and in previous studies, induction with an HFD reliably results in significant weight gain in animal models.

In this study, the efficacy of Nata de Papaya (NdP) supplementation was tested against this HFD-induced weight gain. Following the initial period of weight increase from the HFD, the administration of Nata de Papaya at various doses resulted in significant weight loss. Notably, the higher doses of NdP led to greater reductions in body weight, demonstrating a dose-dependent effect, as also supported by previous research (Od-Ek et al., 2020). The weight loss observed in the NdP groups was comparable to that of the positive control group, proving its potential as an effective alternative for weight management (Kelly et al., 2023). This finding is consistent with broader human and animal research, which has consistently shown that increased dietary fiber intake over time is associated with significant reductions in body weight (Lua et al., 2021).

The weight loss effect of Nata de Papaya is attributed to the fundamental properties of dietary fiber. Fiber reduces the overall energy intake due to its low energy density and ability to increase satiety and reduce palatability, leading to decreased food consumption (Akhlaghi, 2024). Suggested mechanisms include increased gastric distension, altered secretion of gut hormones such as GLP-1 and PYY, and a slight reduction in the absorption of macronutrients (Dayib et al., 2020). Furthermore, the fermentation of soluble fiber by gut microbiota produces short-chain fatty acids (SCFAs), which serve as an energy source for colonocytes and may influence metabolism and energy expenditure. The bacterial cellulose in Nata de Papaya, while primarily insoluble, may possess gel-forming properties that contribute to satiety and fermentation effects, thereby facilitating weight loss (Waddell & Orfila, 2023).

5.3. Rat lipid profile

Nata de Papaya serves as a rich source of dietary fiber, underpinning its mechanism for improving the serum lipid profile. The soluble fiber component exerts its primary effect by binding to bile acids in the intestine, which are normally reabsorbed and recycled (Ge et al., 2024). This binding prevents their reabsorption, forcing the liver to divert cholesterol from the bloodstream to synthesize new bile acids (Lua et al., 2021). This process depletes the hepatic cholesterol pool, leading to a cascade of beneficial effects: the liver increases its uptake of LDL cholesterol from the blood, and the reduced availability of components for VLDL synthesis results in lower production of this triglyceride-rich precursor to LDL (Ghavami et al., 2023). Consequently, this fundamental mechanism drives the reduction in total cholesterol, triglycerides, and LDL levels observed with Nata de Papaya supplementation.

The improvement in lipid parameters is interconnected. As total and LDL cholesterol decrease due to the enhanced clearance facilitated by fiber, a corresponding positive effect on HDL is often observed. HDL, known as "good" cholesterol, transports excess cholesterol from peripheral tissues and arterial walls back to the liver for processing and excretion, a process known as reverse cholesterol transport (Diaz & Bielczyk-Maczynska, 2025). The reduction in the overall cholesterol load appears to create a metabolic environment that favors the function and potential levels of HDL. Therefore, by effectively lowering atherogenic lipids, Nata de Papaya indirectly supports and enhances the cardioprotective role of HDL, contributing to a more balanced and healthier lipid profile (Wang et al., 2017).

The findings of this study confirm the therapeutic potential of Nata de Papaya. In hyperlipidemic rat models, supplementation, particularly at the highest dose (NdP3), significantly reduced total cholesterol, triglycerides, and LDL while concurrently raising HDL levels, as also confirmed by a previous study (Matsuane et al., 2023). Crucially, the efficacy of the high-dose Nata de Papaya was not statistically different from the positive control drug, ezetimibe. This demonstrates that Nata de Papaya is not only an effective intervention for correcting dyslipidemia but also a comparable natural alternative to pharmaceutical options (Thaipitakwong & Aramwit, 2017). As a functional food, it presents a promising and potentially safer strategy for long-term management of lipid levels and reduction of cardiovascular risk.

5.4. Alteration of lipid profile levels

The HFD induction successfully established a dyslipidemic state in the rat models, as evidenced by a significant increase in total cholesterol and triglyceride levels across all groups after 2 weeks, confirming the model's validity for investigating lipid-lowering interventions. The data for serum lipid parameters were confirmed to be homogeneous and normally distributed, satisfying the assumptions for subsequent parametric statistical analyses (Matsuane et al., 2023).. Following this induction period, the administration of both the positive control (ezetimibe) and Nata de Papaya (NdP) at varying doses (0.54, 1.08, and 1.62 g) elicited notable improvements in the lipid profile over the treatment period.

Nata de Papaya supplementation demonstrated a clear, dose-dependent effect on reducing atherogenic lipids. The highest dose (NdP3) was the most effective, resulting in reductions in total cholesterol (5.81%), triglycerides (6.78%), and LDL cholesterol (6.60%) that were comparable to the positive control drug, ezetimibe, which reduced these parameters by 9.20, 7.05, and 8.54%, respectively. Statistical analysis confirmed that the lipid-lowering efficacy of the NdP3 group was not significantly different ($p > 0.05$) from the ezetimibe group, underscoring its therapeutic potential. In stark contrast, the negative control group, which received only water, showed no improvement or a slight worsening in all these lipid markers (Matsuane et al., 2023).

A particularly significant finding was the impact of Nata de Papaya on HDL cholesterol. While the HFD resulted in a reduction in HDL levels in all groups, the NdP3 treatment not only reversed this trend but also produced the greatest increase in HDL (7.31%) among all groups, including the positive control (7.10%) (Thaipitakwong & Aramwit, 2017). This increase in the NdP3 group was statistically significant ($p < 0.05$), suggesting that Nata de Papaya may offer a unique benefit in elevating cardioprotective "good" cholesterol, a crucial aspect of comprehensive cardiovascular risk management not always addressed by all lipid-lowering agents (Matsuane et al., 2023).

The collective improvements observed across the lipid profile—specifically the reduction in total cholesterol, triglycerides, and LDL, coupled with the elevation of HDL—strongly suggest that Nata de Papaya functions through multiple mechanisms. The primary action is likely attributable to its high soluble fiber content, which can bind bile acids in the intestine, increasing their fecal excretion and forcing the liver to utilize circulating cholesterol to synthesize new bile acids, thereby lowering serum LDL levels (Matsuane et al., 2023). Furthermore, the fermentation of this fiber by gut microbiota may produce short-chain fatty acids that can modulate hepatic lipid metabolism and inhibit cholesterol synthesis, as also confirmed by a previous study (Thaipitakwong & Aramwit, 2017).

Furthermore, the findings from this study provide compelling evidence that Nata de Papaya supplementation is effective in ameliorating diet-induced dyslipidemia in rat models. Its efficacy, particularly at the highest dose of 1.62 g, was statistically equivalent to the pharmaceutical agent ezetimibe in improving key lipid parameters (Wang et al., 2017). The most notable outcome was its significant ability to raise HDL cholesterol levels. These results posit Nata de Papaya as a promising natural dietary adjunct for managing dyslipidemia and reducing cardiovascular risk, warranting further investigation into its precise molecular mechanisms and potential applications in human clinical trials.

5.5. Challenges and limitations

A primary challenge in utilizing Nata de Papaya as a therapeutic functional food is its significantly reduced antioxidant content compared to the original papaya fruit, largely due to the high-temperature processing required for its production. This presents a limitation because the full cardioprotective potential of papaya, which relies on the synergistic action of both fiber and antioxidants, may not be fully realized. While the fiber component effectively modulates cholesterol levels, the loss of heat-sensitive antioxidants such as vitamin C means Nata de Papaya offers less protection against the oxidative modification of LDL, a key step in the formation of atherosclerotic plaques. Therefore, achieving the optimal health benefit requires balancing the fiber-enhancing fermentation process with techniques that can preserve these vital antioxidant compounds.

Furthermore, a significant limitation of this research was its confinement to an animal model, which restricted the direct translation of findings to human health. The physiological and metabolic differences between rats and humans mean that the dosage, efficacy, and safety of Nata de Papaya for managing human dyslipidemia require validation through clinical trials. Another practical challenge is the standardization of the product; factors such as fermentation time, bacterial strain, and papaya feedstock can influence the final product's thickness, fiber density, and residual bioactive compound profile, making it difficult to ensure a consistent and reliably potent product for widespread consumer use.

6. CONCLUSION

In conclusion, this study provides compelling evidence that Nata de Papaya is an effective functional food for ameliorating diet-induced dyslipidemia. The supplementation, particularly at the highest dose (1.62 g), demonstrated a significant capacity to improve the overall lipid profile by reducing atherogenic lipids—total cholesterol, triglycerides, and LDL—while concurrently elevating cardioprotective HDL. The efficacy of the high-dose Nata de Papaya was statistically equivalent to the pharmaceutical agent ezetimibe, positioning it as a potent natural alternative for lipid management. This therapeutic effect is primarily attributed to its high dietary fiber content, which acts through bile acid sequestration and excretion mechanisms, thereby enhancing the clearance of LDL cholesterol from the bloodstream.

Despite its promising benefits, the application of Nata de Papaya faces certain limitations. The fermentation process, while creating a dense cellulose matrix rich in fiber, results in a substantial loss of water-soluble antioxidants present in the original papaya fruit, such as vitamin C. This diminishes its potential to combat oxidative stress, a key factor in atherosclerosis, and represents a trade-off between fiber content and antioxidant capacity. Furthermore, the current findings are derived from an animal model, and direct extrapolation to human physiology requires validation through rigorous clinical trials to establish effective dosage, long-term safety, and efficacy in humans.

Notwithstanding these limitations, Nata de Papaya emerges as a viable and promising dietary strategy for managing cardiovascular risk factors. Its ability to significantly improve key lipid parameters underscores its potential as a safe and accessible adjunct to conventional therapies. Future research should focus on optimizing production techniques to retain more bioactive antioxidants, standardizing the product for consistent quality, and conducting human trials to confirm these beneficial effects in clinical practice. Ultimately, Nata de Papaya represents a significant step towards harnessing fermented food products for preventive healthcare.

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None.

ETHICAL APPROVAL

The experimental protocol was reviewed by dr. Firdaus Hamid, PhD, Sp.MK(K) as the Secretary, and approved by the Head of Research Ethics Committee, Faculty of Medicine, Universitas Hasanuddin, Indonesia, Prof. dr. Muh Nasrum Massi, PhD, Sp.MK(K), under Protocol No. 495/UN4,6,4.5.31/PP36/2024. All investigators followed ethical standards and adhered to the principles of replacement, reduction, and refinement (3Rs) to ensure the humane and responsible use of laboratory animals.

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AI-assisted technologies were used for language refinement, editing, visualization support, and organizational purposes. All scientific content, analysis, interpretation, and conclusions were independently reviewed and validated by the authors.

AUTHOR CONTRIBUTIONS

Conceptualization was done by EKD and SK; data curation was done by EKD; formal analysis was the responsibility of EKD and IA; investigation was the concern of EKD and MH; resources was taken care of by MH and IY; methodology was looked into by SK and IA; supervision was done by SK; project administration was handled by ESD; validation was taken care of by ESD and SK; visualization was done by SK and IA; writing—original draft was the responsibility of ESD, SK, and IA; and writing—review & editing was done by MH and IY. All authors approved the final version of the article.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest, financial or nonfinancial, related to this study.

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