Anti-inflammatory properties of Sacha inchi (Plukenetia volubilis) oil in rats fed high-fat and fructose diet: A study of NF-κB, GPR120, 12/15-LOX mRNA expression and TNF-α protein level of visceral adipose tissue

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Background. The diet of modern society tends to be high in fat and fructose. This condition can trigger the accumulation of body fat, causing inflammation. Sacha inchi oil, which contains a lot of polyunsaturated fatty acids (PUFAs), has anti-inflammatory properties so it can be one of the functional food choices to prevent inflammation in adipose tissue.

Method. A total of 30 rats were divided into five groups, namely the normal group (N), the high-fat and fructose diet (HFFD) group, and the sacha inchi oil intervention group with three different doses, which were 0.13 g (S1), 0.26 g (S2), and 0.39 g (S3). Each group underwent examination in visceral adipose tissue, including qPCR analysis to determine NFkβ, GPR 120, and 12/15 LOX mRNA expression, and ELISA analysis to measure TNFα protein levels.

Results. The HFFD group showed inflammation in adipose tissue characterized by increased NFkβ mRNA expression and TNFα protein levels compared to the N group. Improvement in inflammation was indicated by decreased NFkβ mRNA expression and TNFα protein levels and increased GPR 120 and 12/15 LOX mRNA expression in the sacha inchi oil intervention group.

Conclusion. Sacha inchi oil can prevent inflammation in rat adipose tissue induced by a high-fat and fructose diet.

Keywords: *high-fat and fructose diet, visceral adipose, inflammation, sacha inchi oil*

Introduction

Obesity, caused by excessive accumulation of body fat, is a global issue affecting both developed and developing countries, accounting for approximately 13% of the world population (Ambulay et al., 2020). Obesity is often associated with low-grade chronic inflammation, which plays a significant role in the pathophysiology of metabolic complications, potentially reducing adult life expectancy by up to five years (Roy et al., 2022). One of the main causes of fat accumulation is increased calorie intake, particularly from foods high in simple sugars and fats (Setyawati et al., 2024). Fructose consumption has risen significantly in recent years, attributed to the fact that fructose is not always visible to consumers as it is commonly added as a sweetener in food and beverages (Martins et al., 2024). Increased fructose in circulation correlates with greater absorption in adipose tissue, leading to de novo lipogenesis and subsequently enhancing adipose lipogenesis (Song et al., 2018). De novo lipogenesis also promotes fatty acid synthesis, resulting in the formation of Very Low-Density Lipoprotein (VLDL) (Flueck et al., 2023). High circulating VLDL levels increase Free Fatty Acid (FFA) uptake in adipose tissue (Zatterale et al., 2020). Increased FFA uptake in adipose tissue can also be influenced by a high-fat diet (Wijayatunga et al., 2018).

The Western dietary pattern, often referred to as the "Western diet," is characterized by higher fat consumption (Arslan et al., 2024). High fat intake triggers increased chylomicron formation in enterocytes (Giammanco et al., 2015). When the capacity of chylomicrons carrying triglycerides (TG) in circulation is exceeded, free fatty acids bind to albumin in the bloodstream, leading to increased absorption of free fatty acids in adipose tissue (Aher & Mittendorfer, 2024). Adipose tissue rich in triglycerides is prone to lipolysis, leading to lipid deposition in adipocytes, which can impair lipid oxidation (Zhao et al., 2020). Lipid accumulation in adipose tissue causes

cells to undergo hypertrophy, resulting in pathological adipose expansion. Hypertrophic adipose tissue has a reduced capacity to store lipids (Horwitz & Birk, 2023). The accumulation of white fat in obesity, particularly in visceral adipose tissue, results in adipose tissue inflammation, oxidative stress, and irregular adipokine release (Reilly & Saltiel, 2017).

To counteract ongoing inflammation, efforts to inhibit it are necessary through the consumption of functional foods that can help prevent further inflammation. Nutritional intake containing Polyunsaturated Fatty Acids (PUFA) can act as antioxidants by regulating antioxidant signaling pathways and modulating inflammatory processes (Djuricic & Calder, 2021). The active metabolic forms of PUFA are Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA), which are abundant in fish, seafood, and nuts such as canola, flaxseed, chia seed, walnut, and soybean (Takic et al., 2022). Sacha inchi nuts, native to the Peruvian Amazon, have been found to be rich in protein and omega-3 (Ambulay et al., 2020). The essential components of sacha inchi seeds include omega-3 (α-linolenic acid) 40%-50%, omega-6 (linoleic acid) 30%-40%, omega-9 (oleic acid) 6%-10%, vitamin E (α-tocopherol and δ-tocopherol), vitamin A (carotenoids), flavonoids, tannins, phenolic compounds, and β-sitosterol (Maya et al., 2023).

Materials and Method

This study employed a quasi-experimental method with a post-only control group design. A total of 30 male Wistar rats (*Rattus norvegicus*), aged 12 weeks and weighing 280–320 grams on average, were used. The rats underwent a 6-day acclimatization period before being divided into five treatment groups. The intervention lasted for 8 weeks, with each group consisting of 6 rats. The study was conducted after receiving ethical approval from the Medical and Health

Research Ethics Committee (MHREC) of FKKMK Universitas Gadjah Mada, under approval number KE/FK/0651/EC/2024.

The normal control group (N) received a standard AIN-93M diet from the start to the end of the study. The high-fat and fructose diet (HFFD) group received a high-fat and fructose diet throughout the study. The HFFD groups with varying doses of sacha inchi oil received daily doses of 0.13 grams, 0.26 grams, and 0.39 grams, respectively. Daily measurements of food and water intake were recorded, while changes in body weight were monitored weekly. The sacrifice of the animals was carried out after the 8-week intervention.

Gene Expression Analysis

The expression of the genes NFkB, GPR120, and 12/15LOX in visceral adipose tissue, used as markers of inflammation, was analyzed through three main steps: RNA Isolation, RNA was isolated using the PRImeZol reagent kit (Canvax). cDNA Synthesis, cDNA was synthesized using the ABScript Neo RT Master Mix kit (ABclonal). Quantitative PCR (qPCR), Gene expression was quantified using ExcelTaq™ 2X Fast Q-PCR Master Mix (SMOBiO). The primers used for each gene are as follows:

- **NFkB**:
  - Forward: GCTTTGCAAACCTGGGAATA
  - Reverse: CAAGGTCAGAATGCACCAGA
- **GPR120**:
  - Forward: GACCAGGAAATTCCGATTTG
  - Reverse: CTGGTGGCTCTCGGAGTATG
- **12/15LOX**:
  - Forward: AGAATACCTTGGGCCACTGC
  - Reverse: AGGATGCTTCTGCCCTGAAC
- **β-actin** (as a reference gene):
  - Forward: TACAGCTTCACCACCACAGC
  - Reverse: TCTCCAGGGAGGAAGAGGAT

The master mix containing cDNA was loaded into the qPCR machine, and the program was run with the following protocol: Initial denaturation: 95°C for 20 seconds (1 cycle),

Denaturation: 95℃ for 3 seconds, Annealing/Extension: 60℃ for 30 seconds, Total cycles: 40. This protocol ensures accurate and reliable measurement of the target gene expressions.

Protein Level Analysis

The protein level of TNF-α was analyzed using the enzyme-linked immunosorbent assay (ELISA) method with the FineTest® kit. Protein isolation from adipose tissue was performed using the Protein Extraction Reagent kit.

Statistical Analysis

Data were presented as mean ± standard deviation. Normality was tested using the Shapiro-Wilk test, and if the data were normally distributed, Levene's test was conducted to assess homogeneity. For data that met the criteria of normality and homogeneity, a parametric test was performed using One-Way ANOVA. A post hoc Tukey test was applied to examine differences in the means across variables. A significance threshold of $p < 0.05$ with a confidence interval of 95% was set for all statistical analyses.

Results

Gene Expression

The results of mRNA NFkB expression analysis in this study indicate that the administration of sacha inchi oil at low (S1), medium (S2), and high (S3) doses significantly reduced mRNA expression levels. NFkB signaling pathways and target gene expression are often upregulated in pathological conditions, including inflammation. NFkB activity can vary and plays a crucial role in numerous processes requiring the induction of appropriate gene responses to address various stressors and damage, including inflammation (Meier-Soelch et al., 2021).

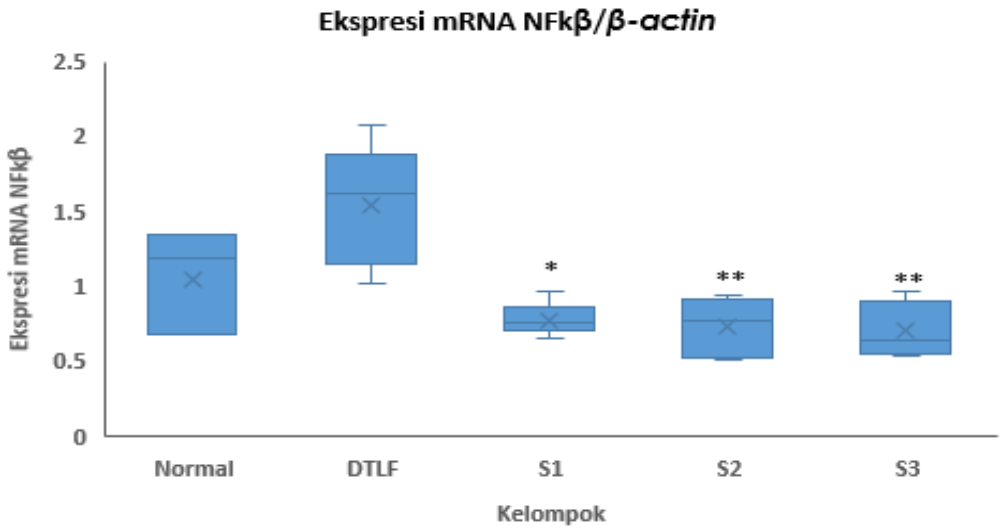

Figure 1. NFkβ mRNA Expression. The DTLF group showed higher expression levels compared to the N group, but the difference was not significant. The S1, S2, and S3 groups had significantly lower expression levels compared to the DTLF group but were not significantly different from the N group. There were no significant differences among the S groups. The significance values between treatment groups were obtained from ANOVA testing, followed by Tukey's Post-Hoc test (* = $p < 0.05$; ** = $p < 0.001$).

mRNA GPR120 Expression

The analysis of mRNA GPR120 expression in this study revealed that the administration of sacha inchi oil at a low dose (S1) increased GPR120 mRNA expression, indicating an initial rise in PUFA active metabolite activity. Administration at medium (S2) and high (S3) doses showed a significant increase in expression. GPR120 acts as an n-3 PUFA sensor in adipose tissue, triggering anti-inflammatory activity. Ligands that activate GPR120 bind to β-arrestin2, forming a complex that interacts with transforming growth factor-β-activated kinase binding protein 1 (TAB1). This interaction blocks key pro-inflammatory signaling molecules, including NFkB, thereby inhibiting inflammation (Song et al., 2017).

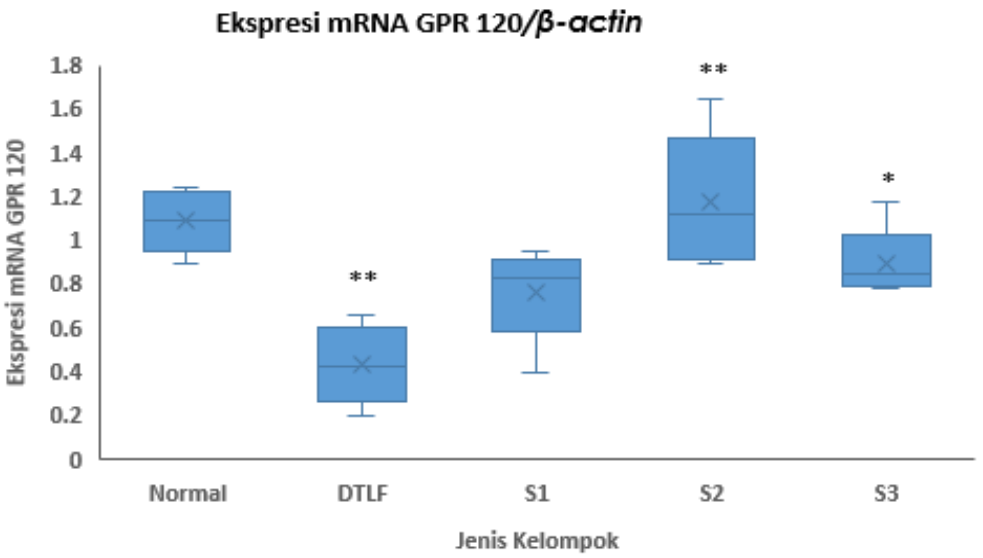

Figure 2. GPR120 mRNA Expression. The DTLF group had significantly lower expression levels compared to the N group. The S groups showed higher expression levels compared to the DTLF group, with significant differences observed in the S2 and S3 groups. Statistical significance between treatment groups was determined using ANOVA, followed by Tukey's Post-Hoc test (* = $p < 0.05$; ** = $p < 0.001$).

mRNA 12/15LOX Expression

The analysis of mRNA 12/15LOX expression in this study showed that administration of sacha inchi oil at a low dose (S1) resulted in decreased expression compared to both the N and DTLF groups. Meanwhile, the medium (S2) and high (S3) dose groups exhibited increased expression compared to the DTLF group, although the increase was not statistically significant and did not reach levels comparable to the N group.

The role of 12/15LOX is associated with various inflammation-related diseases. Its controversial nature in inflammation stems from its metabolites, which have demonstrated both pro-inflammatory and anti-inflammatory properties. 12/15LOX is believed to induce the production of pro-inflammatory cytokines in macrophages.

The anti-inflammatory properties of 12/15LOX metabolites can be observed through mediators such as lipoxins, resolvins, and protectins, which exhibit strong and direct anti-

inflammatory effects on various cell types. Lipoxins have been shown to reduce adipose tissue inflammation in rats, while protectins and resolvins are key anti-inflammatory products of 12/15LOX. This dual effect highlights that 12/15LOX and its metabolites possess both pro- and anti-inflammatory effects. The differing properties of the same metabolites may be influenced by their varying doses (Singh & Rao, 2019).

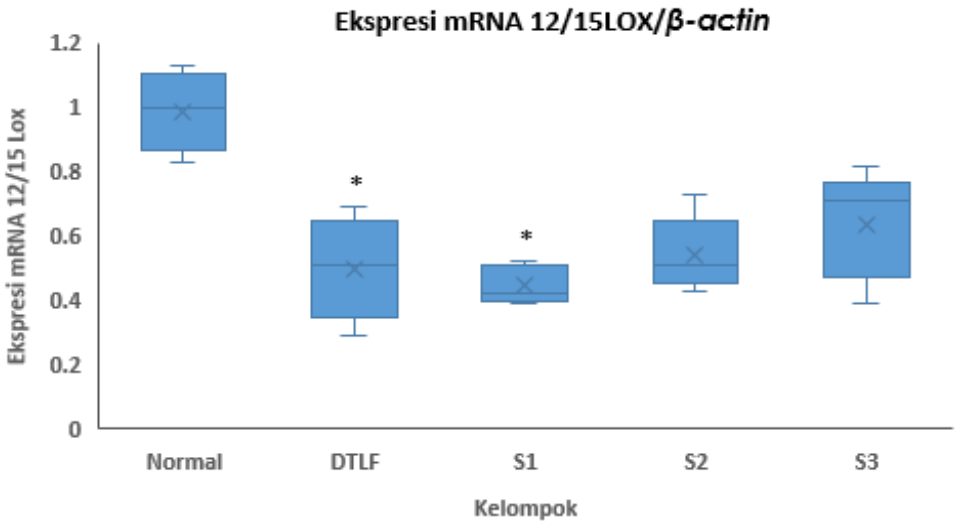

Figure 3. 12/15 LOX mRNA Expression. The DTLF group had significantly lower expression levels compared to the N group. The S2 and S3 groups showed higher expression levels compared to the DTLF group. However, the S1, S2, and S3 groups had lower expression levels compared to the N group. Among the S1, S2, and S3 groups, expression levels increased, but the differences were not significant. Statistical significance between treatment groups was determined using ANOVA, followed by Tukey's Post-Hoc test (* = $p < 0.05$).

Protein Levels

The analysis of TNFα protein levels in this study showed that the administration of sacha inchi oil at low (S1), medium (S2), and high (S3) doses significantly reduced protein levels. TNFα, a pro-inflammatory cytokine, is the first to be released by adipose tissue. It then promotes the induction of lipid dysregulation and inflammation in adipose tissue, such as increasing lipolysis, reducing lipid accumulation, decreasing adiponectin secretion, and increasing the secretion of

other pro-inflammatory adipokines and cytokines, such as MCP-1, IL-6, and IL-1β (Zhang et al., 2022).

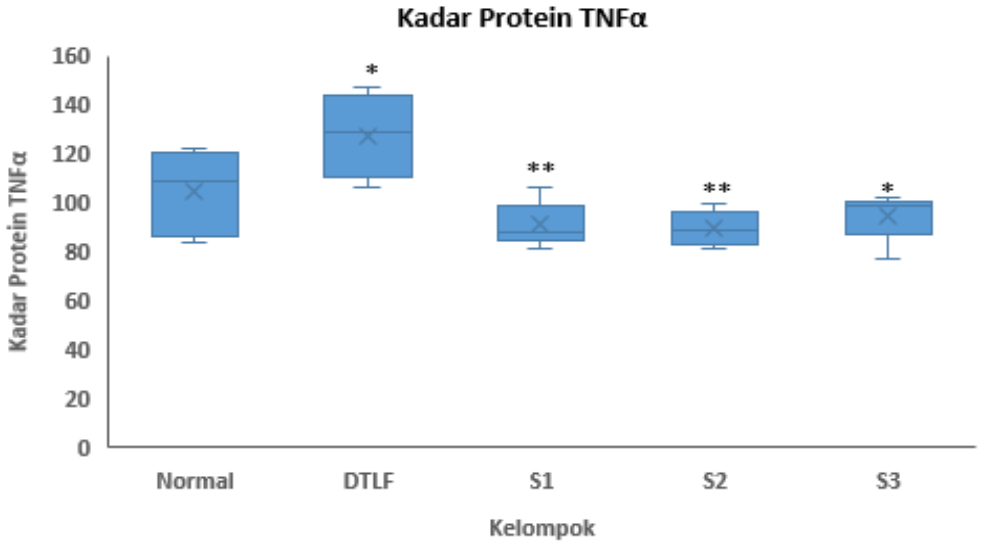

Figure 4. TNFα Protein Levels. The DTLF group showed a significant increase compared to the N group. The S1, S2, and S3 groups had significantly lower levels compared to the DTLF group but were not significantly different from the N group. There were no significant differences among the S1, S2, and S3 groups. Statistical significance between treatment groups was determined using ANOVA, followed by Tukey's Post-Hoc test (* = $p < 0.05$; ** = $p < 0.001$).

Correlation Between Variables

Ratio of Adipose Triglyceride Levels to Visceral Adipose Weight

The result of the ratio of adipose triglyceride levels to visceral adipose weight is obtained from the comparison of both. The data are presented as mean ± standard deviation. The DTLF group, when compared to the intervention group, did not show any significant changes.

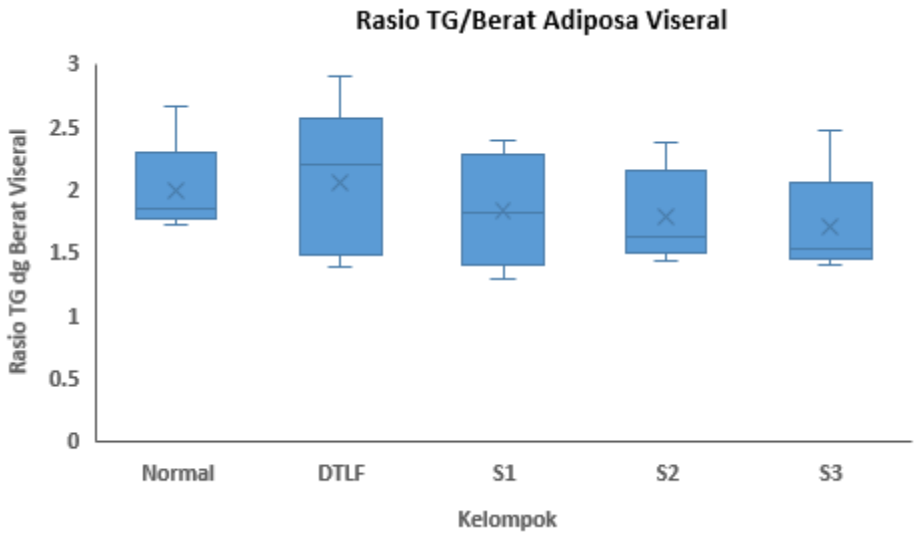

Figure 5. Ratio of Adipose Triglyceride Levels to Visceral Adipose Weight. The DTLF group showed an increase in the ratio compared to the N group, but it was not significant. The ratio in the DTLF group decreased when compared to the S1, S2, and S3 groups; however, this decrease was also not significant. The significance values between treatment groups were obtained using ANOVA, followed by Tukey's Post-Hoc test (* = $p < 0.05$; ** = $p < 0.001$).

Correlation Between Adipose Triglyceride Levels and TNF-α Protein

Correlation between adipose triglyceride levels and TNF-α protein is used to assess the strength and direction of the correlation between these two variables. Pearson correlation analysis resulted in an r-value of 0.423 and a p-value of 0.035. This positive correlation indicates that as visceral adipose triglyceride levels increase, TNF-α protein levels also tend to increase. Although the correlation is not very strong, it is statistically significant.

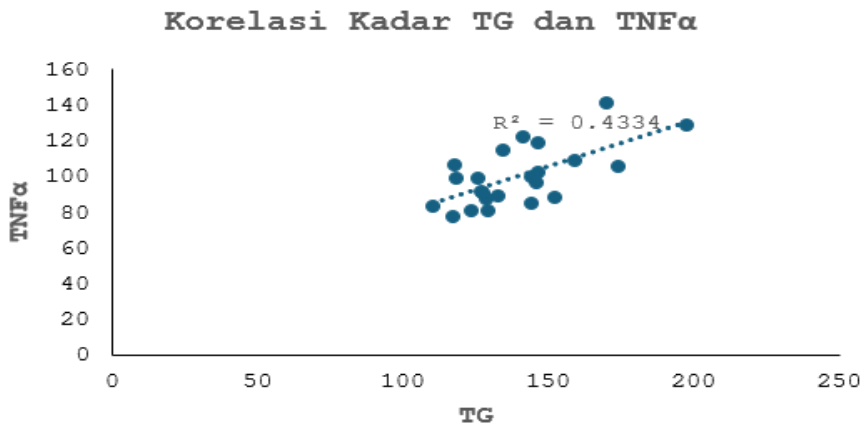

Figure 6. Data Point Distribution of the Correlation Between Triglyceride Levels and TNF-α. Pearson correlation analysis resulted in an r-value of 0.423 and a p-value of 0.035.

Correlation Between mRNA NF-κB Expression and TNF-α Protein Levels

Correlation between NF-κB mRNA expression and TNF-α protein levels is used to assess the strength and direction of the correlation between these two variables. Pearson correlation analysis resulted in an r-value of 0.955 and a p-value of <0.0001. This strong positive correlation indicates that as NF-κB mRNA expression increases, TNF-α protein levels also increase in a consistent manner, and the relationship is statistically significant.

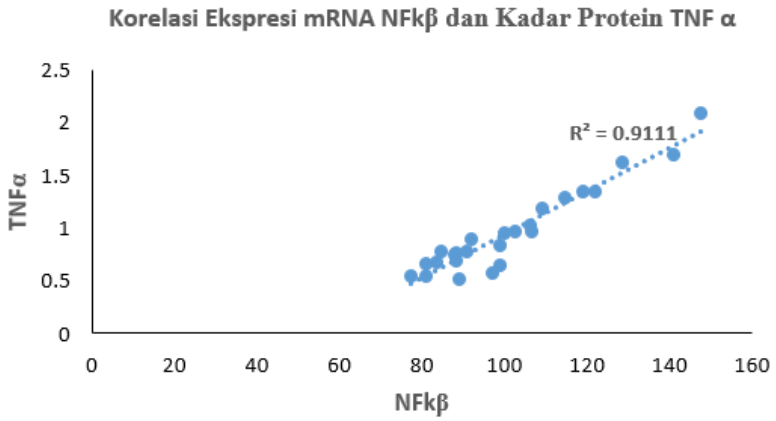

Figure 7. Data Point Distribution of the Correlation Between NF-κB mRNA Expression and TNF-α Protein Levels. Pearson correlation analysis resulted in an r-value of 0.955 and a p-value of <0.0001.

Correlation Between 12/15-Lox mRNA Expression and TNF-α Protein Levels

Correlation between 12/15-Lox mRNA expression and TNF-α protein levels is used to assess the strength and direction of the correlation between these two variables. Correlation analysis resulted in an r-value of 0.105 and a p-value of 0.114. This weak positive correlation indicates that there is almost no relationship between changes in 12/15-Lox mRNA expression and TNF-α protein levels, and this relationship is not statistically significant.

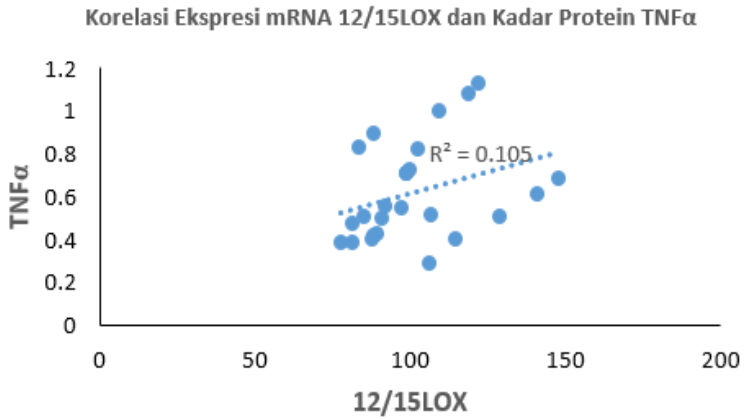

Figure 8. Data Point Distribution of the Correlation Between 12/15-Lox mRNA Expression and TNF-α Protein Levels. Pearson correlation analysis resulted in an **r-value of 0.105 and a p-value of 0.114.**

Correlation Between GPR 120 mRNA Expression and NFκB

Correlation between GPR 120 mRNA expression and NF-κB adipose expression is used to assess the strength and direction of the correlation between these two variables. Correlation analysis resulted in an **r-value of -0.177 and a p-value of 0.397.** This weak negative correlation indicates that as GPR 120 mRNA expression increases, NF-κB levels tend to decrease, but this relationship is not statistically significant.

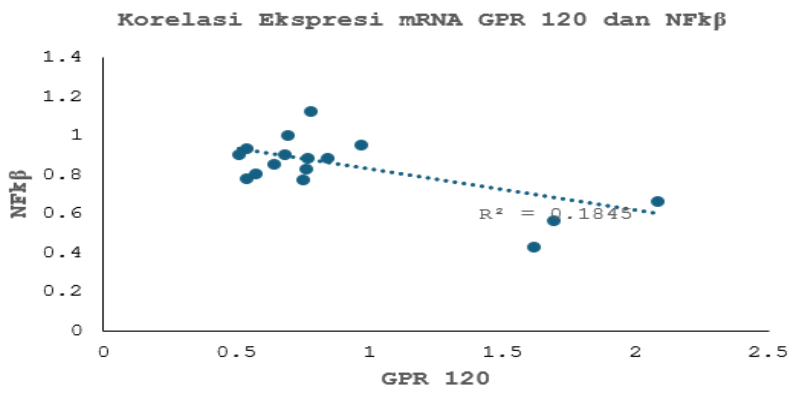

Figure 9. Data Point Distribution of the Correlation Between GPR 120 mRNA Expression and NF-κB. Pearson correlation analysis resulted in an r-value of -0.177 and a p-value of 0.397.

Discussion

In general, the results of this study indicate that the administration of sacha inchi oil can prevent the occurrence of white adipose tissue inflammation in rats induced by a high-fat and fructose diet. This benefit can be observed through the increased activity of active PUFA metabolites and the reduced activation of inflammatory processes as seen from qPCR and ELISA results. The pro-inflammatory cytokine response during the acute phase increases with the growth of adipose tissue, indicating that adipose tissue is an important source of inflammation. Consumption of oil from the *Plukenetia volubilis* species increases α-linolenic acid and EPA levels in plasma and tissues of both humans and rodents. High ω-3 sources like sacha inchi oil emulsions can reduce inflammation (Ambulay et al., 2020).

The cytokine TNFα is produced in adipose tissue by macrophages. Its production is proportional to adipose tissue mass, so the administration of sacha inchi oil significantly improved the inflammatory cytokine levels (Setyawati et al., 2024). In this study, sacha inchi oil significantly reduced TNFα protein levels at all doses, thereby preventing adipose inflammation in rats induced

by a high-fat and fructose diet. The variations in doses did not affect the reduction of TNFα protein levels, indicating that even a low dose of sacha inchi oil can be recommended.

Sacha inchi oil, which is high in PUFA, is one of the dietary components that can help prevent adipose tissue inflammation. Additionally, sacha inchi oil offers the advantage of being a plant-based unsaturated fatty acid, which has a milder smell compared to fish oil. Sacha inchi also holds promise as a sustainable, renewable, and affordable source for functional foods (Supriyanto et al., 2022). The essential fatty acids that serve as precursors for the synthesis of EPA and DHA can modulate adipose tissue function by acting as ligands for GPR120, which inhibits inflammation through the NFkB pathway (Sierra et al., 2021).

Conclusion

The administration of sacha inchi oil can reduce visceral adipose tissue inflammation caused by a high-fat and fructose diet.

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