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Sacha inchi oil suppresses hepatic triglyceride synthesis through inhibition of lipogenic gene expression in rats with high-fat and high-fructose intake

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ABSTRACT

Background: Excessive dietary fat and fructose intake stimulate hepatic fatty acid production by enhancing the expression of lipogenesis-related genes, including sterol regulatory binding protein-1c (SREBP-1c), carbohydrate-responsive element-binding protein (*ChREBP*), acetyl-CoA carboxylase 1 (*ACC1*), fatty acid synthase (*FAS*), and diacylglycerol acyltransferase 2 (*DGAT2*). Polyunsaturated fatty acids (PUFAs) can suppress these genes, thereby attenuating hepatic triglyceride synthesis. *Plukenetia volubilis* L., commonly known as sacha inchi, is a notable source of PUFAs, and may therefore help prevent hepatic triglyceride accumulation.

Objective: This study aimed to investigate the influence of sacha inchi oil on the expression of genes involved in hepatic triglyceride synthesis.

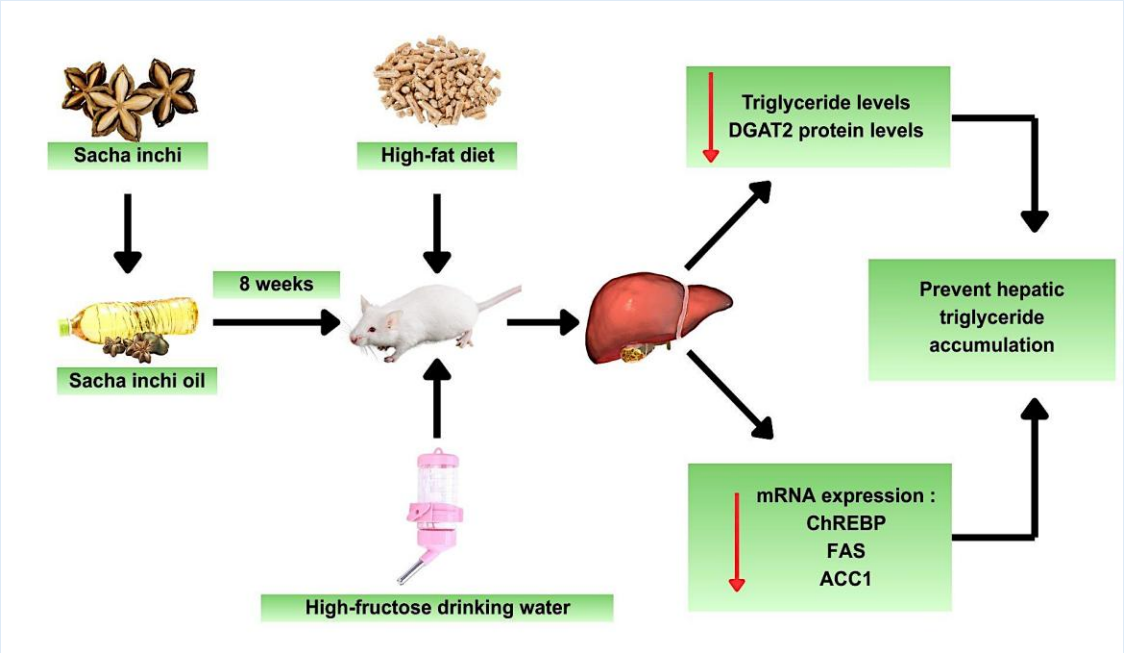
Methods: Twenty-five 12-week-old male Wistar rats were distributed into five groups: (1) normal (N); (2) high-fat diet and fructose-containing drinking water (HFHF); and (3-5) HFHF supplemented with sacha inchi oil at doses of 0.13 g/day (S1), 0.26 g/day (S2), and 0.39 g/day (S3). Sacha inchi oil was administered orally for eight weeks. At the end of the study, hepatic triglyceride and DGAT2 levels were measured using enzymatic colorimetric and ELISA methods, respectively, while gene expression was analyzed using qPCR.

Results: The HFHF group showed significantly higher hepatic triglyceride and DGAT2 levels, as well as *ChREBP*, *ACC1*, and *FAS* gene expression, compared with the normal and sacha inchi oil-supplemented groups ($P < 0.05$). Sacha inchi oil supplementation reduced the hepatic triglyceride and *DGAT2* levels and suppressed the *ChREBP*, *ACC1*, and *FAS* gene expression, without affecting *SREBP-1c* and DGAT2 gene expression ($P > 0.05$).

Novelty: This study provides additional insight into the effects of sacha inchi oil, a PUFAs-rich-oil, on the hepatic lipid metabolism. The present results suggest that this oil may help reduce the expression of key genes involved in triglyceride synthesis, including *ChREBP*, *FAS*, and *ACC1*, under high-fat and high-fructose conditions. These results complement existing literature and support its potential role as a functional food component for preventing hepatic triglyceride accumulation.

Conclusion: These findings suggest that sacha inchi oil may prevent hepatic triglyceride accumulation by suppressing the expression of key genes involved in triglyceride synthesis.

Keywords: high-fat diet, fructose, triglyceride synthesis, sacha inchi oil, PUFA



Graphical Abstract: Sacha inchi oil suppresses hepatic triglyceride synthesis through inhibition of lipogenic gene expression in rats with high-fat and high-fructose intake.

INTRODUCTION

A high-fat diet, particularly dominated by saturated fats, combined with excessive fructose intake, promotes intrahepatic triglyceride synthesis and increases susceptibility to non-alcoholic fatty liver disease (NAFLD) [1-2]. Excessive fat intake stimulates lipogenesis by elevating the expression of sterol regulatory binding protein 1c (*SREBP-1c*) gene [3]. In addition, high fructose consumption enhances de novo lipogenesis (DNL) by increasing the expression of the *SREBP-1c* and

carbohydrate response element binding protein (*ChREBP*) genes [4-5].

SREBP-1c and *ChREBP* are the two majors transcription factors responsible for the induction of lipogenic genes [6]. These transcription factors regulate the gene expression of acetyl-CoA carboxylase-1 (*ACC1*) and fatty acid synthase (*FAS*), which are key enzymes that play a pivotal role in hepatic fatty acid synthesis [7-8]. An increase in *ACC1* and *FAS* gene expression has been reported to enhance hepatic triglyceride synthesis through lipogenesis and the DNL pathway [8-9]. The function of *ACC1* is to convert acetyl-CoA into malonyl-CoA, whereas *FAS* mediates fatty acid elongation through the use of malonyl-CoA as its primary carbon substrate, ultimately producing palmitate, the predominant product of fatty acid synthesis [10]. Palmitate is subsequently esterified into triglycerides through a series of enzymatic steps, with diacylglycerol acyltransferase 2 (*DGAT2*) catalyzing the final step, thereby promoting the triglycerides storage [11]. According to Giudetti et al. [12], overexpression of *DGAT2* may stimulate hepatic triglyceride accumulation. However, suppression of the *DGAT2* gene expression has been shown to prevent hepatic triglyceride accumulation [13].

Recent evidence highlights the importance of functional food in the dietary management strategies for preventing and treating hepatic triglyceride accumulation [14]. Polyunsaturated fatty acids (PUFAs) are bioactive food compounds commonly present in functional foods in relatively small amounts yet provide several health benefits [15-17]. Several studies have demonstrated that PUFAs supplementation may suppress triglyceride synthesis by downregulating key genes involved in this pathway, thereby preventing hepatic triglyceride accumulation [18]. One source of PUFAs is *Plukenetia volubilis* L., commonly known as sacha inchi or inca peanut. Previous studies have shown that sacha inchi oil is rich in PUFAs, particularly alpha-linolenic acid (51.5%) and linoleic acid (32.5%) [19]. PUFA intake has been reported to downregulate *SREBP-1c* and *ChREBP* expression [20-21], leading to reduced expression of downstream lipogenic enzyme genes, such as *ACC1* and *FAS* [18]. Therefore, we investigated the effects of sacha inchi oil supplementation on hepatic triglyceride synthesis in rats consuming a high-fat diet and drinking fructose-containing water.

MATERIALS AND METHODS

Oil Preparation: The sacha inchi used in this study was obtained from Wonosobo, Central Java, Indonesia. The oil extraction was carried out according to the protocol reported by Supriyanto et al. [22]. Briefly, the kernels were manually separated from their shells using a small hammer and air-dried to reduce the moisture content. The dried kernels were then cold pressed to yield sacha inchi oil. The extracted oil was stored in a dark bottle at 4 ^{o}C until further use.

The fatty acids of the extracted oil were analyzed using agas chromatography (GC) method at Balai Besar Standardisasi dan Pelayanan Jasa Industri Agro, Bogor, West Java, Indonesia. The analysis showed that sacha inchi oil contained 76.65% PUFAs, dominated by α-linolenic acid (48.98%) and linoleic acid (36.90%), along with 7.45% oleic acid and 5.90% saturated fatty acid.

Animals: Twenty-five male Wistar rats aged 12 weeks and weighing 240-320 g were included in this study. The rats were obtained and housed in the animal laboratory of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia. The animals were housed in square cages under controlled conditions with a constant room temperature of 22-25 ^{o}C, relative humidity of 30-70%, and a 12-h light/dark cycle. Before the study began, the rats were acclimatized to a standard diet formulated based on the modified AIN 93M [23]. All experimental procedures were reviewed and approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and

Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia (KE/FK/1865/EC/2024).

Experimental Study: After a week of acclimatization, 25 rats were randomly distributed into five experimental groups (n = 5), which included a normal control group (N): fed a standard diet and water; HFHF: fed a high-fat diet and fructose-containing drinking water; and HFHF with sacha inchi oil (S1, S2, and S3) gat doses of 0.13 g/day (S1), 0.26 g/day (S2), and 0.39 g/day (S3), respectively. The composition standards and the high-fat diet are shown in Table 1.

Table 1. Diet composition.

Composition	Standard diet (g/kg)	High-fat diet (g/kg)
Cornstarch	621	361
Casein	140	140
Butter	-	300
Sucrose	100	100
Corn oil	40	50
Alpha cell	50	50
Mineral mix	35	35
Vitamin mix	10	10
Methionine	1.8	1.8
Choline chloride	2.5	2.5

Sacha inchi oil was administered orally by gavage once daily for eight weeks. Feed and fructose intake were recorded daily. At the end of the study, the rats underwent an overnight fast (10-12 hours) prior to anesthesia and were subsequently euthanized in accordance with the ethical guidelines. Following this, the livers were excised, weighed, and rinsed with ice-cold saline. Liver samples were then stored at -80 ^{o}C for triglyceride content and *DGAT2* protein level determination. A portion of liver tissue was immediately preserved in RNA stabilization solution (ELK Biotechnology, Denver, USA) and stored at -20 ^{o}C for subsequent RNA extraction.

Histological Examination: Liver tissues were preserved in formalin, processed for paraffin embedding, sliced into sections, and stained using hematoxylin and eosin (H&E). A blinded assessment of hepatic triglyceride accumulation was performed by an expert pathologist. Histological grading was performed according to a previously described protocol, with scores assigned as follows: grade 0: normal (<5% lipid accumulation); grade 1: mild (5-33%); grade 2: moderate (34-66%), and grade 3: severe (>66%) [24].

Hepatic Triglyceride Levels Determination: Lipid extraction from the liver was performed using the Folch method. Liver tissue was homogenized in a mixture of chloroform: methanol with a ratio of 2:1 (v/v). Following homogenization, the sample was centrifuged at 3,000 × g for 10 minutes. The resulting organic phase, which contained the extracted lipids, was subsequently transferred to a new tube. To promote the phase separation, 0.9% saline was added to the supernatant and thoroughly mixed. To separate the lipid, the mixture was centrifuged again at 1,200 × g for 10 minutes. The upper layer was discarded, and the lipid-containing phase was retained. The lipid extract was then dried in an oven at 37 ^{o}C overnight, allowing complete evaporation of the organic solvents. The dried lipid residue was subsequently dissolved in isopropanol for triglyceride determination. Liver triglyceride concentration was

determined using a DiaSys kit (Holzheim, Germany) following the manufacturer's protocol.

Hepatic DGAT2 Levels Determination: Hepatic DGAT2 levels were determined using an enzyme-linked immunosorbent assay (ELISA) method (FineTest, Wuhan, China), according to the manufacturer's instructions. Frozen liver tissue samples were processed for protein extraction using the ExKine™ Total Protein Extraction Kit (Abbkine Scientific, Atlanta, Georgia, USA). The protein concentration in the extract was then quantified using a bicinchoninic acid (BCA) assay with a Protein Quantification Kit (BCA Assay) (Abbkine Scientific, Atlanta, Georgia, USA).

RNA Extraction Protocol: Total RNA was extracted from approximately 50 mg of liver tissue using PRImeZOL Reagent (Canvax Reagent, Boecillo, Valladolid, Spain) according to the manufacturer's protocol. Tissue samples were homogenized in 1 mL of PRImeZOL Reagent using a mechanical homogenizer, followed by phase separation with chloroform and RNA precipitation using isopropanol. The RNA pellet was washed using 70% ethanol and resuspended in nuclease-free water. RNA purity and concentration were determined using a MaestroNano Pro Spectrophotometer (Maestrogen, Taiwan), and samples with an A260/A280 ratio of 1.8-2.0 were considered acceptable for further analysis.

qPCR Analysis Protocol: cDNA synthesis was carried out from 1 µg of total RNA using the ExcelRT Reverse Transcription Kit (SMOBIO Technology Inc., Taiwan). qPCR reactions (20 µL) were performed using SensiFast SYBR (Meridian Bioscience, London, United Kingdom). Amplification was conducted on a CFX96 real-time PCR system (Bio-Rad, Hercules, CA, USA) using the following thermal cycling program: 95°C for 2 minutes, 95°C for 5 seconds, followed by annealing temperature for 10 seconds, repeated for 40 cycles. The annealing temperature used as follows: SREBP-1c (57 °C), ChREBP (57 °C), ACC1 (56.3 °C), FAS (56.3 °C), and DGAT2 (63 °C). Results were normalized against β-actin, which functioned as the internal control. Relative mRNA expression was calculated using $2^{-}\Delta\Delta Ct$ method. The sequences of primers applied in this study are: *SREBP-1c* (Forward: 5'- CTGTCGTCTACCATAAGCTGCAC-3'; Reverse: 5'- ATAGCATCTCCTGCACACTCAGC-3'); *ChREBP* (Forward: 5'-GAAGACCCAAAGACCAAGATGC -3'; Reverse: 5'-TCTGACAACAAAGCAGGAGGTG-3'); *ACC1* (Forward: 5'-AACATCCCGCACCTTCTTCTAC-3'; Reverse: 5'-CTTCCACAAACCAGCGTCTC-3'); *FAS* (Forward: 5'-ACCTCATCACTAGAAGCCACCAG -3'; Reverse: 5'-GTGGTACTTGGCCTTGGGTTTA-3') [25]. *DGAT2* (Forward: 5'- AGTCCTACAGTGGGTCCTATC-3'; Reverse: 5'-GGCGTGTTCCAGTCAAATGC-3') [26]. β-actin (Forward: 5'-TGTGGATTGGTGGCTCTATC-3'; Reverse: 5'-TGTGGATTGGTGGCTCTATC-3') [27].

Statistical analysis: Data are expressed as mean ± standard deviation (SD). Data normality was assessed using the Shapiro-Wilk test, and homogeneity of variances was evaluated using Levene's test. Differences in liver weight, hepatic triglyceride levels, and mRNA expression of *SREBP-1c*, *ChREBP*, *ACC1*, *FAS*, and *DGAT2* among groups were analyzed using one-way ANOVA followed by Tukey's post-hoc test. Pearson's correlation analysis was performed to evaluate relationships between dietary fat and sugar intake and hepatic triglyceride levels; furthermore, correlations were assessed between fat intake and *SREBP-1c* mRNA expression, and between sugar intake and *ChREBP* mRNA expression. Additional Pearson's correlation analyses were also conducted to evaluate the relationship between *SREBP-1c* and its downstream targets (*ACC1* and *FAS*) and between *ChREBP* and its downstream targets

(*ACC1* and *FAS*). A p-value < 0.05 was considered statistically significant.

RESULTS

In the present study, rats receiving a high-fat diet and fructose-containing drinking water had significantly higher liver weight compared to the normal group and the HFHF supplemented with sacha inchi oil groups (P = 0.002). Hepatic triglyceride levels were significantly lower in the sacha inchi oil-supplemented groups compared with the HFHF group (P = 0.0003) and remained similar to that of the normal group (Figure 1).

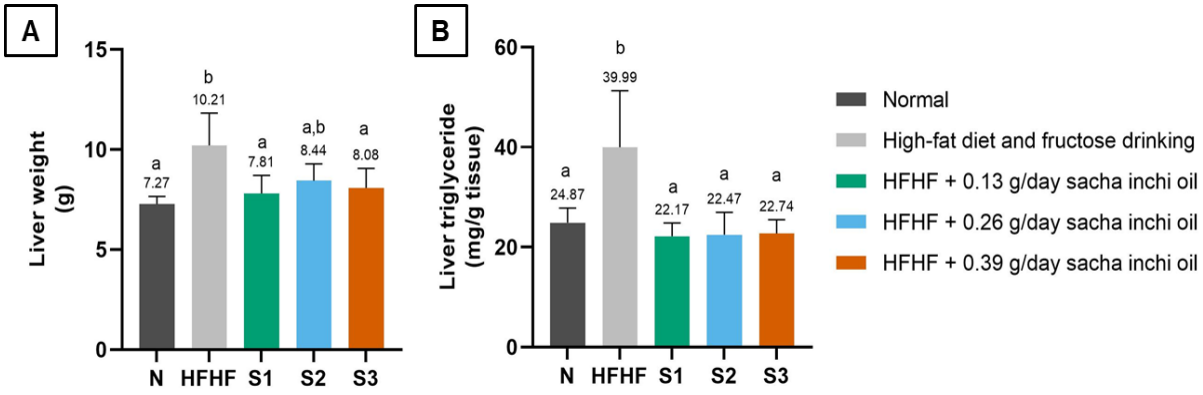


Figure 1. Liver weight (A) and Liver triglyceride levels (B). Values are presented as mean ± standard deviation (SD) of five rats. N: normal control; HFHF: high-fat and fructose water; S1: HFHF + 0.13 g/day of sacha inchi oil; S2: HFHF + 0.26 g/day of sacha inchi oil; S3: HFHF + 0.39 g/day of sacha inchi oil. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. Groups marked with different superscript letters are significantly different (P < 0.05), while those sharing the same letter do not differ significantly.

Hepatic triglyceride levels are closely related to the amount and composition of dietary intake. Excessive fat and sugar intake, particularly fructose, may contribute to increased hepatic triglyceride levels. The correlation between dietary fat and sugar intake and hepatic triglyceride levels was examined, as presented in Figure 2.

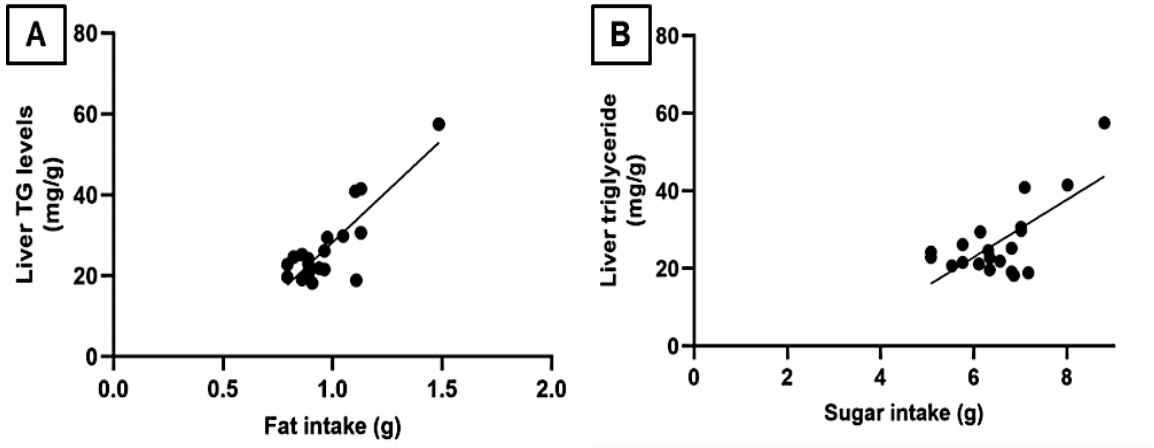


Figure 2. Relationship between hepatic triglyceride levels and fat intake (A) and dietary sugar intake (B). Correlation analysis was performed using Pearson's correlation test. Hepatic triglyceride levels were positively correlated with dietary fat intake (A: r = 0.714; P < 0.0001) and dietary sugar intake (B: r = 0.691; P = 0.0007).

Our study showed that both fat and sugar intake were positively correlated with hepatic triglyceride levels according to Pearson's analysis. A strong correlation was observed between dietary fat intake and hepatic triglyceride levels (r = 0.714; P < 0.0001), while dietary sugar intake demonstrated a moderate correlation (r = 0.691; P = 0.0007). Our findings imply that overconsumption of both dietary fat and sugar contributes to hepatic triglyceride accumulation.

To further support the biochemical findings, the histological analysis of H&E-stained liver sections was performed. After the 8-week intervention, representative liver histology is shown in Figure 3A-E, with corresponding quantitative data summarized in Table 2.

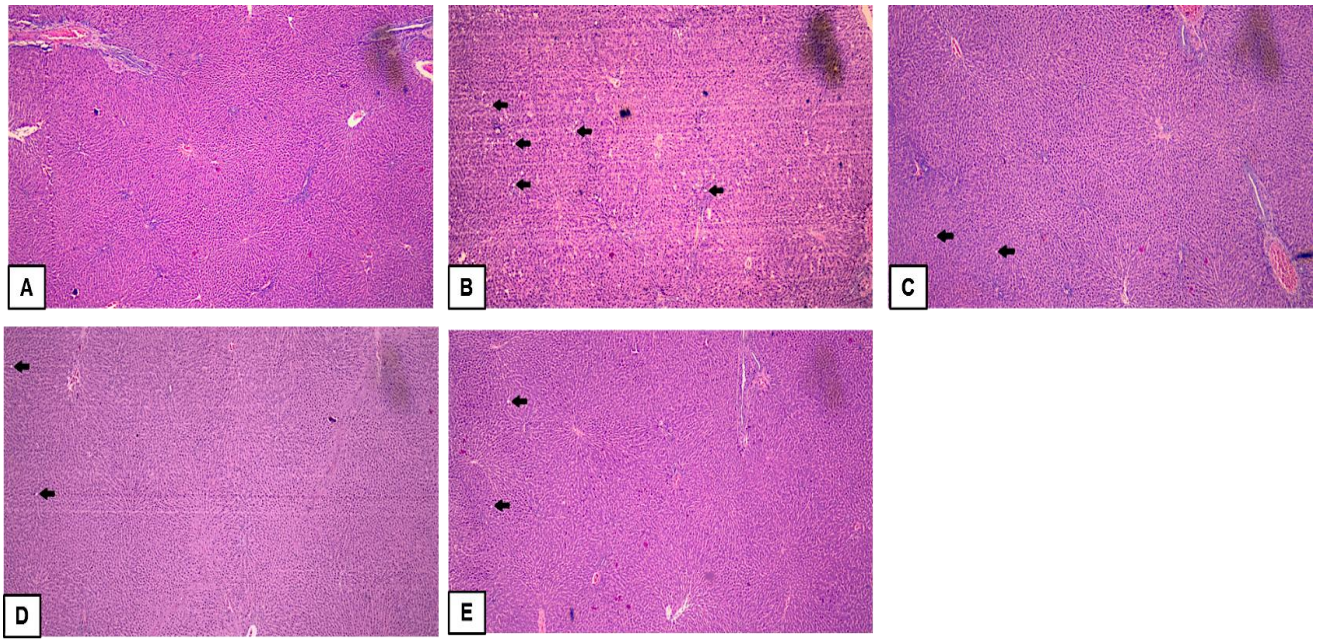


Figure 3. Representative liver histology after 8-week intervention at x40 magnification. (A) normal liver histology of rats; (B) HFHF liver histology of rats; (C) HFHF + 0.13 g/day sacha inchi oil; (D) HFHF + 0.26 g/day sacha inchi oil; (E) HFHF + 0.39 g/day sacha inchi oil. Arrows indicate lipid droplet.

Table 2. Grading of steatosis after 8 weeks of intervention.

Groups	Mean percentage of steatosis	Grade
Normal	0%	Grade 0
HFHF	8%	Grade 1
S1	1%	Grade 0
S2	1%	Grade 0
S3	2%	Grade 0

In our study, the HFHF group (Figure 3B and Table 2) exhibited grade 1 steatosis, characterized by an average lipid accumulation of 8%. However, the sacha inchi-oil supplemented groups (Figures 3C-D and Table 2) exhibited grade 0 steatosis with an average lipid accumulation of <5%. These findings suggest that supplementation of sacha inchi oil may prevent hepatic triglyceride accumulation.

To investigate the regulatory mechanism influenced by supplementation with this oil, we examined the transcription factor gene expression (Figure 4) and its downstream enzyme gene expression involved in triglyceride synthesis (Figure 5).

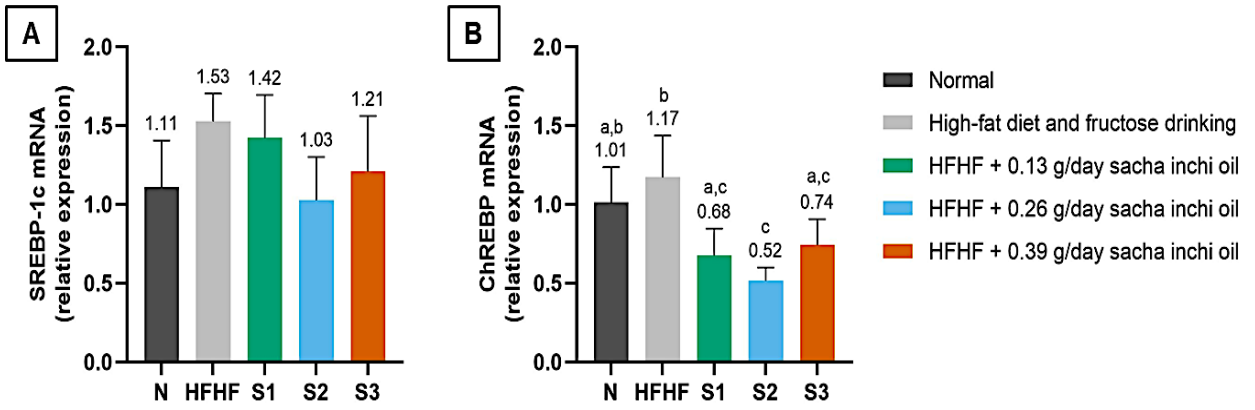


Figure 4. Effects of sacha inchi oil supplementation on hepatic mRNA expression of *SREBP-1c* (A); and *ChREBP* (B). Values are presented as mean ± standard deviation (SD) of five rats. N: normal control; HFHF: high-fat and fructose water; S1: HFHF + 0.13 g/day of sacha inchi oil; S2: HFHF + 0.26 g/day of sacha inchi oil; S3: HFHF + 0.39 g/day of sacha inchi oil. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. Groups marked with different superscript letters are significantly different, while those sharing the same letter do not differ significantly.

No significant differences in hepatic *SREBP-1c* mRNA expression were observed among the groups (P = 0.05), indicating that supplementation with sacha inchi oil did not alter the expression of this gene. To further explore the mechanism, we also examined the hepatic *ChREBP* mRNA expression. Our results demonstrated that high-fat and high-fructose intake significantly induced *ChREBP* mRNA expression compared with sacha inchi oil-supplemented groups (P = 0.0002). These findings suggest that sacha inchi oil supplementation may suppress *ChREBP* mRNA expression compared with the HFHF group. However, the groups receiving varying doses of sacha inchi oil exhibited no significant differences in *ChREBP* mRNA expression.

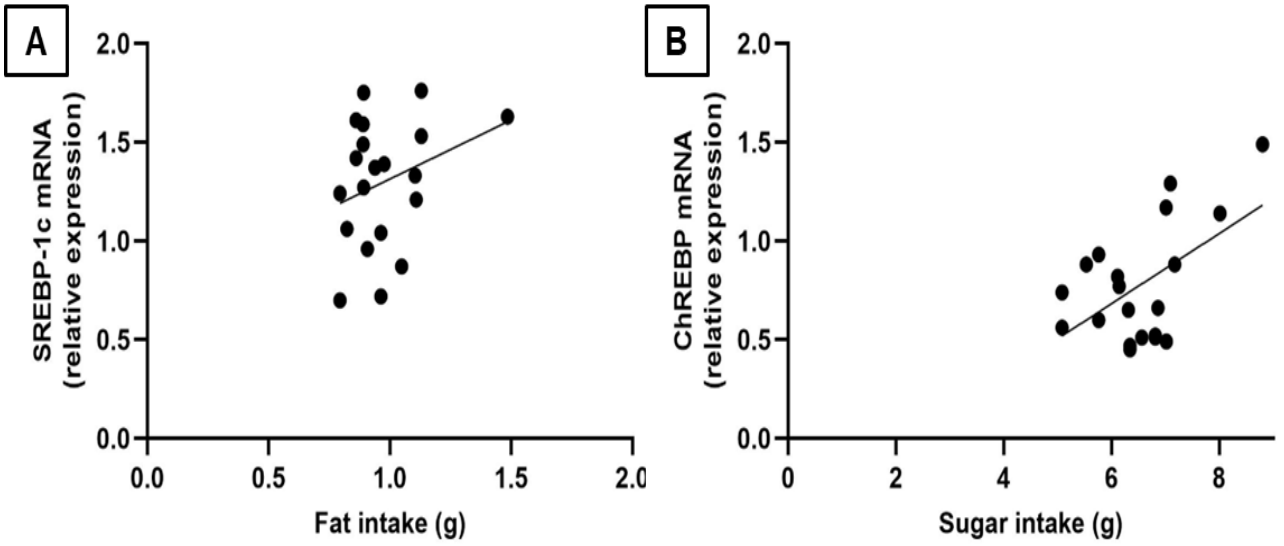


Figure 5. Relationship between *SREBP-1c* mRNA expression and fat intake (A) and relationship between *ChREBP* mRNA expression and dietary sugar intake (B). Correlation analysis was performed using Pearson's correlation test. Dietary intake was positively correlated with *SREBP-1c* mRNA expression (A: r = 0.301; P = 0.196), and dietary sugar intake was positively correlated with *ChREBP* mRNA expression (B: r = 0.538; P = 0.01).

Although dietary fat intake was weakly correlated with *SREBP-1c* mRNA expression and did not reach statistical significance (r = 0.301; P = 0.196), dietary sugar intake demonstrated a moderate and significant positive correlation with *ChREBP* mRNA expression (r = 0.538; P = 0.01). The results suggest that *ChREBP* mRNA expression may be more influenced by dietary sugar intake than *SREBP-1c* mRNA expression is by fat intake (Figures 5A and B).

In this study, excessive consumption of dietary fat and fructose significantly increased hepatic *ACC1* mRNA expression compared with the sacha inchi oil-supplemented groups (P = <0.0001). Supplementation with sacha inchi oil at all doses (0.13 g/day, 0.26 g/day, and 0.39 g/day) markedly suppressed hepatic *ACC1* mRNA expression. Despite the absence of statistically significant differences among the supplemented groups, the S2 group exhibited the lowest *ACC1* mRNA expression (Figure 6A).

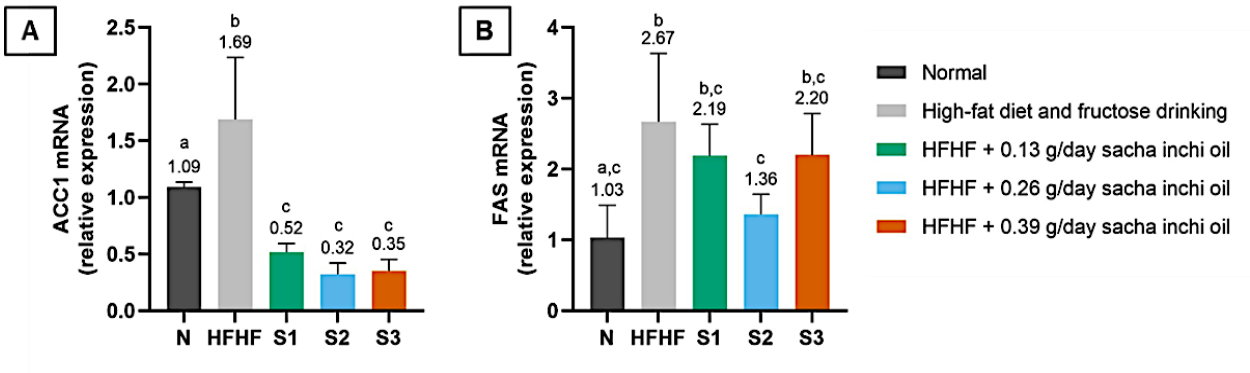


Figure 6. Effects of sacha inchi oil supplementation on hepatic mRNA expression of *SREBP-1c* (A); and *ChREBP* (B). Values are presented as mean ± standard deviation (SD) of five rats. N: normal control; HFHF: high-fat and fructose water; S1: HFHF + 0.13 g/day of sacha inchi oil; S2: HFHF + 0.26 g/day of sacha inchi oil; S3: HFHF + 0.39 g/day of sacha inchi oil. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. Groups marked with different superscript letters are significantly different, while those sharing the same letter do not differ significantly.

Our findings also demonstrated that high-fat and high-fructose intake significantly induced hepatic *FAS* mRNA expression compared with the normal and sacha inchi oil-supplemented groups (P = 0.0017). The HFHF group did not differ significantly from the S1 or S3 groups (Figure 6B). Although all supplemented groups showed lower *FAS* mRNA expressions, the S2 group exhibited the lowest; nevertheless, the differences among the S1, S2, and S3 groups were not statistically significant (Figure 6B).

We further examined hepatic *DGAT2* mRNA expression, a key enzyme that catalyzes the final reaction of triglyceride synthesis. Our results indicated that excessive intake of dietary fat and fructose induced hepatic *DGAT2* mRNA expression compared with the normal group (P = 0.03). However, in this study, sacha inchi oil supplementation did not significantly affect the hepatic *DGAT2* mRNA expression (Figure 7A). Although sacha inchi oil supplementation did not alter the *DGAT2* mRNA expression, we further assessed the *DGAT2* protein levels. Rats receiving a high-fat diet along with fructose-containing drinking water had significantly higher *DGAT2* protein levels compared to the normal group and the HFHF supplemented with sacha inchi oil groups (P < 0.0001).

To further investigate the regulatory relationship between lipogenic genes, correlation analysis was performed between the transcription factors and their downstream target genes (Figure 8).

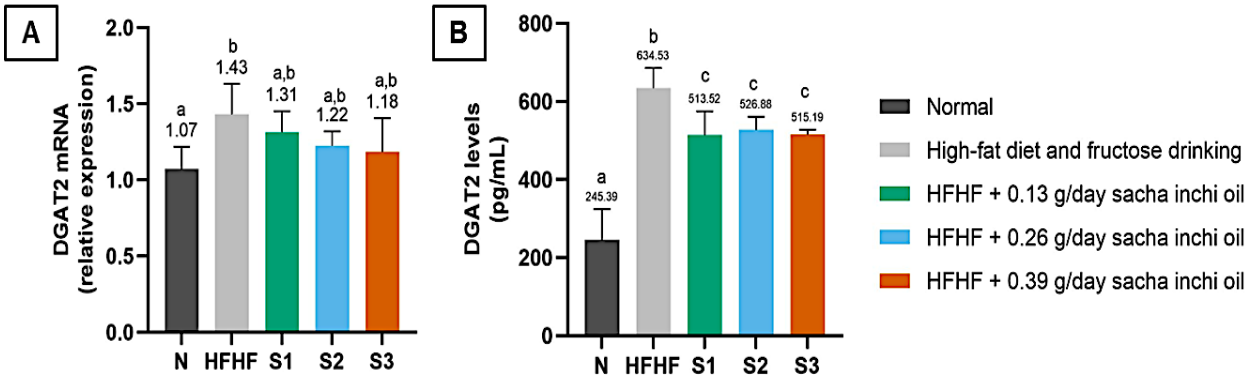


Figure 7. Effects of sacha inchi oil supplementation on hepatic mRNA expression of *DGAT2* (A); and protein levels of *DGAT2* (B). Values are presented as mean ± standard deviation (SD) of five rats. N: normal control; HFHF: high-fat and fructose water; S1: HFHF + 0.13 g/day of sacha inchi oil; S2: HFHF + 0.26 g/day of sacha inchi oil; S3: HFHF + 0.39 g/day of sacha inchi oil. Statistical analysis was performed using one-way ANOVA followed by Tukey's post-hoc test. Groups marked with different superscript letters are significantly different, while those sharing the same letter do not differ significantly.

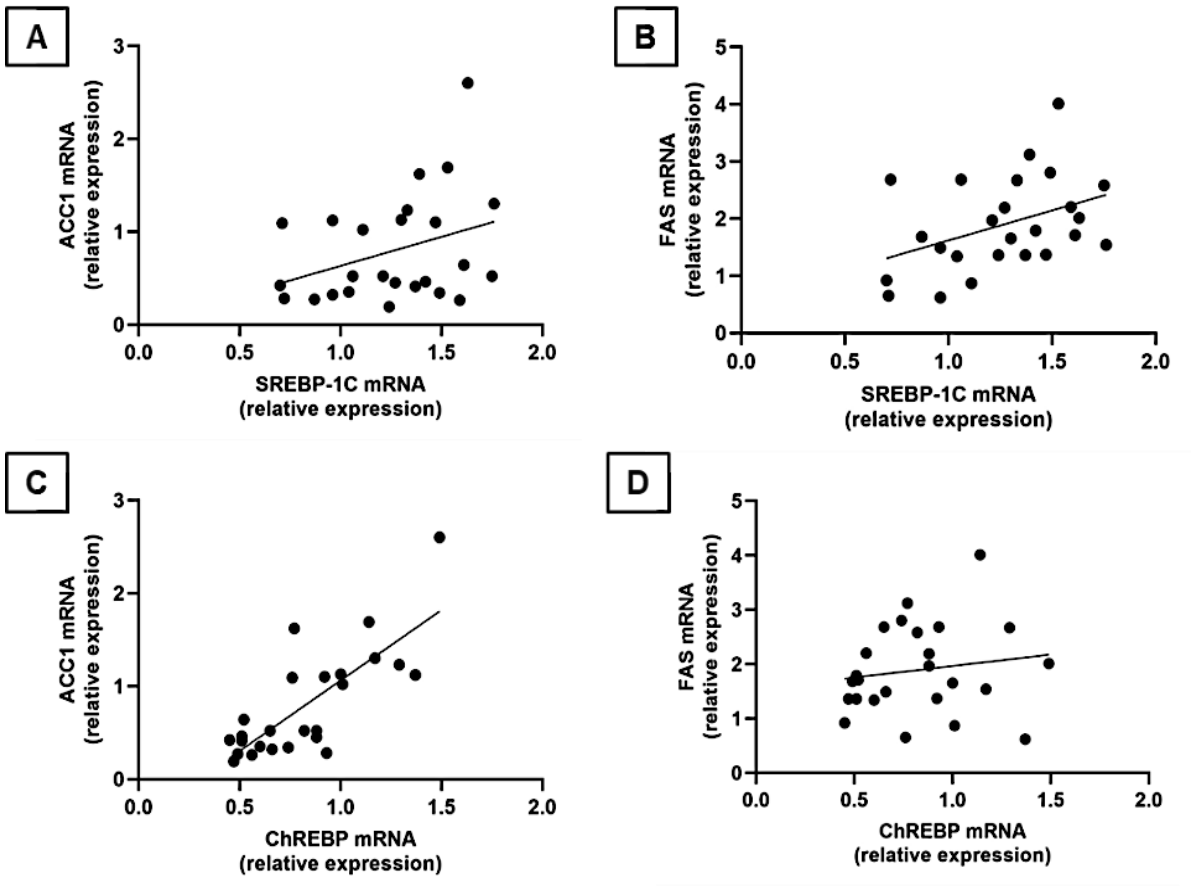


Figure 8. Relationship between *SREBP-1c* mRNA and *ACC1* mRNA expression (A); relationship between *SREBP-1c* mRNA and *FAS* mRNA expression (B); relationship between *ChREBP* mRNA and *ACC1* mRNA expression (C); and relationship between *ChREBP* mRNA and *FAS* mRNA expression (D). Correlation analysis was performed using Pearson's correlation test. (A) $r = 0.340$; $P = 0.09$; (B) $r = 0.408$; $P = 0.042$; (C) $r = 0.770$; $P < 0.0001$; (D) $r = 0.153$; $P = 0.463$).

Our study showed that *SREBP-1c* and *ACC1* mRNA expressions displayed a weak positive correlation (r = 0.340; P = 0.09; Figure 8A), whereas a moderate and statistically significant positive correlation was observed between *SREBP-1c* and *FAS* mRNA (r = 0.408; P = 0.042, Figure 8B). Similarly, *ChREBP* and *ACC1* mRNA expression demonstrated a strong and statistically significant positive correlation (r = 0.770; P<0.0001; Figure 8C), whereas a weak positive relationship was detected between *ChREBP* and *FAS* mRNA expression (r = 0.153; P = 0.463; Figure 8D). The present findings suggest that *FAS* mRNA expression is more closely associated with *SREBP-1c*, whereas *ACC1* mRNA expression is strongly linked to *ChREBP*. This might indicate differential transcriptional regulation of hepatic lipogenic genes under high-fat and high-fructose intake.

DISCUSSION

In the current study, the effect of sacha inchi oil supplementation on triglyceride synthesis in rats receiving a high-fat diet and drinking fructose-containing water was evaluated. Our results showed that high-fat and high-fructose intake induced hepatic triglyceride accumulation, as indicated by higher hepatic triglyceride levels in the HFHF group. The elevated hepatic triglyceride levels observed in the HFHF group were accompanied by increased liver weight, suggesting excessive lipid deposition within hepatocytes [28]. As previously reported, elevated hepatic triglyceride levels reflect excessive lipid deposition within hepatocytes, whereas an increase in liver weight often correlates with the severity of steatosis [29-30].

Our results demonstrated a strong positive correlation between dietary fat intake and hepatic triglyceride levels, whereas dietary sugar intake showed a moderate positive correlation. These results suggest that the dietary fat intake may have a more pronounced impact on hepatic triglyceride levels than dietary sugar intake. Several studies have reported that excessive fat intake contributes to increased hepatic triglyceride levels [31-32]. Excessive fat consumption has been shown to increase hepatic triglyceride accumulation by elevating fatty acid flux and promoting lipogenic pathways, while reducing the assembly and secretion of very-low-density lipoprotein (VLDL) triglycerides [33-35]. Although the relationship between dietary sugar intake and hepatic triglyceride levels was moderate, it still represents a meaningful contribution to hepatic triglyceride accumulation. Excessive consumption of dietary sugar, particularly fructose, is known to stimulate the DNL pathway by upregulating transcription factors such as *SREBP-1c* and *ChREBP* genes [4-5].

Despite exposure to a high-fat and fructose-containing drinking water, rats supplemented with sacha inchi oil showed lower hepatic triglyceride levels compared with the HFHF group. This suggests that PUFAs contained in sacha inchi oil may exert protective effects against the hepatic triglyceride accumulation. These findings indicate that supplementation with sacha inchi oil may attenuate hepatic triglyceride accumulation, possibly by modulating lipogenic pathways.

Histological analysis further supported these biochemical findings. Previous studies have reported that a combination of dietary fat and fructose can induce mild or simple hepatic steatosis [36]. In contrast, the livers of sacha inchi oil-supplemented groups showed fewer lipid droplets, consistent with previous findings by Samrit et al [37]. These findings suggest that sacha inchi oil supplementation attenuated hepatic lipid accumulation and helped preserve normal liver architecture under high-fat and high-fructose intake. Furthermore, to elucidate the mechanism underlying these protective effects, we next analyzed mRNA expression of several genes involved in triglyceride synthesis.

Excessive dietary fat and fructose intake are known to stimulate hepatic *SREBP-1c* mRNA expression [38]. In the present study, although *SREBP-1c* expression was not significantly different between groups, the HFHF group showed higher expression than both the normal and

sacha inchi oil-supplemented groups. This finding suggests that sacha inchi oil supplementation may not directly affect its transcription but could influence the activity through other mechanisms. Previous studies have demonstrated that PUFAs inhibit *SREBP-1c* at the post-translational level. This occurs by inhibiting the proteolytic cascade that converts precursor *SREBP-1c* into its mature form, thereby reducing mature *SREBP-1c* levels [39]. Therefore, the lack of changes in *SREBP-1c* mRNA expression observed in this study may be due to the post-translational regulation, whereby PUFA-rich sacha inchi oil reduces the amount of mature *SREBP-1c* without altering the mRNA expression. Unfortunately, *SREBP-1c* protein expression was not analyzed in this study; thus, further investigation is required to confirm this mechanism.

In contrast to *SREBP-1c* mRNA expression, our results demonstrated that *ChREBP* mRNA expression differed significantly among the groups. Excessive dietary fat and fructose intake induced the hepatic *ChREBP* mRNA expression compared with sacha inchi oil-supplemented groups. The upregulation of *ChREBP* mRNA may reflect enhanced carbohydrate-responsive lipogenesis, as *ChREBP* is a transcription factor that mediates glucose- and fructose-induced activation of lipogenic enzymes such as *ACC1* and *FAS* [40]. Consistent with this, a moderate positive correlation was observed between dietary sugar intake with *ChREBP* mRNA expression, supporting the notion that excessive dietary sugar intake may induce *ChREBP* mRNA expression [41]. This response may arise from sugar-derived metabolites, which act as activators of *ChREBP* transcriptional activity in the liver [42]. Furthermore, analysis of correlation demonstrated that *ChREBP* mRNA expression was strongly correlated with *ACC1* mRNA expression but weakly correlated with *FAS* mRNA expression, suggesting that *ACC1* mRNA expression is predominantly regulated by *ChREBP*, whereas *FAS* mRNA expression may be more closely associated with *SREBP-1c* [40-43].

Suppression of *ChREBP* mRNA expression may lead to decreased expression of its downstream targets, *ACC1* and *FAS*, which play a role in triglyceride synthesis [44]. This downregulation may contribute to the reduced hepatic triglyceride accumulation observed in sacha inchi oil-supplemented groups, likely mediated through the action of PUFAS. PUFAs have been reported to promote *ChREBP* mRNA decay and inhibit the translocation of *ChREBP* from the cytosol into the nucleus, thereby suppressing the expression of downstream lipogenic genes [45].

Consistent with these reports, our findings showed that *ACC1* and *FAS* mRNA expressions in sacha inchi oil-supplemented groups were lower than in the HFHF group. Although no significant differences were found in *SREBP-1c* mRNA expression among the groups, the lower *ACC1* and *FAS* mRNA expression may be attributed to reduced maturation *SREBP-1c* protein due to inhibition of its proteolytic processing, leading to diminished transcriptional activation of target genes [39,46-47]. The observed downregulation of transcription factors and their downstream lipogenic targets in the sacha inchi oil-supplemented groups may reflect a reduced lipogenic potential at the enzymatic level. This transcriptional downregulation could consequently influence downstream pathways involved in fatty acid synthesis, including those contributing to malonyl-CoA and palmitate generation, thereby potentially limiting substrate availability for triglyceride formation [48-50]. This reduction in substrate availability could influence *DGAT2* activity, as *DGAT2* catalyzes the final step of triglyceride synthesis. In our study, sacha inchi oil supplementation did not affect *DGAT2* mRNA expression. This observation aligns with prior reports demonstrating that PUFAs supplementation did not alter *DGAT2* mRNA expression [51]. However, in this study, hepatic *DGAT2* protein levels were markedly lower in the sacha inchi oil-supplemented groups compared with the HFHF group. A possible explanation for this discrepancy is enhanced

degradation of *DGAT2* in response to reduced substrate availability, since *DGAT2* stability has been reported to be regulated by lipid intermediate such as fatty acids and diacylglycerol [52]. Additionally, omega-3 PUFAs contained sacha inchi oil may contribute to the reduction of *DGAT2* levels through the ubiquitin-proteasome system, similar to the reported degradation of *FAS* by omega-3 PUFAs [53]. This mechanism may partly explain the lower *DGAT2* levels observed in sacha inchi oil-supplemented groups; however, further investigation is warranted.

In the present study, our findings suggest that sacha inchi oil supplementation may suppress the hepatic *ChREBP*, *ACC1*, and *FAS* mRNA expression, along with a reduction in *DGAT2* protein levels. These alterations may act synergistically to attenuate triglyceride synthesis and accumulation. These effects appear to be mediated by the PUFAs contained in sacha inchi oil, which regulate the triglyceride synthesis pathway. These findings provide additional support to the current evidence and highlight the potential of sacha inchi oil as a functional food component that may help promote metabolic health.

Considering these coordinated regulatory effects on hepatic lipogenic pathways, the observed metabolic responses may reflect source-specific properties of sacha inchi oil that contribute to its metabolic effects beyond the general biological actions of PUFAs. Although the lipid-regulatory effects observed in the present study are broadly consistent with those previously reported for other PUFA-rich dietary oils such as fish oil, flaxseed oil, and perilla oil, the biological relevance of sacha inchi oil may be partly influenced by factors beyond its PUFA content. Unlike marine-derived oils, sacha inchi oil represents a sustainable plant-based source of omega-3 fatty acids, avoiding issues related to marine resource depletion and contaminant exposure [54]. Sacha inchi oil provides a plant-based lipid characterized by a high α-linolenic acid (ALA) content, along with additional bioactive compounds, including tocopherols, polyphenols, and phytosterols, which may exert synergistic effects [55].

Within the framework of functional food development, the present study supports the preclinical mechanistic stage by providing *in vivo* evidence for the metabolic regulatory effects of sacha inchi oil as a functional dietary oil [56]. The PUFA-rich composition of sacha inchi oil may exert functional relevance through regulatory pathways involved in triglyceride synthesis, particularly by suppressing *ChREBP*-mediated downstream targets such as *ACC1* and *FAS*. The present findings indicate that low-dose sacha inchi oil supplementation may be sufficient to suppress lipogenic gene expression under high-fat and high-fructose dietary conditions. This finding is aligned with the previous report showing that low doses of PUFAs may suppress the expression of lipogenic enzyme mRNAs [57].

Although the high-dose group showed a trend toward lower lipogenic gene expression compared with the HFHF group, all sacha inchi-oil supplemented groups exhibited relatively lower expression than the HFHF group. However, no statistically significant differences were observed among the supplemented groups, suggesting that even the lowest dose was sufficient to reduce the expression of *ChREBP*, *ACC1*, and *FAS* mRNA, with the moderate dose showing the lowest mean mRNA expression. Within the tested dose range, increasing the dose did not result in additional reductions in mRNA expression among the supplemented groups. A similar pattern was observed for *DGAT2* protein levels, which were lower in the sacha inchi-oil supplemented groups than the HFHF group, without significant differences among the doses. Collectively, these findings provide biological plausibility for the application of sacha inchi oil as a functional dietary component within a dietary strategy to support the regulation of genes involved in hepatic triglyceride synthesis, which may be relevant to the attenuation of hepatic triglyceride accumulation.

From a translational perspective, these findings suggest that sacha inchi oil supplementation may be

functionally relevant as a dietary lipid source that can regulate hepatic triglyceride synthesis under high-fat and high-fructose dietary conditions. The observed suppression of *ChREBP*-mediated lipogenic gene targets, along with reduced *DGAT2* protein levels, suggests an alteration in hepatic lipid metabolic regulation that may limit triglyceride synthesis and accumulation. Within the context of functional food development, such regulatory effects may support the incorporation of PUFA-rich plant-based oils into a nutritional strategy to regulate hepatic lipid metabolism under diet-induced lipogenic conditions. Although further studies are required to confirm the applicability of these findings in humans, the present results provide mechanistic support for the role of sacha inchi oil in dietary approaches targeting metabolic disturbances associated with excessive fat and sugar intake. Further studies could compare the effects of sacha inchi oil with PUFAs from other dietary sources, investigate upstream signaling pathways such as (AMP-activated protein kinase) *AMPK* and insulin, and perform additional protein-level mechanistic validation to confirm and extend the current findings.

CONCLUSION

In conclusion, sacha inchi oil supplementation exerts a protective effect against hepatic triglyceride accumulation by regulating key genes involved in triglyceride synthesis. Specifically, sacha inchi oil downregulated *ChREBP*, *ACC1*, and *FAS* mRNA expression and reduced *DGAT2* protein levels.

List of Abbreviations: PUFAs, Polyunsaturated fatty acids; *SREBP-1c*, Sterol regulatory element binding protein 1c; *ChRE,* Carbohydrate response element binding protein; *ACC1*, Acetyl-CoA carboxylase-1; *FAS*, Fatty acid synthase; *DGAT2*, Diacylglycerol acyltransferase 2; DNL, De novo lipogenesis; AMPK, AMP-activated protein kinase

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