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Solanum lycocarpum St. Hill. fibrous fraction intake can contribute to counteract diet-induced obesity co-morbidities

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ABSTRACT

Solanum lycocarpum St. Hill is a Brazilian Cerrado fruit popularly known as wolf-apple, lobeira or fruta-do-lobo. The proximate composition of fruta-do-lobo showed that the flour prepared from the fruit's pulp has 23g/100g of fiber, which is considered rich in fiber. Data from the literature suggest that dietary fiber intake can positively decrease body weight gain and its adverse side effects through physiological effects and metabolism modulation. From this perspective, this study aimed to analyze the nutritional effects of the fibrous fraction (FF) obtained after extraction of resistant starch from fruta-do-lobo flour in mice with diet-induced obesity. Swiss mice (n = 22) were randomized into three different groups according to the diet offered: control (AIN 93-G diet), HF (high-fat diet – 4% vegetable oil; 31% lard), and FF (HF diet + 3% fibrous fraction of fruta-do-lobo). It was observed that consuming a diet containing the fibrous fraction (FF) promoted histological changes compared to the obese control group (HF) since the liver weight was lower and there was an improvement in hepatic steatosis. Even so, some biological results were observed in the FF group with a profile more similar to the lean control group than the HF group, namely epididymal tissue weight, liver weight, and kITT. It is important to point out that many variables, such as the duration of the protocol and the doses of supplemented dietary fiber, may be associated with the results observed in the present study. However, there is some evidence that the fibrous fraction of fruta-do-lobo can be used as an ingredient to supplement dietary fiber intake and contribute to health promotion.

1. Introduction

Obesity is a chronic non-communicable disease (CNCD), and its etiology is multifactorial and may be related to genetic, environmental, socioeconomic, endocrine, and metabolic disorders (Gonzalez-Chávez et al., 2018). Also, eating habits are directly associated with the development of obesity, with the imbalance between food consumption and energy expenditure resulting in an excessive accumulation of adipose tissue, which can cause damage to health. It is considered one of the main causes of economic loss, death, and suffering (Rodrick & Deborah, 2016). In addition, the abnormal accumulation of adipocytes in the liver and skeletal muscle stimulates pathways that interfere with insulin signaling, causing decreased muscle glucose uptake and decreased hepatic glycogen synthesis, which may lead to insulin resistance and the development of type 2 diabetes mellitus (T2DM), heart disease, hypertension, stroke, and cancer (Blüher, 2019; Samuel & Shulman, 2016).

Insulin resistance (IR) is characterized as an inadequate metabolic response of circulating insulin levels in the body. Before this metabolic alteration, as a compensating mechanism, pancreatic β-cells increase insulin production and releasement, causing hyperinsulinemia to try to maintain glycemic homeostasis (Yaribeygi, Farrokhi, Butler, & Sahebkar, 2019). However, obesity and its metabolic changes could cause overload and failure of pancreatic β-cells, causing damage to them and contributing to the development of glucose intolerance and,

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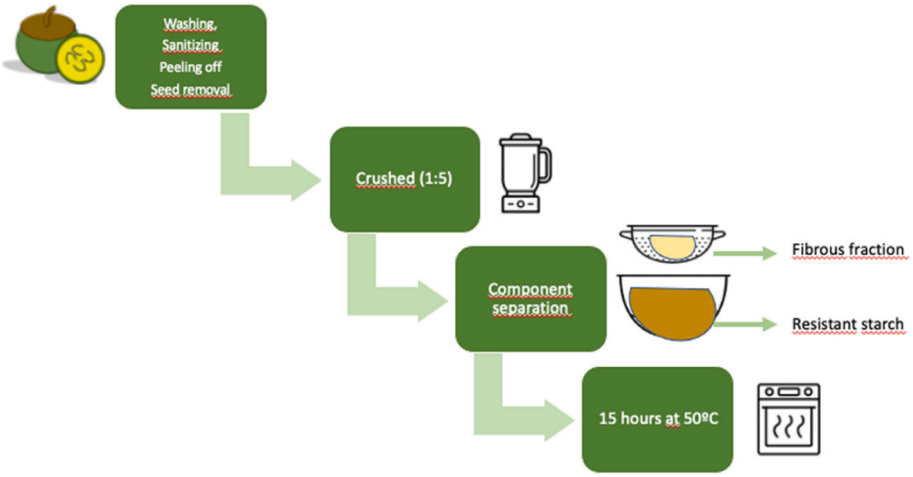

Fig. 1. Schematic illustrating obtaining the fibrous fraction (FF) from fruta-do-lobo. Adapted from Clerici et al. (2011).

Table 1
Proximate composition of fruta-do-lobo fibrous fraction (FF) powder.

Components	Content (g/100g)	SD
Moisture (Instituto Adolfo Lutz, 2008)	0.35	0.07
Lipids (Bligh, E.G. and Dyer, 1959)	0.18	0.02
Ash (AOAC & Helrich, 1990)	1.69	0.10
Protein (AOAC & Helrich, 1990)	3.76	0.06
Carbohydrates*	94.02	–
Total fibers	47.94	0.27
Insoluble fibers	47.38	0.01
Soluble fibers	0.56	0.01

Data are expressed as a means ± SD. The assays were done in triplicate. *Value calculated by difference.

subsequently, T2DM (Aguayo-Mazzucato et al., 2017; Czech, 2017).

The bad association between obesity and IR is related to abnormal secretion of pro-inflammatory cytokines that impair insulin signaling (Ortega-Loubon, Fernández-Molina, Singh, & Correa, 2019). For example, the TNF-α/JNK pathway stimulates IR by phosphorylation of serine present in insulin receptor substrate 1 (IRS-1), making intracellular signaling of this hormone difficult, and IL-1β causes toxicity in pancreatic β-cells, generating a progressive loss of their function and later cell death (Akash, Rehman, & Liaqat, 2018). In addition, in obesity, the macrophages of the white fat deposit produce reactive oxygen species (ROS) and reactive nitrogen species (RNS), increasing the levels of free radicals, unbalancing the oxidative and antioxidant system, with consequent oxidation of biomolecules, loss of biological function, and damage to the structural tissue that triggers the pro-inflammatory state (Rendra et al., 2019).

Among the modifiable variables associated with the development of obesity, we can highlight food intake. The low fiber intake has gained attention since ingestion of this type of carbohydrate is essential for some health benefits and prevents the development of many CNCDs. Among these beneficial effects, literature data suggest that fibers can exert anti-inflammatory activity, hypoglycemic, satiety since lower concentrations of inflammatory markers were observed due to their consumption (Veronese et al., 2018a). Therefore, consuming a diet with adequate amounts of fiber has been shown to be a convincing alternative for the control, maintenance, and prevention of inflammatory diseases (Pituch-Zdanowska, Banaszkiewicz, & Albrecht, 2015).

Solanum lycocarpum St. Hill is a Brazilian fruit widely found in the Cerrado biome, popularly known as the "wolf apple" or "fruta-do-lobo" because it makes up about 50% of the maned wolf's diet (Clerici et al., 2011; Farina, Piassi, Moysés, Bazzolli, Bissoli, et al., 2010; Perez, Franca, Daldegan, & Duarte, 2006). In folk medicine, it is used as a sedative in treating epilepsy, diabetes, obesity, reduction of cholesterol levels, and renal and abdominal pain (Morais et al., 2020). Clerici et al. (2011), by a study of the physical-chemical composition of fruta-do-lobo, demonstrated that the flour prepared with the pulp of the fruit, without the peel and seeds, has 23g/100g of fibers.

In the past two decades, the incidence of obesity has increased worldwide, and the use of foods capable of providing a protective effect, in addition to nourishing, is being used as a strategy for the prevention and treatment of clinical symptoms of chronic diseases, such as diabetes (Ballard et al., 2020; Loubet Fil et al., 2022; Nascimento et al., 2021; Tijani et al., 2022). From this perspective, this study aimed to analyze the protective effects of the fibrous fraction of fruta-do-lobo obtained after starch extraction on a diet-induced obesity model.

2. Materials and methods

2.1. Fibrous fraction of fruta-do-lobo

Fruta-do-lobo was collected in June 2017 in Carmo do Rio Claro (S20.555.209; W46.145.379), located in the state of Minas Gerais, Brazil. Specimens were identified by Ingrid Koch PhD and Leandro Giacomini PhD, and a voucher specimen was deposited at UNICAMP herbarium (UEC 197248). The access to Brazilian genetic heritage was registered at the Ministry of the Environment via SISGEN (protocol ADBCB71). The fibrous fraction of fruta-do-lobo fruit used in this study comes from all the remaining fruit left after the extraction of resistant starch, according to the methodology described by Pereira et al. (2019) (Fig. 1).

The proximate composition of the fibrous fraction of the fruta-do-lobo was performed by means of the quantification of moisture by the method described by Instituto Adolfo Lutz (2008); the quantification of ash by AOAC and Helrich (1990); lipids by Bligh and Dyer (1959); proteins by Kjeldahl (1883) and total fibers by enzymatic method AOAC official (Method 991.43) (Table 1). The available carbohydrate concentration was calculated according to the difference between 100 and the total percentage of protein, fat, moisture and ash content, according to the following equation:

$$\text{Available Carbohydrate (\%)} = 100 - (\text{protein} + \text{lipids} + \text{ash} + \text{fibers} + \text{moisture})$$

2.2. In vivo experimental protocol

This study was carried out following the Brazilian National Council

Table 2
Diets composition (g/kg of diet).

Ingredients (g)	CONTROL	HF	FF
Casein	140.00	145.00	145.00
Corn starch	458.00	268.00	268.00
Maltodextrin	132.00	77.00	77.00
Sucrose	100.00	58.50	58.50
Soybean oil	70.00	41.00	41.00
Cellulose	50.00	50.00	50.00
Mineral mix	35.00	35.00	35.00
Vitamin mix	10.00	10.00	10.00
L-cysteine	3.00	3.00	3.00
Choline bitartrate	2.50	2.50	2.50
Tert-Butylhydroquinone (TBHQ)	0.014	0.014	0.014
Lard	–	310.00	310.00
Fruta-do-lobo fibrous fraction	–	–	30.00
Total weight	1000	1000	1030
Total energy $_{cal}$	3950	5353	5473

Diets were prepared according to the American Institute of Nutrition for AIN 93-G with modified protein content to 12% (Reeves, 1997). Control = normal diet (AIN-93G); HF = high-fat control diet; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction.

for Animal Experimentation Control (CONCEA), and it was approved by the Animal Research and Ethics Committee of the Universidade Estadual de Campinas (Brazil) (protocol 5083-1/2018).

Twenty-two Swiss 28-day-old mice started acclimating in individual cages with water and standard commercial chow (LABINA-PURINA) under the free access system for one week. After this period, the animals were randomized into two experimental groups, lean (control, n = 6) and obese (n = 1), where the control group (C) received the AIN 93-G diet, and the obesity group received the high-fat (HF) diet for four weeks for obesity induction (Table 2) (Reeves, 1997). Subsequently, the obesity group was randomized again into two groups, in which the obese (n = 6) maintained the intake of an HF diet, and the other group of animals (n = 8) started to receive an HF diet supplemented with 3% of the fruta-do-lobo fibrous fraction (FF) for more 6 weeks (Fig. 2). In addition, the environment had controlled temperature and air humidity, in a range of 22 ± 1 °C and 60–70%, respectively, in a 12-h light/dark cycle, throughout the experimental period. The animals' dietary intake was monitored every two days, and the weight was verified once a week during the experimental period.

After 6 h of fasting, the animals were anesthetized with ketamine chloride 300 mg/kg and xylazine chloride 30 mg/kg for blood collection in tubes containing separator gel. The tubes were centrifuged at 3500×*g* for 15 min to separate the serum, which was stored at −80 °C until analysis. After exsanguination under anesthesia, the liver, epididymal adipose tissue, spleen, and kidneys were removed, cleaned with saline solution, weighed, and, subsequently, frozen in liquid nitrogen and stored in an ultra-freezer at −80 °C for future analysis. Cholesterol and triglycerides were evaluated in the serum using commercial colorimetric kits (LabtestDiagnóstica S.A., Lagoa Santa, MG, Brazil).

2.3. Insulin resistance assessment

The oral glucose tolerance test (OGTT) was performed on the 9th week after 6h fasting. First, basal glucose (time 0) was measured from the tail vein, then a D-glucose solution (2 g/kg) was administered by gavage to the mice, and blood glucose was monitored after 0, 3, 6, 9, 12, 15, 30 using glucometer and respective test strips (G-Tech – Free lite, Infopia Co, South Korea).

The insulin tolerance test (ITT) was performed on the 10th week under fasting conditions (2 h). The baseline blood glucose level was measured via the tail vein, then a 0.9% saline solution (w/v) containing 0.50 units/kg of insulin (NovolinR, Novo Nordisk Bagsvaerd, Denmark) was injected intraperitoneally (i.p.), which was monitored after 3, 6, 9, 12, 15, and 30 min, as described above. The plasma glucose half-time (T½) was calculated from the slope of the least square analysis considering the linear decay range of the plasma glucose concentrations after insulin injection. The constant of glucose decay (kITT) was calculated using the formula 0,693/T½.

2.4. Liver analysis

Lipid peroxidation was quantified in liver tissue by thiobarbituric acid reactive substances (TBARS) according to the methodology described by Cazarin et al. (2015). The results are expressed as nmol MDA equivalents/mg tissue. Liver samples were macerated in liquid nitrogen, and 10 mg/mL was sonicated in acetate buffer (pH 3.5) on ice. The samples were mixed with 8.1% sodium dodecyl sulfate (SDS) plus a working reagent (TBA, 20% acetic acid, and 5% sodium hydroxide). After heating at 95 °C for 60 min, the samples were maintained in an ice bath for 10 min and centrifuged at 10,000×*g* for 10 min. The supernatant was read at 532 nm using a clear 96-well microplate. The results are expressed as nmol MDA equivalents/mg tissue.

Liver fatty acids were extracted using the Folch methodology for fatty acids methyl ester (FAME) identification and quantification (Folch et al., 1957). FAMEs were analyzed in a Shimadzu gas chromatograph, model GC-2014 (Shimadzu, Kyoto, Japan), coupled to a flame ionization detector (FID), equipped with a fused silica capillary column with SupelcoWAX modified polyethylene glycol stationary phase (30 m × 0.25 mm di x 0.25 μm), under the following chromatographic conditions: injector at 250 °C operating in split mode 1:10 per 1.0 min; 1.0 mL/min helium carrier gas; oven temperature program starting at 150 °C (3 min); followed by an increment of 5 °C/min until the temperature of 205 °C (10 min); detector temperature of 250 °C. A standard solution of saturated and unsaturated fatty acid methyl esters GLC-85 (Nu-check Prep. Inc., USA), and saturated fatty acid methyl esters, C4 – C24 (Sigma-Aldrich, USA), were used to identify the compounds in the samples. Also, an internal standard was added to the samples before the analysis (Visentainer, 2012).

Also, another portion of the colon was collected and stored in RNAlater® (Sigma-Aldrich, St. Louis, MO, USA) for further analysis of

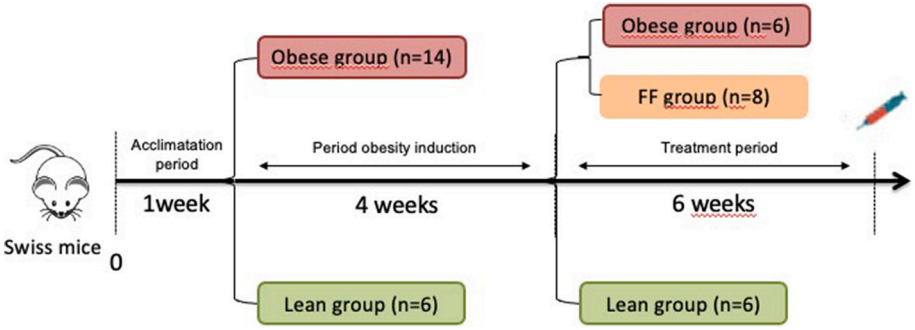

Fig. 2. Schematic representation of the experimental protocol of interventions. Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction.

Table 3
Effects of fruta-do-lobo fibrous fraction on food intake, weight body, and different tissues.

	CONTROL	HF	FF
Epididymal tissue (mg/kg bw)	38.8 ± 0.60[b]	67.7 ± 0.78[a]	58.0 ± 0.71[ab]
Liver (mg/kg bw)	45.9 ± 0.14[ab]	51.2 ± 0.33[a]	45.5 ± 0.24[b]
Hepatic lipid content (mg/100g)	0.7 ± 0.06	1.3 ± 0.25	1.0 ± 0.20
Kidney (mg/kg bw)	7.8 ± 0.05	6.7 ± 0.03	6.9 ± 0.02
Spleen (mg/kg bw)	3.2 ± 0.04	2.3 ± 0.01	2.8 ± 0.02
Cecum (mg/kg bw)	6.6 ± 0.03[a]	4.2 ± 0.07[b]	6.3 ± 0.03[a]
Excreted feces (g)	2 ± 0.12[a]	1.75 ± 0.11[ab]	1.8 ± 0.09[b]
Body weight gain (g)	13.4 ± 6.56	21.5 ± 6.02	14.4 ± 6.63
Feed intake (mg/kg bw)	5.1 ± 1.01	4.4 ± 0.82	4.3 ± 1.02
Energy intake$_{cal}$	19.9 ± 3.94	23.2 ± 4.34	23.1 ± 5.52

Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction). Parametric data (ANOVA and Tukey's tests) were expressed as the mean ± SD (standard deviation). Different letters indicate statistical significance ($p < 0.05$). Epididymal tissue $p = 0.038$ (Control x FF), Liver $p = 0.031$ (HF x FF), Cecum $p = 0.045$ (Control x HF) e $p = 0.049$ (HF x FF). Excreted feces $p = 0.023$ (Control x RE). Body weight gain $p = 0.016$ (HF x FF).

the gene expression of the tight junction proteins occlusion zone-1 (ZO-1,Rn.PT.58.37382645, Integrated DNA Technologies, Coralville, Iowa, EUA) and tumor necrosis factor-alpha (TNF-α,Rn.PT.58.11142874, Integrated DNA Technologies), by quantitative polymerase chain reaction analysis in real-time (RT-PCR) (Illumina, CA, USA). Additionally, glyceraldehyde-3-phosphate dehydrogenase (GAPDH, PN4352338E, Thermo Fisher Scientific) was used as a house keeping gene.

2.5. pH and SCFA analysis

Sample preparation followed the protocol described by Zhao, Nyman, and Jönsson (2006), with minor modifications described below. Approximately 50 mg of stool sample was weighed into 1600 µL amber vials. The samples were diluted with 500 µL of MilliQ water, vortexed for 30 s, and their pH adjusted to 2 by the addition of 54 µL of 3M HCl. The pH of the samples was measured with the aid of pH measuring tapes. Afterwards, the samples were centrifuged at 3000×*g* for 60 min. Ninety-six microliters of the supernatant was collected and transferred to a new vial with insert, receiving the addition of 4 µL of the internal standard 2-ethyl-butyric acid at a concentration of 1.59 mM. Once prepared, the samples (1 µL) were injected into a gas chromatograph coupled to a flame ionization detector (GC-FID) model Ai20, in a GC-FID Shimadzu, model GC-2010 plus, equipped with a capillary column of Nukol fused silica (30 m × 0.25 mm, i.d. x 0.25 µm), under the following chromatographic conditions: inlet at 200 °C operating in 1:5 split mode for 1.0 min; helium carrier gas at 1 mL/min; oven temperature ramp starting at 100 °C, increasing by 8 °C/min to 190 °C, remaining at this temperature for 3.25 min; detector at 200 °C. The identification of analytes was performed by co-injection of authentic standards. All chromatographic analyses were performed in triplicate. To quantify the area of the analytes of interest and express it in terms of concentration, the internal standard method was used, as described by Li, Yu, Wang, and Zhao (2016) and Zhao et al. (2006).

3. Statistical analysis

Data are represented in means and standard deviation (SD). In addition, data normality was evaluated by the Shapiro–Wilk test, and the comparisons between the FF group vs. Control and FF group vs. HF were made using the student t-test. The statistical analyses were performed in GraphPad Prism (GraphPad Software, Boston, MA, USA), and the significance level was set to $p < 0.05$.

4. Results and discussion

Epidemiological evidence has suggested that a higher dietary fiber intake is associated with a reduced risk of several chronic diseases, including obesity, T2DM, cardiovascular diseases (CVDs), and cancer (Dreher, 2018; Noce, Romani, & Bernini, 2021; Rezende, Lima, & Naves, 2021; Soliman, 2019). The recommended daily intake of dietary fiber for adults, according to Dietary Reference Intakes, ranges from 21 to 38

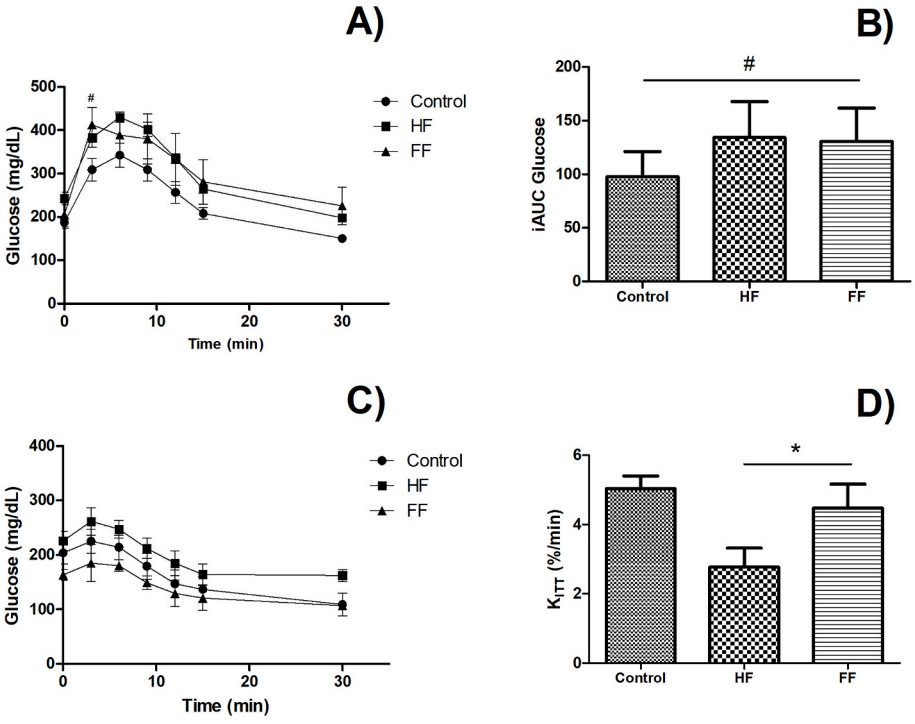

Fig. 3. Effects of fruta-do-lobo fibrous fraction administration on glucose homeostasis and insulin sensitivity. (A–B) oral glucose tolerance test, (*C*–D) insulin tolerance test. Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction. Data are represented in means and standard deviation (SD). In addition, data normality was evaluated by the Shapiro–Wilk test, and the comparisons between the FF group vs. Control and FF group vs. HF were made using the Student t-test. The statistical analyses were performed in GraphPad Prism (GraphPad Software, Boston, MA, USA), and the significance level was set to $p < 0.05$. # means that there is a statistical difference between the Control x FF and * means that there is a statistical difference between the HF x FF.

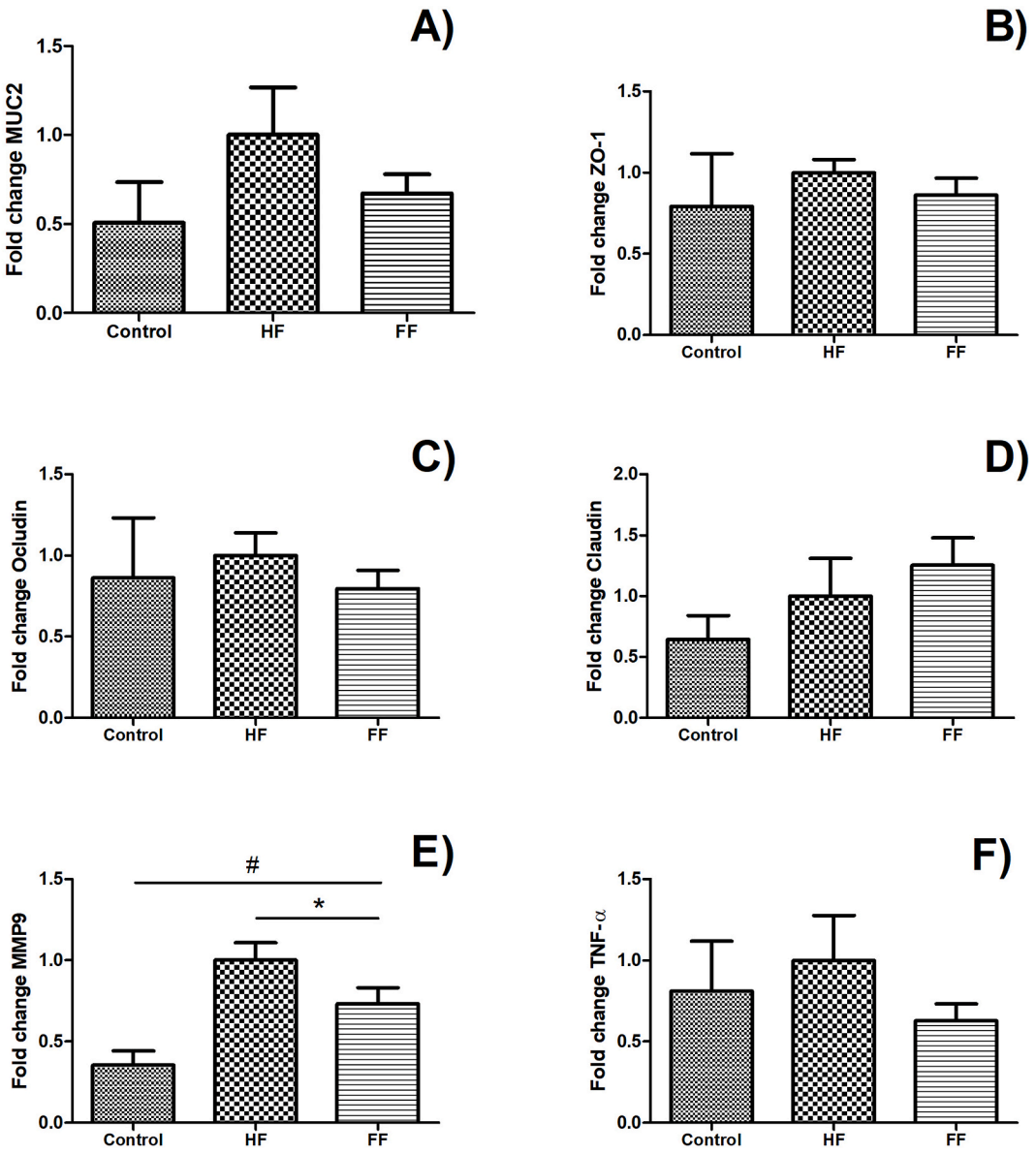

Fig. 4. Effects of fruta-do-lobo fibrous fraction administration on mucin-2(A), zonula occludens-1 (B), occludin (C), claudin-2 (D), metalloproteinase-9 matrix enzyme (E), and tumor necrose factor-α (F). Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction. Data are represented in means and standard deviation (SD). In addition, data normality was evaluated by the Shapiro–Wilk test, and the comparisons between the FF group vs. Control and FF group vs. HF were made using the Student t-test. The statistical analyses were performed in GraphPad Prism (GraphPad Software, Boston, MA, USA), and the significance level was set to $p < 0.05$. # means there is statistical difference between Control x FF and * means there is statistical difference between HF x FF.

g (Soliman, 2019). The last Brazilian food intake census, in 2020, showed that the population consumed around 15.6 g/day; in Spain, consumption was 12.5 g/day in 2017, and in the USA, 15 g/day in 2009/10 (González-Rodríguez et al., 2017; Hoy & Goldman, 2014). The fibrous fraction of fruta-do-lobo obtained before resistant starch extraction has 47 g of dietary fiber per 100 g, 47.38% represented by insoluble fibers. There is no data in the literature about the characterization and uses of this fibrous fraction; however, compared to other fruit residues, it is evident that fruta-do-lobo fibrous fraction has more fibers than pineapple fruit residue (19.76 g/100 g), apple pomace (30 g/100 g), and jabuticaba peel (33.77 g/100 g) (Batista et al., 2017; Gowda et al., 2015; Gowe, 2015; Vuolo et al., 2020). In this sense, the fruta-do-lobo fibrous fraction presented significant values of total fibers.

Some mechanisms associated with fiber-related beneficial health effects have been studied, one of them being the satiety-promoting effect by delayed gastric emptying and slower absorption of nutrients, which can favor weight loss and reduce food intake (Veronese et al., 2018b; Warrilow, Mellor, McKune, & Pumpa, 2019). Some *in vivo* experimental protocols have shown the effect of different sources of insoluble fiber in decreasing daily dietary intake and weight gain (Carvalho et al., 2019; Chang et al., 2017; Drew et al., 2018). In line with these studies, in the present study, the consumption of fruta-do-lobo fibrous fraction (FF) decreased the body weight gain compared to the HF group, even though the animals were fed a hypercaloric diet (Table 3). Also, the HF diet had promoted 1.7 times more epididymal fatty acid accumulation in the animals than the control AIN-93 diet ($p = 0.04$) (Table 3). The effects of preventing weight gain may be associated with a lower caloric efficiency promoted by the FF or increased lipid excretion due to the fiber content. In addition, insoluble fibers also accelerate intestinal transit, thus increasing stool weight and desiring to reduce the risk of gastrointestinal tract diseases (Mayengbam et al., 2019). In addition, the results of our study show the greater weight of the cecum of animals in the FF group

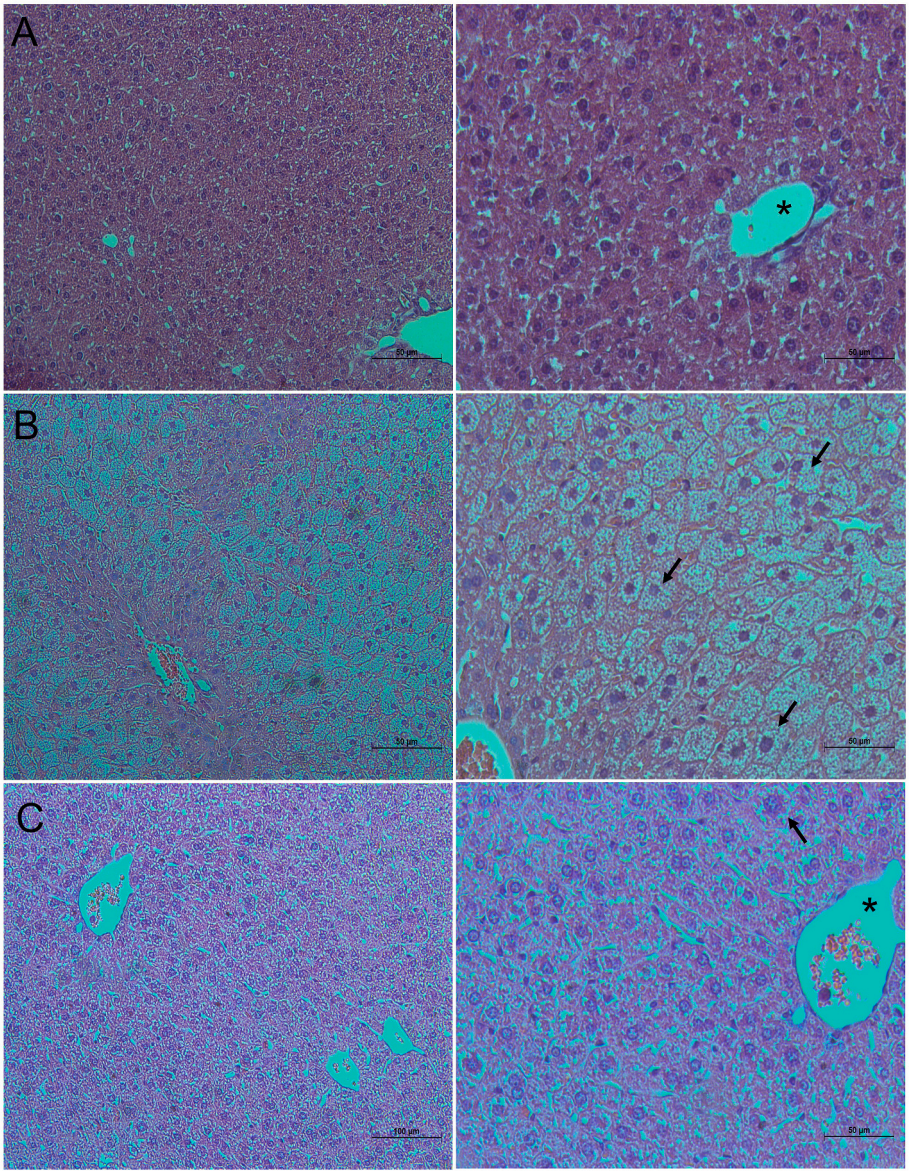

Fig. 5. Histological evaluation of the hepatic structure. A: Control = normal diet (AIN-93G) group; B: HF = high-fat control diet group; C: FF = high-fat diet + 3% fruta-do-lobo fibrous fraction. The Red arrows indicate the difference in adipocyte size between the 3 groups. *centrilobular vein; microvesicular steatosis (arrow).

compared to the HF, probably due to the action of insoluble fibers present in the FF diet in the gastrointestinal tract (Table 3).

Impaired glucose tolerance and insulin resistance are very important physiological alterations that contribute to the development of T2DM (Czech, 2017). Diets rich in fiber tend to have a low glycemic index due to the viscosity of soluble fiber, which can reduce the speed and amount of glucose absorbed into the blood in a given period, thus decreasing the hyperglycemic peaks typical in T2DM, also prolonging satiety (Weickert & Pfeiffer, 2018). He low soluble fiber content in the fibrous fraction of fruta-do-lobo can explain the similar profile observed between the HF and FF groups during the GTT test, since no statistical difference was observed between the groups ($p > 0.05$) (Fig. 3A–B).

Although no changes were observed in the glycemic response of the animals fed the FF diet in the OGTT, it is possible to see a significant improvement in the insulin tolerance test, providing the animals with a similar response to the lean control group (Fig. 3D). This result agrees with other scientific studies in which the intake of foods rich in insoluble fiber improved the insulin response (Barber, Kabisch, Pfei, & Weickert, 2020; Higa et al., 2019; Li et al., 2020). Some factors that may explain the action of insoluble fibers on ITT are related to reduced body weight gain and, consequently, lower risk of developing obesity. In addition, the network-like structure of insoluble fiber particles contributes to the trapping of glucose, slowing its diffusion and prolonging the absorption of glucose in the gastrointestinal tract (Davison & Temple, 2018; Li et al., 2020; Qi et al., 2016; Zheng et al., 2019). Although no difference was observed in the dietary intake and weight gain of the animals, it is possible to observe that the consumption of the FF diet guaranteed some metabolic protection to the animals against the development of insulin resistance even consuming a high-fat diet.

The consumption of the FF diet did not impact the gene expression of tight-junction proteins or MUC-2. However, it was observed changes in MMP-9 expression. The stromal matrix remodeling carried out by matrix metalloproteinases (MMPs) and their endogenous tissue inhibitors (TIMPs) is another characteristic associated with increased adipose tissue and fat cells (Andrade et al., 2012). MMP-9 seems to play an important role in this process due to its high plasma concentrations in mice and individuals with obesity (dos Santos-Macedo et al., 2019; García-Prieto et al., 2019; Vieira et al., 2003). The results of our study are in agreement with the literature since the animals fed with an HF diet showed the highest expression of MMP-9 compared to the lean

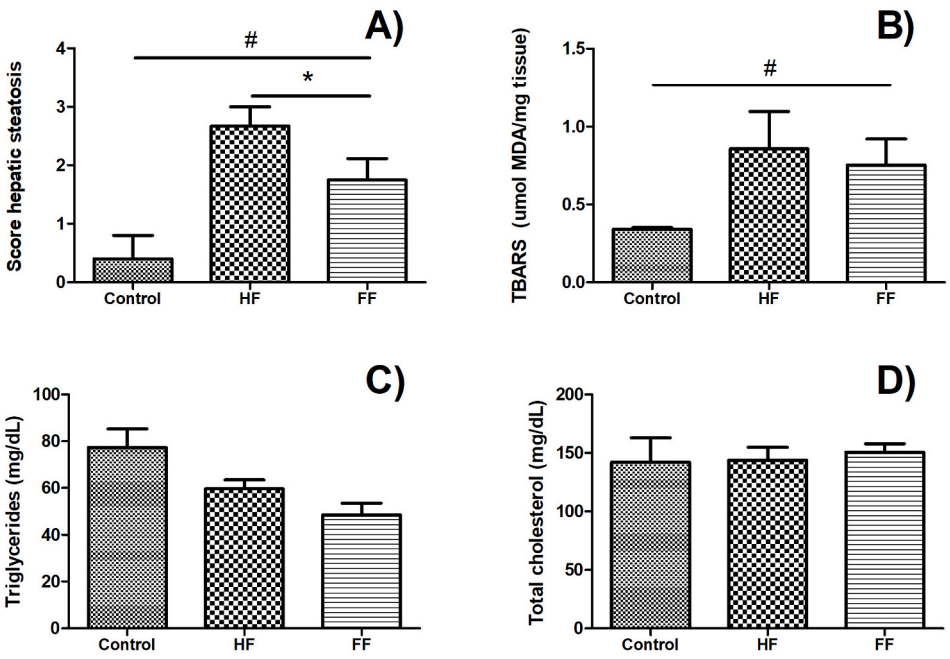

Fig. 6. Effects of fruta-do-lobo fibrous fraction administration on steatosis development (A), hepatic TBARS level (B), serum triglycerides (C), and total cholesterol leves (D). Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction. Data are represented in means and standard deviation (SD). In addition, data normality was evaluated by the Shapiro–Wilk test, and the comparisons between the FF group vs. Control and FF group vs. HF were made using the Student t-test. The statistical analyses were performed in GraphPad Prism (GraphPad Software, Boston, MA, USA), and the significance level was set to $p < 0.05$. # means there is statistical difference between control x FF and * means there is statistical difference between HF x FF.

Table 4
Fatty acid composition (FAME) contents from liver of experimental groups (%/total fatty acids).

FAMEs	CONTROL	HF	FF
C10:0	0.065 ± 0.02 [a]	0.016 ± 0.01[b]	0.018 ± 0.01[b]
C16:0	21.6 ± 3.1	21.7 ± 10.4	21.3 ± 6.5
C16:1-n7	1.71 ± 0.7 [a]	0.8 ± 0.3 [b]	0.7 ± 0.2 [b]
C18:2-n6	19.8 ± 3.6	25.4 ± 11.4	22.4 ± 6.0
C18:3-n3	0.38 ± 0.2	0.43 ± 0.26	0.40 ± 0.15
C24:1-n9	5.5 ± 0.37	3.5 ± 2.22	0.04 ± 0.04
Total SFA	43.5 ± 1.63	36.6 ± 1.75	39.8 ± 4.2
Total MUFA	19.1 ± 6.0	26.3 ± 1.89	22.1 ± 3.8
Total PUFA	37.7 ± 5.5	37.2 ± 1.65	38.0 ± 2.0
PUFA/SFA	0.87	1.03	0.95
n6: n3	21.71	23.84	24.65

Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction. Parametric data (ANOVA and Tukey's tests) were expressed as the mean ± SEM.

control group (Fig. 4E). The consumption of the FF diet decreased the MMP-9 expression compared to the HF group, probably due to the anti-obesogenic action of the fibers and their impact on lipid absorption and enterohepatic circulation. Finally, no statistically significant change was observed in the expression of TNF-α among the groups (Fig. 4F). However, it is possible to observe that the RE group showed the lowest values compared to the other groups.

Dysfunctions in adipose tissues are associated not only with obesity but also with the occurrence of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (Brunner, Henneberg, Wilechansky, & Long, 2019). Some studies show an association between dietary fiber intake and decreased risk of NAFLD and NASH. In this sense, a cross-sectional survey carried out in the Netherlands presented a high rate of fatty liver in individuals with low dietary fiber intake (Rietman, Sluik, Feskens, Kok, & Mensink, 2018). Another Chinese study showed a direct association between total dietary fiber intake and the low prevalence of newly diagnosed NAFLD (Xia et al., 2020). Furthermore, Di et al., (2019) reported that a water-insoluble polysaccharide used in mice for treating metabolic syndrome improved glucose and lipid metabolism and reduced inflammation and hepatic steatosis by suppressing the gut microbiota. Wu et al. (2020) found that insoluble fibers from bamboo shoots positively affected hyperlipidemia and hepatic steatosis by regulating the gut microbiota. We can see in the results of the present study that the consumption of a high-fat diet promoted the accumulation of fat in the hepatocytes of the animals; however, the

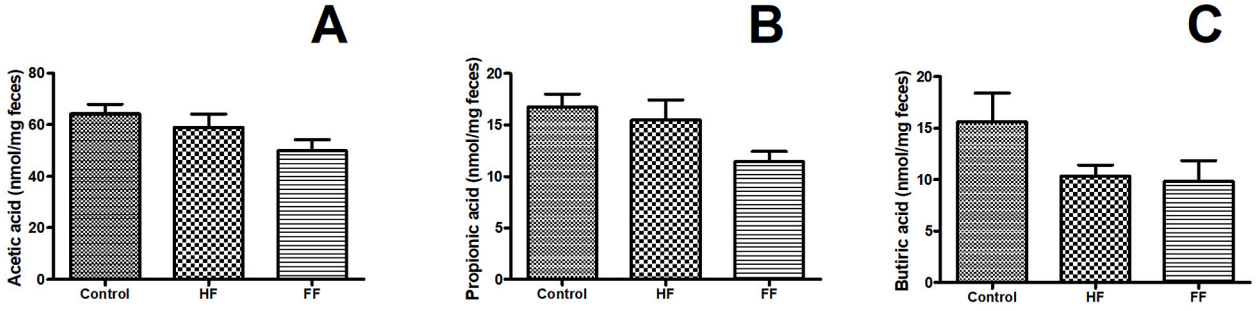

Fig. 7. Effects of fruta-do-lobo fibrous fraction administration on acetic acid (A), propionic acid (B), and butyric acid (C) content in the feces. Control = normal diet (AIN-93G) group; HF = high-fat control diet group; FF = high-fat diet + 3% fruta-do-lobo fibrous fraction. Data are represented in means and standard deviation (SD). In addition, data normality was evaluated by the Shapiro–Wilk test, and the comparisons between the FF group vs. Control and FF group vs. HF were made using the student t-test. The statistical analyses were performed in GraphPad Prism (GraphPad Software, Boston, MA, USA), and the significance level was set to $p < 0.05$.

inclusion of the fibrous fraction of fruta-do-lobo in the diet of the animals promoted a reduction in the steatosis score compared to the group HF (Figs. 5 and 6A). Thus, we recognize the importance of future studies on the effects of FF intake on enterohepatic circulation, including the quantification of fat intake and bile excretion in animal feces, to better elucidate the impact of fiber on the gastrointestinal tract.

Triglyceride accumulation in hepatocytes can be related to the dietary uptake of fatty acids or increased lipolysis and fat oxidation in adipose tissue, increasing the liver's sensitivity to oxidative stress (Batista et al., 2018). In this way, an energy-rich diet can lead to oxidative stress by activating intracellular pathways such as NADPH oxidase, glycosidation, and oxidative phosphorylation in mitochondria. Thiobarbituric acid reactive substances (TBARS), such as malondialdehyde (MDA), are considered an important biomarker of oxidative damage (Tsikas, 2017). Experiments with animal models indicate that dietary fiber intake is associated with lower concentrations of inflammatory and oxidative stress biomarkers (Miller et al., 2016; Xu et al., 2014). It is possible to see that obesity increased the level of TBARS in the hepatic tissue of the animals; however, the consumption of FF did not effectively decrease lipid peroxidation in the animals compared to the other groups (Fig. 6B). Oxidative stress caused by the excessive production of ROS is one of the factors associated with the development of chronic inflammatory processes associated with several chronic diseases (Sharifi-Rad et al., 2020). In this way, it was evaluated if an HF or FF diet could change the gene expression of an important pro-inflammatory cytokine since it was not observed differences related to lipid peroxidation. The gene expression of the inflammatory marker TNF-α in the liver tissue of the animals did not show a significant difference among the groups. This result indicates that neither the consumption of the high-fat diet (pro-inflammatory) nor the FF diet altered the gene expression of this marker in the animals (Fig. 4F).

The hepatic profile of fatty acid methyl esters was analyzed using 21 standards, including saturated fatty acids (SFA), monounsaturated fatty acids (MUFA), and polyunsaturated fatty acids (PUFA). The results showed a higher content of capric acid (C10:0, SFA), palmitoleic acid (C16:1 n7, MUFA), and nervonic acid (C24:1 n9, MUFA) in the lean control group compared to HF and FF groups (Table 4). The lower concentration of palmitoleic acid in the obesity-induced groups (HF and FF) may be one of the reasons for developing hepatic steatosis, as this free fatty acid has shown a protective effect against fat accumulation in hepatocytes (Cruz et al., 2020). Also, the higher amount of MUFA observed in the HF group may be explained by the oleic acid content (C18:1), representing 41% of the fatty acids in the lard (Silva et al., 2018). (Table 4). We recognize the importance of future studies on the effects of FF intake on enterohepatic circulation, including the quantification of fat intake and bile excretion in animal feces, to better elucidate the impact of fiber on the gastrointestinal tract and lipid metabolism.

Soluble fibers are fermented by intestinal bacteria and therefore have some prebiotic functions, acting as a substrate for the formation of short-chain fatty acids (SCFA) (Prasad &Bondy, 2019). In our study, no increase in SCFA production was observed in the FF group compared to the other groups (Fig. 7). This data can be explained due to the high content of insoluble fiber present in the fibrous fraction of fruta-do-lobo.

The increase in serum cholesterol levels confirmed by clinical studies has elucidated the importance of dyslipidemias in the pathogenesis of obesity (Oussaada et al., 2019; Vekic, Zeljkovic, Stefanovic, Jelic-Ivanovic, & Spasojevic-Kalimanovska, 2019). It is recognized in the literature that propionic acid decreases hepatic cholesterol synthesis, lowering blood cholesterol levels (Soliman, 2019) Additionally, consumption of dietary fiber has been linked to lower cholesterol levels. However, the present study did not show changes in serum cholesterol between groups (Fig. 6D), nor the SCFA concentration in the feces sample (Fig. 6D). A possible explanation for this result is that FF is a rich source of insoluble fibers rather than soluble fibers, and the amount of substrate for the microbiota was insufficient to increase SCFA production. Regarding the results of triglycerides, there was a statistical difference between the Control group and the other obese groups (HF and FF). It is important to highlight that our research group previously showed that the AIN93G diet might not be the best formulation to be used as a normolipidemic diet and control in a diet-induced obesity protocol (Aguiar et al., 2022).

We conclude that a diet containing a fibrous fraction of fruta-do-lobo rich in insoluble fiber contributes to controlling body weight gain, the development of hepatic steatosis, and insulin resistance, which are characteristics of the HF diet intake. However, more detailed molecular pathways need to be investigated to better describe the mechanisms associated with the beneficial effects of fruta-do-lobo fibrous fraction intake to prevent obesity and its comorbidities associated.

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Amanda Maria Tomazini Munhoz Moya: Conceptualization, Validation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. **Thaís Dolfini Alexandrino:** Investigation. **Joseane Morari:** Investigation, Resources. **Leandro Bertacchini de Oliveira:** Investigation. **Adriana Souza Torsoni:** Investigation. **Ana Paula Aparecida Pereira:** Investigation. **Livia Mateus Reguengo:** Investigation. **Licio Augusto Velloso:** Resources, Writing – review & editing. **Stanislau Bogusz Junior:** Writing – review & editing. **Glaucia Maria Pastore:** Resources, Writing – review & editing. **Juliano Lemos Bicas:** Writing – review & editing. **Cinthia Baú Betim Cazarin:** Conceptualization, Validation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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