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Chemical Composition and Antidiabetic Potential of a Phenolic-Rich Extract from Cashew Fiber

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ABSTRACT: Cashew fiber is a byproduct used as an ingredient in food products; however, little is known about its functional properties. Therefore, we evaluated the chemical composition and antidiabetic potential of a phenolic-rich extract from the cashew fiber (PECF) using spectrometric techniques and experiments with C57BL/6 mice to assess its effect on glycemia and insulin resistance. In the glucose tolerance test, fasted animals received PECF (1−100 mg/kg i.p.) followed by a glucose load of 2 g/kg. Dexamethasone was used to induce insulin resistance, and the animals received PECF daily for 5 days. As a result, PECF (1 mg/kg) reduced blood glucose, triglycerides, and total cholesterol levels; meanwhile, HDL levels and insulin sensitivity were increased. Its mechanism of action seems to be related to α-glucosidase inhibitory and antioxidant activities of phenolic acids and flavonol glycosides by increasing glutathione and reducing TBARs. Thus, cashew fiber was shown to be a good source of hypoglycemic compounds for plant-based foods and nutraceuticals potentially useful for diabetes control.

KEYWORDS: *anacardium occidentale, anacardic acid, polyphenols, hypoglycemic, diabetes*

1. INTRODUCTION

Long-term postprandial hyperglycemia is a primary risk factor for the development of chronic metabolic diseases, including Type II diabetes mellitus (DM2), obesity, and cardiovascular diseases. DM2 is the most frequently diagnosed chronic disease, affecting more than 536 million people worldwide.[1] Insulin resistance is the main cause of uncontrolled increases in the levels of postprandial blood glucose and lipids.[2] Nevertheless, foods containing dietary fibers and phenolic compounds or polyphenols, such as cereals, vegetables, and fruits, can contribute to glycemic regulation in diabetic patients by reducing the carbohydrate absorption.[3−5]

Dietary fibers are nonhydrolyzable carbohydrate polymers by the endogenous enzymes in the small intestine of humans, hence nondigestible and nonabsorbable. They are sourced from fruits, grains, and vegetables, where they are important components of their cell walls, and have been classified into two types based on their water solubility: (i) soluble dietary fiber- noncellulosic polysaccharides (e.g., gums, pectins, mucilages, and galactomannans); (ii) insoluble dietary fiber, which consists of cellulose and/or hemicelluloses linked to lignin.[3]

Phenolic compounds are secondary metabolites that possess a benzenic ring bearing one or more hydroxyl groups (−OH) biosynthesized through the shikimate pathway. They are found in all parts of food plants and possess a great diversity in size and scaffold (phenolic acids, flavonoids, phenylpropanoids, stilbenes, lignans, and tannins). These compounds in plants occur basically in two forms: (i) free phenolic compounds, which do not bind with other matrix molecules, therefore are easily extractable by polar solvents and more bioaccessible; (ii) bound phenolic compounds, which are embedded or linked to macromolecules such as cellulose, protein, and lignin by means of physical or chemical interactions (ester, ether, or C−C bonds) composing the primary cell walls, hence are more difficult to be extracted and have lower bioaccessibility.[4,5]

Dietary fibers, in combination with phenolic compounds, can improve glucose metabolism, increase insulin sensitivity, as well as inhibit α-glucosidase enzymes in the small intestine.[2] There are several studies describing the potential role of phenolic compounds from whole grains and fruits in the prevention and treatment of metabolic diseases, such as obesity and DM2.[6] The consumption of fibers combined with a set of phenolic compounds may reduce the development of DM2 in about 37% of cases.[7]

Cashew fruit is composed of a nut attached to a peduncle, namely the cashew apple, which possesses an edible pulp rich in bioactive phenolic compounds (phenolic acids, anthocyanins, flavonoids, and tannins), carotenoids, vitamins (ascorbic acid, riboflavin, and thiamine), and minerals (Ca, P, and Fe), besides being a good source of dietary fiber after processing.

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Nevertheless, the cashew apple has been considered a byproduct of the cashew industry, which is traditionally focused on its nut. This situation becomes clearer when one observes the global disposal of millions of tons of cashew apples. A large amount of waste is due to the short postharvest lifespan, limited industrial use, and the lack of feasible preservation techniques for this raw material.[8,9]

On the other hand, there are many possible pharmaceutical and food applications using cashew fiber and its phenolic compounds as ingredients for plant-based products (e.g., hamburgers, sausages, and meatballs) and nutraceuticals.[10,11] Previous studies have reported that the consumption of cashew dietary fiber can be useful for appetite control and the prevention of hyperglycemia, hyperinsulinemia, and hypertriglyceridemia.[10] Among the phenolic compounds present in cashew apples, anacardic acids (salicylic acid derivatives bearing an aliphatic side chain) are phenolic acids found in all parts of the cashew plant that stand out for their diverse pharmacological activities, such as antioxidants, anti-inflammatory effects,[12] and antidiabetic properties.[13] Furthermore, phenolic acids, such as ferulic and gallic acids, have demonstrated antioxidant and anti-inflammatory properties that help regulate metabolic processes associated with diabetes and obesity by modulating pathways like AMPK and PI3K1.[14]

Therefore, our study aimed to investigate the chemical composition of free phenolic compounds present in cashew fiber and their effects on blood glucose regulation, lipid profile, redox status, and insulin resistance.

2. MATERIALS AND METHODS

2.1. Chemicals and Standards. Methanol (purity ≥99%) was obtained from Lichrosolv Merck (Darmstadt, Germany), and ultrapure water was obtained from a Milli-Q system (São Paulo, Brazil). Analytical standards (gallic acid, ellagic acid, myricetin, and quercetin), besides the pharmaceutical reagents dapagliflozin, dimethyl sulfoxide (DMSO), Tween-80, tetramethoxypropane (TMP), and 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), were purchased from Sigma-Aldrich (Saint Louis, USA). Dexamethasone was acquired from Aché (São Paulo, Brazil). Anacardic acids (15:3, 15:2, and 15:1) were isolated from cashew nut shell liquid by Oiram Filho et al..[15]

2.2. Plant Material. Cashew fiber was kindly provided by Natvita Company, a juice industry located in Fortaleza, Ceará State, Brazil. The fiber was immersed in water at a ratio of 1:2 (fiber:water), followed by filtration and lyophilization. Afterward, the fiber was ground using a mortar and pestle and then sieved to obtain cashew fiber powder, presenting the following centesimal composition: 78.39% carbohydrates (dietary fibers and sugars), 13.60% proteins, 2.38% lipids, 4.25% moisture, and 1.38% ash.

2.3. Animals. Male C57BL/6 mice (7 weeks old, 10−20 g) were kept in cages at 21 ± 2 °C with a 12-hour light−dark cycle lights on from 6:00 a.m. to 6:00 p.m.) and provided with food (Nuvital, Curitiba, PR, Brazil) and water *ad libitum*. The experiments were carried out in the bioterium of the Center for Research and Development of Medicines (NPDM) at Federal University of Ceará, in accordance with the Ethics Committee on Animal Use (CEUA-NPDM/UFC: No 37270922−0). The bioterium is certified by the Association for Assessment and Accreditation of Laboratory Animals (AAALAC).

2.4. Sample Preparation of the Phenolic-Rich Extract from the Cashew Fiber (PECF). Ten grams of cashew fiber powder were extracted with 250 mL of methanol (MeOH) at 30 °C for 1 h for extraction of free phenolics, according to the method described by Alu'datt et al.[16] Later on, the methanolic solution was filtered through filter paper and dried, yielding a brown solid referred to as the phenolic extract of cashew fiber (PECF: 376.9 mg; 3.77% w/w), which was kept in the freezer until analysis.

2.5. Chemical Analysis of PECF. *2.5.1. Total Phenolics Content.* The content of phenolic compounds was quantified according to the method of Singleton and Rossi with modifications.[17] The extract PECF (30 mg) was suspended in an aqueous solution of 10% ethanol and mixed with 0.5 mL of Folin−Ciocalteu reagent, 0.5 mL of 20% sodium carbonate, and 3.5 mL of water. After 90 min at rest, the absorbances were read in a Varian Cary 300 UV spectrophotometer (Palo Alto, CA, USA) at 725 nm. The results were expressed as milligrams of gallic acid equivalent per gram of dried extract (mg of GAE/g).

2.5.2. Nuclear Magnetic Resonance (NMR) Analysis. NMR spectra were recorded on an Agilent DD2 600 MHz spectrometer equipped with a One Probe with a 5 mm internal diameter (H−F/15N-31P) for inverse detection and a field gradient on the "z" axis. A PECF sample (5.1 mg) was prepared by adding 600 μL of deuterated methanol (MeOD, 99.8%, Sigma-Aldrich). Then, ^{1}H NMR spectrum was acquired with a waiting time between each acquisition of 2 s, an AQ of 3.33 s, a gain of 32, 32 transients in a spectral window of 16 ppm, and 32k real points at 26 °C. The identification of the constituents present in the matrix was performed by means of two-dimensional NMR experiments of ^{1}H−^{1}H correlation (COSY), heteronuclear single quantum coherence for ^{1}H−^{13}C (HSQC), and heteronuclear multiple bond correlation ^{1}for ^{1}H−^{13}C (HMBC) by comparing with literature data and spectra of authentic standards from our local database.[18−20]

2.5.3. Ultra-Performance Liquid Chromatography High-Resolution Mass Spectrometry (UPLC-HRMS) Analysis. The chemical composition of the PECF extract was determined by UPLC-HRMS analysis using the method previously described by Lopes et al. with some modifications.[21] The analyses were performed on an Acquity UPLC chromatograph (Waters, USA) coupled to quadrupole and time-of-flight mass spectrometers (Xevo Q-TOF, Waters), equipped with a Waters Acquity BEH C18 column (150 mm × 2.1 mm, 1.7 μm) at 40 °C. The separation was carried out using a mobile phase composed of deionized water (A) and acetonitrile (B), both containing formic acid (0.1% v/v). The extracts were subjected to the following elution gradient: 2−100% B (22.0 min), 100% B (22.1−25.0 min), and 2% B (26.0−30 min), with a flow rate of 0.3 mL/min. Ionization was performed through an electrospray ionization source in positive mode (ESI), acquired in the range of 110−1180 Da, and the optimized instrumental parameters were as follows: capillary voltage at 3.2 kV, cone voltage at 15 V, source temperature at 120 °C, desolvation temperature at 350 °C, and desolvation gas flow at 500 L/h. The system was controlled using MassLynx software (Waters Corporation). Before analysis, the PECF extract (20 mg) was cleaned up with a Supelclean SPE cartridge (500 mg) by eluting the sample with a 90% MeOH solution, and subsequently filtered through 0.22 μm PTFE syringe filters (Nova Analitica, São Paulo, Brazil). The compounds were characterized based on the molecular formula provided by the MassLynx 4.1 program from their accurate masses (error <5 ppm), isotopic patterns (i-fit), and MS fragmentation patterns, as well as a literature survey on previous occurrences in the *Anacardiaceae* family using the SciFinder Scholar database. In addition, the compounds were identified by comparison with analytical reference standards when available.

2.6. *In Vitro* α-Glucosidase Inhibition Assay. The assessment of α-glucosidase inhibitory activity was conducted following the methodology adapted from Vinholes et al., with specific adjustments.[22] Initially, 100 μL of various sample concentrations, previously dissolved in 0.1 M phosphate buffer solution at pH 6.8, were distributed in triplicate into a microplate. Afterward, 50 μL of glutathione was added to each well containing the samples. Subsequently, 50 μL of the α-glucosidase enzyme, diluted to a final concentration of 0.4 U/mL in 0.1 M phosphate buffer solution, was added. The microplates were incubated at 37 °C for 5 min, and the initial absorbance value (T0') was recorded at 415 nm using an Eon BioTek spectrophotometer (Winooski, VT, USA). The enzymatic reaction was activated by adding 50 μL of substrate (4-nitrophenyl α-

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D-glucopyranoside at 10 mM in 0.1 M phosphate buffer solution) and incubated in the dark for 10 min (T10'). At the end of this period, a new absorbance reading was taken at 415 nm. Acarbose, solubilized in 0.1 M phosphate buffer solution at different concentrations, served as the positive control of this assay. Also, an absorbance reading for the negative control was performed using phosphate buffer in place of the sample. The inhibitory activity was calculated using the following equation:

$$\text{Inhibitory activity \%} = ((\text{Control}) - (\text{Sample})/(\text{Control})) \times 100$$

The sample concentration required to inhibit enzyme activity by 50% (IC_{50}) was calculated by nonlinear regression analysis.

2.7. *Ex Vivo* Intestinal α-Glucosidase Inhibition Assay. The activity of α-glucosidases, including maltase, sucrase, and lactase, was determined following the methodology described by Dahlqvist with modifications.[23,24] To do this, PECF samples were prepared at dilutions of 1.0, 0.1, and 0.01 mg/mL. Acarbose was used as a positive control and assessed at concentrations of 500 μM (0.32 mg/mL), 700 μM (0.45 mg/mL), and 900 μM (0.58 mg/mL), with the intermediate concentration being used as a reference. C57/Bl6 mice were euthanized, and a segment of the small intestine was removed, homogenized in saline solution, and centrifuged at 8000 rpm for 8 min. Subsequently, the supernatant was used for *ex vivo* evaluation of the α-glucosidase activity and determination of total proteins. The samples were read at 500 nm using a spectrophotometer. The values were expressed as enzyme activity (U) per milligram of protein. Additionally, values of IC_{50} were estimated based on the aforementioned doses used for the sample and positive control.

2.8. Experiments of *In Vivo* Biological Activities. *2.8.1. Glucose Tolerance Test and Glycogen Assay.* Mice fasted for 6 h were divided into different groups, containing 7 animals each. For the positive control, normoglycemic mice received dapagliflozin (3 mg/kg). The vehicle (distilled water, 0.1% DMSO, and 5% Tween-80) was used as the negative control. Finally, the last group received doses of PECF (100, 10, and 1 mg/kg). Before the start of the treatment, blood glucose levels were measured using a Bioland G-500 blood glucose meter (Shenzhen, Guangdong, China) via a tail cut, corresponding to time zero (T0'). Next, the mice received PECF, and 30 min later, they were subjected to a glucose load (2 g/kg). The glucose tolerance curve was initiated 15 min after the glucose load, and measurements were taken at 15, 30, 60, and 120 min.[24,25] All treatments were administered intraperitoneally (i.p.). The liver, muscle, kidneys, and pancreas were collected for the determination of biochemical parameters. The concentrations of hepatic and muscle glycogen were determined by colorimetric analysis according to the method of Krisman[26] with slight modifications, using approximately 400 mg of liver and 300 mg of muscle (quadriceps).[24]

2.8.2. Insulin Tolerance Test. The insulin tolerance test was conducted at the NPDM Animal Facility, where the mice were divided into five groups: (1) mice received a vehicle (saline solution); (2) dexamethasone (0.1 mg/kg subcutaneous); (3) PECF (1 mg/kg intraperitoneal, i.p.); (4) PECF (1 mg/kg i.p.) plus dexamethasone (0.1 mg/kg s.c.); and (5) dapagliflozin (3 mg/kg i.p.) plus dexamethasone (0.1 mg/kg s.c.). Mice were administered with daily subcutaneous injections from 8:30 to 9:30 in the morning for 5 consecutive days.[24] On the fifth day, the animals underwent a 4-h fast, and the insulin tolerance test (ITT) was performed. The first blood sample for glucose measurement (T0) was collected by making an incision at the tip of the animal's tail. Subsequently, 2 IU of insulin per kilogram of body weight was injected intraperitoneally, and blood samples were collected from the tail at 7, 14, and 28 min to determine serum glucose levels. The constant rate of glucose decay (kITT) was calculated using the formula $0.693/t_{1/2}$. The glucose $t_{1/2}$ was calculated from the least-squares analysis of the serum glucose concentration during the linear decay phase.[27]

2.8.3. Determination of Reduced Glutathione (GSH) Concentration. The quantification of GSH was performed using the modified method of Sedlak and Lindsay.[28] This method is based on the development of a yellow color when adding 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB), known as Ellman's reagent, to sulfhydryl compounds. The reaction between DTNB and GSH leads to the formation of 2-nitro-5-thiobenzoic acid and GSSG. For this, a standard curve with known concentrations of GSH was used for method calibration. Tissue samples were homogenized at 10% (w/v) with a 0.02 M EDTA solution. Subsequently, 60 μL of 10% trichloroacetic acid (TCA) was added to 40 μL of each sample to precipitate the proteins present in the biological material. The material was then centrifuged (5000 rpm, 15 min, 4 °C), and 60 μL of the resulting supernatant was plated on an ELISA plate. At the time of reading, 102 μL of Ellman's reagent was added, and its absorbance was immediately measured (412 nm) on a microplate reader. The entire experiment was conducted under refrigeration (10−15 °C).

2.8.4. Determination of Thiobarbituric Acid-Reactive Substances (TBARS) Production. The determination of TBARS production was performed using the method of Draper and Hadley with some modifications.[29] Initially, a standard curve of TMP (tetramethoxypropane) was built. Afterward, a 10% homogenate of liver, muscle, and kidneys was prepared in 0.05 M potassium phosphate buffer (w/v). Then, a 35% perchloric acid solution was added. The mixture was centrifuged at 14,000 rpm for 15 min (4 °C), and 600 μL of the supernatant was withdrawn and homogenized with 200 μL of 0.8% thiobarbituric acid. This mixture was placed in Eppendorf tubes wrapped in aluminum foil and kept in a water bath at 95−100 °C for 30 min. Finally, a 96-well plate was assembled, and the result was evaluated using a plate reader at λ = 532 nm.

2.8.5. Analysis of GLUT-4 Gene Expression by RT-PCR. Initially, RNA was extracted from cells or tissues using Trizol, followed by a purification process that included centrifugation and washes with 2-propanol and ethanol, ending with the solubilization of RNA in RNase-free water. After extraction, RNA quantification was performed using a Nanodrop ThermoFisher spectrophotometer (Waltham, MA, USA). For cDNA synthesis, a specific master mix was used, and a thermocycler was programmed with optimized conditions. The PCR reaction was conducted by adding specific primers to the cDNA and using a thermocycler for amplification. Finally, the PCR products were analyzed using a QuantStudio real-time PCR apparatus (Thermo Fisher), following a rigorous protocol that included specific dilutions and mixture preparations to ensure amplification specificity and efficiency.[30] Gene expression of GLUT-4 was quantified by real-time PCR, using the housekeeping gene *Ppia* as an internal control for normalization. After the extraction and quantification of total RNA, cDNA synthesis was carried out as previously described. For the amplification of GLUT-4 and *Ppia*, specific primers were used with the following real-time PCR steps: an initial denaturation step followed by 40 cycles of denaturation, annealing, and extension. The annealing conditions were adjusted according to the specific sequences of the primers. The relative quantification of gene expression was calculated using the ΔΔCt method, normalizing the Ct values of GLUT-4 to the Ct values of *Ppia* for each sample.

2.9. Statistical Analysis. Animal weight values, toxicity, and biochemical parameters were expressed as mean ± standard deviation using GraphPad Prism 8 software (La Jolla, CA, USA). Weight values for fasting blood glucose experiments, water intake, and food intake were expressed as mean ± standard deviation and analyzed through multiple comparisons of parametric results using ANOVA followed by Tukey's posttest. The adopted significance level was $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1. Total Phenolics. Agroindustrial byproducts from various fruits, such as avocado, mango, papaya, pineapple, guava, orange, and passion fruit, have been identified as sources of dietary fibers containing polyphenols. The concentrations of polyphenols vary according to the fruit part and the extraction method, ranging from 546 to 0.47 mg of GAE/g for mango peel and papaya pulp, respectively. In general, higher polyphenol contents are present in the peels.[31] This finding is particularly useful, since positive correlations

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have been previously reported between the total content of polyphenols in fruit extracts and their biological activities.[32]

In our work, the total content of phenolic compounds in the cashew fiber was found to be 533.98 ± 2.67 mg GAE/g extract PECF (i.e., 20.1 mg GAE/g cashew fiber), using cold maceration with methanol for 1 hour as the extraction method (yield = 3.8%). However, different values can be found in the literature, showing that the method of extraction significantly impacts the final yield, directly affecting the total phenolic content found in the samples. Lima and colleagues carried out a hydroalcoholic extraction (42% ethanol) of powdered cashew bagasse using an ultrasound bath for 37 min, obtaining a concentration of 3950 mg GAE/100 g of dry extract (yield = 9%).[33] Finally, Lopes and colleagues used a methanol extract obtained by Soxhlet extraction of cashew bagasse for 20 h (yield = 11%), after being defatted with hexane for 6 h, resulting in a final concentration of 62.50 mg GAE/g of extract.[21] Sonication appears to be the most efficient extraction method for obtaining all types of phenolic compounds (bound and free polyphenols), while Soxhlet extraction leads to a higher extraction yield but with low contents of polyphenols, possibly due to their thermal decomposition. On the other hand, in spite of lower yield, our choice of cold maceration targeted the extraction only of free phenolic compounds, as these were the components of interest for our research due to their higher bioaccessibility.

3.2. Chemical Profile of PECF. NMR spectrum (Figure 1) showed that PECF is composed predominantly of the phenolic

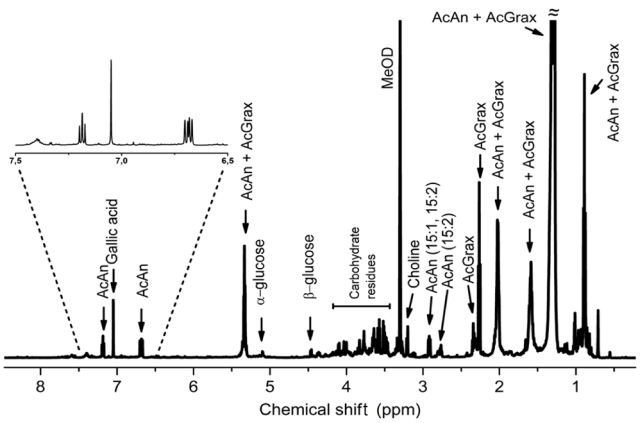

Figure 1. ^{1}H NMR spectrum of PEFC labeled with the respective characterized compounds. Legend: AcAn: anacardic acid, AcGrax: fatty acid, MeOD: deuterated methanol.

acids gallic acid and anacardic acids, besides residual sugars (glucose) and fatty acids. The assignment of the resonances was based on their correlations observed through the two-dimensional experiments (COSY, HSQC, and HMBC), as well as by comparison with literature data and a local database.[18−20]

UPLC-HRMS analysis allowed the identification of more compounds in the PECF extract, as shown in the chromatogram (Figure S1). Compounds were characterized based on their molecular formula, MS fragmentation pattern, and comparison with authentic standards. Twenty-three compounds were tentatively identified, including 16 flavonoids, 6 phenolic acids, and 1 fatty acid (trihydroxy-octadecenoic acid, 19). Overall, the chemical composition was in agreement with previous studies.[21,33]

The flavonoids consisted of myricetin (**10**), quercetin (**12**), and kaempferol (**16**), along with their glycosylated derivatives: myricetin 3-*O*-hexoside (**2**, **3**), myricetin-*O*-xyloside (**4**), myricetin 3-*O*-rhamnoside (**6**), quercetin-3-D-xyloside (**7**, **8**), quercetin 3-*O*-rhamnoside (**9**), quercetin-3-*O*-rutinoside (**11**), kaempferol-*O*-*p*-coumaroyl rhamnoside (**18**), myricetin derivate (**13**, **14**), and quercetin derivate (**15**, **16**) (Table 1).

Myricetin (**10**) and its derivatives (**13** and **14**) are commonly found in various plants, including cashew, and have demonstrated antioxidant and hypoglycemic properties.[34] In a preclinical study conducted with diabetic rats induced by a high-fat diet and streptozotocin, the continuous administration of myricetin (50 and 200 mg/kg body weight) reduced glucose and serum insulin in a dose-dependent manner. This compound increased the expression of the insulin receptor (InsR) and glucose transporter 4 (GLUT4) but also reduced the expression of glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK).[35]

Quercetin (**12**) and its derivatives (**7**, **8**, **11**, **12**, **15**, and **17**) have been previously reported in the literature for their antioxidant and anti-inflammatory activities.[36−40] Quercetin presents multiple benefits for glucose metabolism and diabetes management. It can act by inhibiting enzymes such as α-glucosidase and α-amylase, which are essential in the digestion of carbohydrates, thereby reducing glucose absorption and postmeal glycemic response (Jhong et al.).[41] Additionally, it stimulates glucose uptake by cells, particularly in muscle and adipose tissues, by activating the insulin pathway and increasing the expression of glucose transporters such as GLUT4. This effect is complemented by an improvement in insulin sensitivity, particularly relevant in the context of type 2 diabetes.[42]

Kaempferol (**16**) and its derivative, kaempferol-*O*-*p*-coumaroyl rhamnoside (**18**), have been reported in cashew earlier. Many studies have described the antioxidant capacity of kaempferol in reducing the risk of chronic diseases, including diabetes.[43] Kaempferol diminishes hyperinsulinemia and glycoxicity, which is damage to the body's cells due to a high glucose concentration. Furthermore, kaempferol has shown potential in protecting pancreatic β-cells, which are responsible for insulin secretion. By inhibiting the apoptosis of these cells, kaempferol may preserve the pancreas' function, consequently, the regulation of glucose. This effect is of great importance, as the loss of β-cells is one of the main factors in the development of type 2 diabetes.[44] Additionally, kaempferol appears to offer protection against lipotoxicity, a state where excess lipids and their derivatives exist (e.g., nonesterified fatty acids, triglycerides, and diacylglycerol) exist in the blood and cause toxic effects on cells and consequent metabolic dysfunction. The inflammatory processes driven by cytokines, such as IL-1β, TNF-α, and IL-6, are also targets of kaempferol's inhibitory action, suggesting that this flavonoid may also play a role in the attenuation of hyperlipidemia and its pathological consequences.[44]

Among phenolic acids, we found gallic acid (**1**), ellagic acid (**5**), anacardic acid (**22**), and anacardic acid derivatives: triene (**20**), diene (**21**), and monoene (**23**). Gallic acid has a significant hypoglycemic effect by acting through various mechanisms in hepatic carbohydrate metabolism. It is responsible for increasing glucose uptake in insulin-resistant cells and alleviating hyperglycemia in diabetic rats, demonstrating an improvement in insulin sensitivity. Moreover, it acts by modulating the expression of proteins related to insulin

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Table 1. Compounds Tentatively Identified in PECF by UPLC-HRMS Analysis

# Peak	Rt Time (min)	$[M-H]^-$ Observed	$[M-H]^-$ Calculated	Product Ions (MS/MS)	Empirical Formula	ppm (error)	Name
01	2.43	169.0132	169.0137	125	$C_7H_5O_5$	−3.0	Gallic acid[a]
02	5.33	479.0836	479.0826	317, 316	$C_{21}H_{19}O_{13}$	2.1	Myricetin 3-*O*-hexoside
03	5.40	479.0844	479.0826	317, 316	$C_{21}H_{19}O_{13}$	3.8	Myricetin 3-*O*-hexoside
04	5.56	449.0722	449.0720	317, 316	$C_{20}H_{17}O_{12}$	0.4	Myricetin-*O*-xyloside
05	5.80	300.9973	300.9984	-	$C_{14}H_5O_8$	−3.7	Ellagic acid[a]
06	5.94	463.0884	463.0877	317, 316	$C_{21}H_{19}O_{12}$	1.5	Myricetin 3-*O*-rhamnoside
07	6.31	443.0756	443.0771	301, 300	$C_{20}H_{17}O_{11}$	−3.5	Quercetin-3-D-xyloside
08	6.44	443.0765	443.0771	301, 300	$C_{20}H_{17}O_{11}$	−1.4	Quercetina-3-D-xyloside
09	6.70	447.0938	447.0927	301, 300	$C_{21}H_{19}O_{11}$	2.5	Quercetin 3-*O*-rhamnoside
10	7.18	317.0303	317.0297	271	$C_{15}H_9O_8$	1.9	Myricetin[a]
11	7.83	609.1235	609.1244	301	$C_{30}H_{25}O_{14}$	−1.5	Quercetin-3-*O*-rutinoside (rutin)[a]
12	8.47	301.0341	301.0348	255, 371	$C_{15}H_9O_7$	−2.3	Quercetin[a]
13	8.82	609.1257	609.1244	317, 316	$C_{30}H_{25}O_{14}$	2.1	Myricetin derivative
14	9.16	609.1241	609.1244	317, 316	$C_{30}H_{25}O_{14}$	−0.5	Myricetin derivative
15	9.51	593.1282	593.1295	301, 300	$C_{30}H_{25}O_{13}$	−2.2	Quercetin derivative
16	9.63	285.0387	285.0399	257	$C_{15}H_9O_6$	−4.2	Kaempferol[a]
17	9.79	593.1290	593.1295	301, 300	$C_{30}H_{25}O_{13}$	−0.8	Quercetin derivative
18	10.21	577.1346	577.1346	285, 284	$C_{30}H_{25}O_{12}$	0.0	Kaempferol-*O*-*p*-coumaroylrhamnoside
19	10.53	329.2330	329.2328	229, 211, 171	$C_{18}H_{33}O_5$	0.6	Trihydroxy-octadecenoic acid
20	21.09	341.2114	341.2117	297	$C_{22}H_{29}O_3$	−0.9	Anacardic acid (15:3)[a]
21	22.11	343.2260	343.2273	299	$C_{22}H_{31}O_3$	−3.8	Anacardic acid (15:2)[a]
22	22.57	369.2430	369.2430	325	$C_{24}H_{33}O_3$	0.0	Anacardic acid (17:3)[a]
23	23.28	345.2433	345.2430	301	$C_{22}H_{31}O_3$	0.9	Anacardic acid (15:1)[a]

[a]Identified with authentic standards.

signaling and carbohydrate metabolism in the liver, including the regulation of gluconeogenesis, glycogenesis, and glycolysis. These actions result in overall health benefits, such as reducing serum C-peptide and fructosamine levels, and lowering cardiovascular risk.[45,46]

Ellagic acid (**5**) possesses strong antioxidant activity.[47] A compilation of preclinical and clinical studies has pointed out that ellagic acid exerts its hypoglycemic effect by promoting glucose uptake and reducing glucose intolerance. It also acts by improving insulin sensitivity, involving the activation of PPAR-γ, a nuclear receptor that plays a crucial role in regulating glucose and lipid metabolism.[48]

With relation to the hypoglycemic effect of anacardic acids, various mechanisms may be involved, including the inhibition of metabolic enzymes. Anacardic acids are able to inhibit key enzymes in carbohydrate metabolism, such as α-glucosidase and α-amylase, leading to a decrease in the rate of carbohydrate digestion and, consequently, a reduction in glucose absorption in the intestine; therefore, resulting in a lower postprandial glycemic response.[49] Concomitantly, anacardic acids improve the insulin sensitivity by modulating insulin signaling pathways, resulting in a better glucose absorption by the cells.[50] In addition, they possess antioxidant properties that may help in protecting against cellular damage caused by reactive oxygen species, contributing to the prevention or management of diabetes.[11]

3.3. Biological Activities. *3.3.1. In Vitro and Ex Vivo α-Glucosidase Activities.* Intestinal α-glucosidases are enzymatic complexes that hydrolyze oligosaccharides or larger polysaccharides, releasing α-D-glucose monomers from the nonreducing end of the substrate. Patients with diabetes have increased α-glucosidase enzyme activity due to the lack of glucose uptake by muscle and adipose tissues.[51] In addition, insulin deficiency induces abnormal increases in the activity and expression of intestinal α-glucosidase in animals under diabetic conditions.[14] In this context, the inhibition of α-glucosidase has proven to be an interesting target for reducing glucose absorption, thereby attenuating postprandial blood glucose levels.

Therefore, α-glucosidase inhibitory assays are useful experiments for screening hypoglycemic compounds and investigating their mechanisms of action in diabetes control. This evaluation can be performed with either commercial α-glucosidase enzymes, which are generally sourced from baker's yeast (*Saccharomyces cerevisiae*), or homogenates produced from mammalian intestines, consisting of different α-glucosidase enzymes, including maltase, sucrase, and lactase. Enzymatic assays conducted with mammalian enzymes are preferred since the experimental conditions employed are closer to those found in preclinical and clinical trials, leading to a higher success rate in the search for hypoglycemic compounds. On the other hand, commercial α-glucosidase assays have been most commonly used because of their lower cost, higher reproducibility, and ease of use.[52]

In our study, PECF demonstrated an α-glucosidase inhibitory action similar to that of acarbose (positive control), which is a known α-glucosidase inhibitor and a widely used drug for the treatment of type 2 diabetes. PECF exhibited an IC_{50} of 0.747 mg·mL^{-1} for α-glucosidase, while acarbose presented an IC_{50} of 0.157 mg·mL^{-1} in *in vitro* assays (Figure 2). This result is much better than the α-glucosidase activity of a polyphenol-enriched fraction extracted from quinoa seeds (IC_{50}= 2.12 mg.mL^{-1}), which is considered a good source of hypoglycemic compounds.[53]

Also, we evaluated the inhibition of PECF against intestinal α-glucosidase enzymes, including maltase, sucrase, and lactase, from mice. The group treated with PECF at concentrations of 1.0, 0.1, and 0.01 mg·mL^{-1} inhibited the maltase enzyme by

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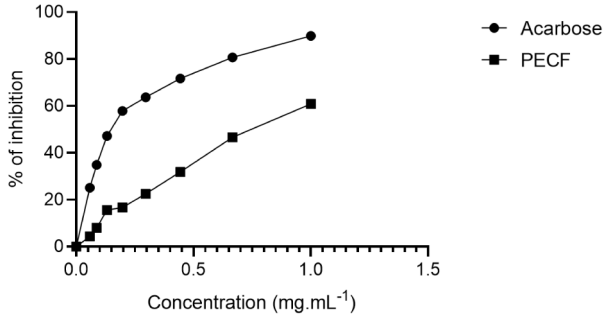

Figure 2. Percentage of inhibition of PECF against α-glucosidases at different concentrations, using acarbose as the positive control.

Table 2. Inhibitory Activity of PECF and Acarbose (Positive Control) Against Different Enzymes, α-Glucosidases, Performed Through *In Vitro* and *Ex Vivo* Assays[a]

	IC_{50} Values ($mg{\cdot}ml^{-1}$)	
Enzymes	PECF	Acarbose
α-glucosidase[b]	0.747 ± 0.032	0.157 ± 0.002
Maltase[c]	0.114 ± 0.089	0.290 ± 0.030
Sucrase[c]	0.014 ± 0.000	0.269 ± 0.044
Lactase[c]	0.738 ± 0.216	0.318 ± 0.085

[a]The effect was measured as half-maximal inhibitory concentration (IC50). [b]Commercial enzyme sourced from baker's yeast. [c]Homogenate from mice small intestine.

around 65%, 49%, and 39%, respectively, when compared to the control group. For the sucrase enzyme (Figure 3B), the group treated with PECF reduced its activity by 67%; 72%, and 64%. In Figure 3C, the group treated with PECF was found to decrease lactase activity by 60% and 57.5% in the two largest concentrations when compared to the control group. Acarbose, at a concentration of 700 μM (0.45 $mg{\cdot}mL^{-1}$), reduced the activity of these α-glucosidase enzymes by 72%, 89%, and 70%, in maltase, sucrase, and lactase, respectively, when compared to the control group (Figure 3A–C). Furthermore, the values of IC_{50} of PECF were estimated to be 0.11 $mg{\cdot}mL^{-1}$, 0.01 $mg{\cdot}mL^{-1}$, and 0.73 $mg{\cdot}mL^{-1}$ for maltase, sucrase, and lactase, respectively (Table 2). Thus, PECF presented greater inhibitory activity than acarbose, except for lactase.

The difference in IC_{50} values between PECF and acarbose observed in the two tests is due to various factors, such as the biological source and chemical structures of the enzymes, which possess different catalytic sites, resulting in different specificity and affinity. Our findings are in agreement with previous studies that showed great discrepancies between the values of IC_{50} of acarbose for maltase and sucrase from rat intestine, as well as in comparison with its IC_{50} for α-glucosidase from baker's yeast.[52]

Previous studies have demonstrated the effects of flavonoids (quercetin and kaempferol) in inhibiting α-glucosidase activity for diabetes treatment.[54] Similarly, anacardic acids have also demonstrated significant inhibitory activities for the enzymes α-glucosidase and α-amylase.[49] Furthermore, diabetic animals receiving a diet supplemented with flavonoids/phenolic compounds had reduced activity of intestinal α-glucosidases.[55] Hence, our results indicate that PECF can regulate blood glucose by inhibiting α-glucosidase enzymes.

3.3.2. Glucose Tolerance Test and Glycogen Analysis. PECF was initially administered at the highest dose (100 mg/kg i.p.), resulting in 14% reduction in blood glucose levels at 15 min compared to the hyperglycemic control group. When lower dosages were used (10 and 1 mg/kg i.p.), they led to reductions of 24%, 16%, and 22%, and 45%, 43%, and 28% at 15, 30, and 60 min, respectively, as compared to the hyperglycemic control group. Dapagliflozin reduced blood glucose levels by approximately 42%, 35%, and 31% at 15, 30, and 60 min, respectively, in relation to the hyperglycemic control group (Table 3).

Figure 4A illustrates the effect of PECF (1 mg/kg) on blood glucose levels in relation to the dapagliflozin and hyperglycemic groups. In Figure 4B, reductions of 32% and 34% in the area under the curve of blood glucose levels were observed for the PECF and dapagliflozin groups, respectively, when compared to the hyperglycemic group.

For the PECF group, a higher hypoglycemic activity was achieved at lower concentrations, suggesting a hormetic effect, where a lower dose promotes the therapeutic effect.[56] In

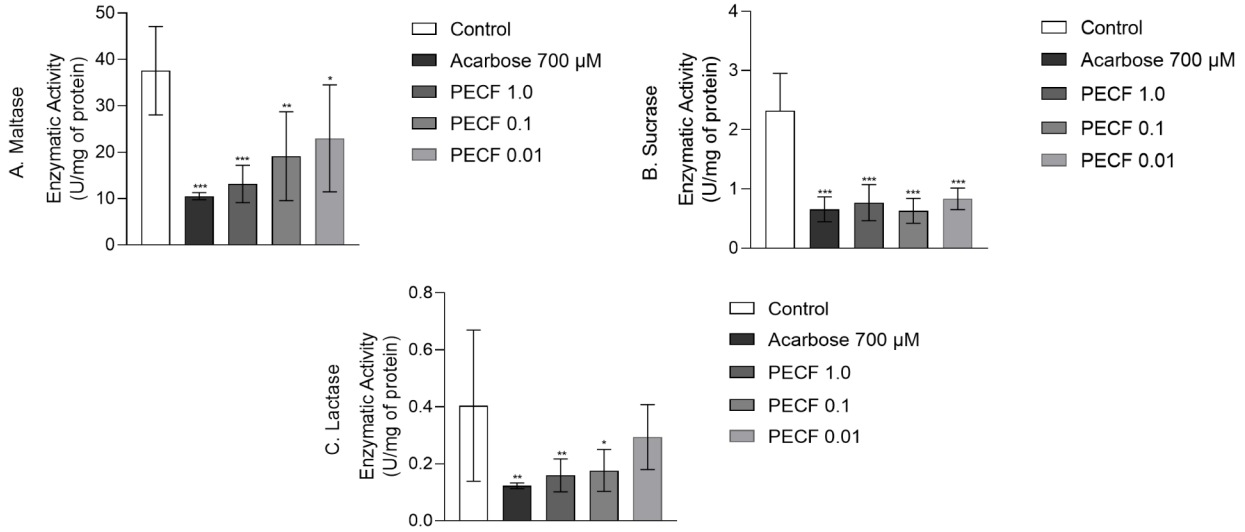

Figure 3. Inhibitory activity of PECF (1.0, 0.1, and 0.01 mg/mL) against different intestinal disaccharidase enzymes. (A.) Maltase. (B.) Sucrase. (C.) Lactase. *Each value represents the mean ± SEM of seven determinations. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p < 0.0001$.

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Table 3. Effect of PECF and Dapagliflozin on Fasting Blood Glucose Levels Measured in C57BL/6 Mice at Different Time Intervals After a Glucose Load (2 g/Kg)

	Blood Glucose (mg/dL), Time (min)				
Groups	0	15	30	60	120
Hyperglycemic	192.4 ±10.82	444.7 ± 15.82	341.6 ±7.29	236.6 ±12.22	193.6 ± 12.87
Dapaglifozin 3 mg/kg	208.7 ± 10.53	260.3 ± 5.31[a]	222.1 ± 8.17[a]	163.1 ± 15.35[a]	112.7 ± 6.380[a]
PECF 1 mg/kg	149.0 ± 5.32	241.6 ± 22.34[b]	195.0 ± 18.16[b]	169.7 ± 20.16[c]	149.0 ± 8.76
PECF 10 mg/kg	155.1 ± 14.65	335.3 ± 19.62[a]	283.7 ± 17.36[d]	184.0 ± 12.22[d]	138.3 ± 10.18[d]
PECF 100 mg/kg	169.0 ± 11.07	380.3 ± 11.64[c]	357.6 ± 13.27	244.1 ± 12.04	181.9 ± 11.93

[a]****$p < 0.0001$. [b]***$p \leq 0.001$ [c]**$p \leq 0.01$. [d]*$p \leq 0.05$.

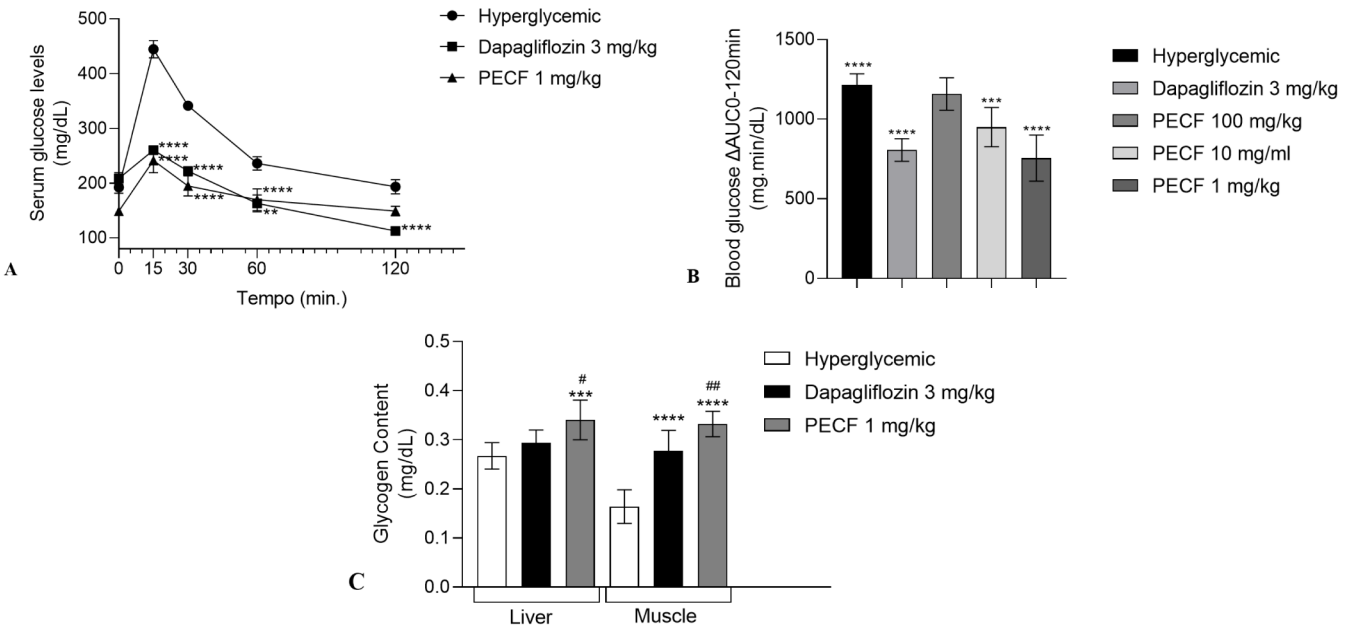

Figure 4. (A) Effect of PECF (1 mg/kg) on the glucose tolerance test in C57B/6 mice. (B) Area under the curve of blood glucose levels in response to PECF (1 mg/kg) in the glucose tolerance test. (C) Effect of PECF 1 mg/kg on muscular and hepatic glycogen content. *Each value represents the mean ± SEM of seven determinations. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p < 0.0001$. #$p \leq 0.05$, ##$p \leq 0.01$, ###$p \leq 0.001$, ####$p < 0.0001$ refer to the comparison between PECF (1 mg/kg) and dapagliflozin (3 mg/kg).

pharmacology, the term ″hormesis refers to a dose-dependent response characterized by opposing effects at different concentrations of a substance. Strikingly, low doses of an agent can induce a beneficial or stimulatory response, while high doses result in detrimental or inhibitory effects. This dose−response relationship is often represented by an inverted ″U″ or ″J″ shaped curve. The hormetic dose−response can occur as an overcompensation for a disruption in homeostasis or as a direct stimulation. The hormetic effect has been previously reported for the antidiabetic drug metformin.[57,58] Therefore, we suggest that small concentrations of these phenolic compounds existing in the cashew fiber could be sufficient to exhibit functional properties when applied in plant-based products.

We have attributed this glycemia-lowering effect to the combination of phenolic compounds found in the extract, since many of them have demonstrated actions on blood glucose, such as anacardic acids and flavonoids.

In *in vitro* models, anacardic acids acted in a dose-dependent manner to stimulate glucose transport in C_2C_{12} myotubes.[59] Also, anacardic acid led to a reduction in lipid accumulation in 3T3-L1 cells and the expression of fatty acid synthase and peroxisome proliferator-activated receptor gamma (PPARγ).[50] The reduction in the synthesis of these proteins has been considered beneficial for diabetes, as it improves insulin sensitivity and controls lipogenesis. Through the modulation of PPARγ, it is possible to reduce insulin resistance.[60] Meanwhile, a decrease in the activity of fatty acid synthase contributes to the reduction of lipid accumulation, which is crucial for preventing long-term complications of diabetes.[61] These changes ultimately favor more effective glycemic control and improve the metabolic profile in diabetic patients. Furthermore, Chung et al. demonstrated the antidiabetic effect of anacardic acids (500 μg/kg body weight) through a 12-week chronic *in vivo* study using mice fed with a high-fat diet.[50] Anacardic acid slowed lipid accumulation rates in the liver and alleviated insulin resistance.

With regard to flavonoids, the activity of myricetin, quercetin, and kaempferol, as well as their glycosides (myricetin derivative, quercetin derivative, quercetin-3-*O*-rutinoside, and kaempferol-*O*-*p*-coumaroyl rhamnoside) on glucose tolerance tests and glycemic regulation, has been reported.[62−65]

When the glycogen content in mice treated in the glucose tolerance test was evaluated (Figure 4C), PECF exhibited increases of 27% and 102% in the liver and muscle, respectively, compared to the hyperglycemic group. Dapagli-

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flozin showed an increase of 9% and 69% in the liver and muscle, respectively, compared to the hyperglycemic group.

PECF at 1 mg/kg had a difference of 16% (liver) and 19% (muscle) compared with the dapagliflozin-treated mice. Therefore, PECF proved to be more efficient in increasing glycogen storage as compared to dapagliflozin at 3 mg/kg (Figure 5C). Previous studies reported that myricetin, quercetin, and kaempferol increased hepatic and muscular glycogen.[62,63,65]

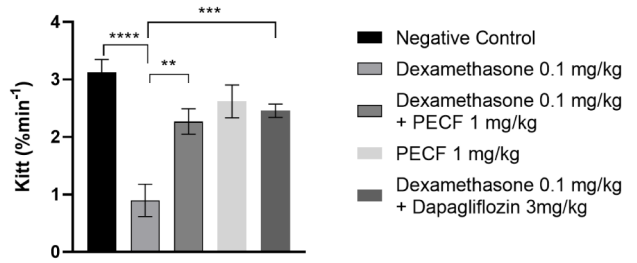

Figure 5. Chronic insulin resistance test induced by dexamethasone in mice using PECF at doses of 0.1 mg/kg and 1 mg/kg, besides dapagliflozin as positive control. *Each value represents the mean ± SEM of seven determinations. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p < 0.0001$.

3.3.3. Insulin Tolerance Test (ITT). The induction of insulin resistance by dexamethasone over 5 days is a reference model for the study of insulin resistance in skeletal muscle and adipose tissue. In our model, dexamethasone at a dose of 0.1 mg/kg s.c. was responsible for the expected loss of insulin sensitivity. On the other hand, the group of insulin-resistant mice treated with PECF and dapagliflozin (3 mg/kg i.p.) showed strong sensitivity, corresponding to an increase of 153% and 173% when compared to the dexamethasone group (Figure 5).

The results obtained from the glucose tolerance test and insulin resistance test are consistent with studies showing that the intake of phenolic compounds can reduce blood glucose levels, subsequently decreasing the risk of type 2 diabetes.[65−68] Therefore, the effect of PECF (1 mg/kg) in reversing insulin resistance can be attributed to anacardic acids[49,55] in combination with the flavonoids myricetin, quercetin, kaempferol, and their glycosides.[61−64]

Carvalho et al. observed that whole cashew fiber was not able to reduce glucose levels in animals fed for 15 weeks.[69] On the other hand, the consumption of cashew fiber devoid of low molecular weight compounds promoted the reduction of glycemia, insulin, and ghrelin. Later on, Carvalho et al.[10] also found that cashew fiber without low molecular weight compounds managed to reverse insulin resistance based on the HOMA-IR index (calculated as the product of fasting blood glucose concentration multiplied by fasting insulin concentration, divided by 22.5).[10] These findings revealed that cashew's dietary fibers can exert some beneficial effects on insulin regulation, even after the extraction of low molecular weight compounds, which are composed of phenolic compounds, as well as fatty acids and sugars. Indeed, dietary fibers may act as prebiotic components by feeding beneficial gut bacteria that produce short-chain fatty acids, which play a role in glucose regulation and improving metabolic health.[70] Meanwhile, phenolic compounds can exert antidiabetic effects through different mechanisms of action, depending on the polyphenol type, such as suppression of gluconeogenesis, inhibition of the enzymes dipeptidyl peptidase-4 (DPP-4), α-amylase and α-glucosidase, decrease of insulin resistance, and enhancement of insulin secretion.[53]

In our study, we used ITT, which is the more accurate tool for evaluating insulin sensitivity.[71] In this regard, since we have described herein the positive effects of the phenolic compounds from the cashew fiber for the improvement of insulin sensitivity in insulin-resistant animals, careful evaluation is needed before considering a possible removal of low molecular weight compounds from its dietary fibers.

3.3.4. Determination of the Oxidative Stress Biomarkers GSH and TBARS. Various noncommunicable diseases (NCDs), such as diabetes, are associated with oxidative stress. Glutathione is a tripeptide containing thiol (g-L-glutamyl-L-cysteinyl-glycine) present in the human body and in rodents in its reduced form (GSH). When glutathione reacts with reactive oxygen species (ROS), it is oxidized to glutathione radical (GSSG), which is regenerated to its reduced form through the action of glutathione reductase.[71] The TBARS test is commonly used to assess the level of lipid peroxidation and serves as a good indicator of oxidative stress in biological samples.[65] In addition to reducing oxidative damage, it has the advantages of improving glycemic control and reducing cardiovascular risk, since lipid oxidation may lead to the development of atherosclerosis and other heart diseases.[72,73] In animal models of diabetes that mimic hyperglycemic states, there is a reduction in the amount of glutathione in the liver, skeletal muscle,[74] and kidneys.[75−77]

In our study, the group treated with PECF 1 mg/kg showed an increase in GSH concentration in the liver (159%), kidneys (163%), and muscle tissue (80%) in the glucose tolerance test when compared to the hyperglycemic group, indicating that PECF possesses good antioxidant activity (Figure 6A).

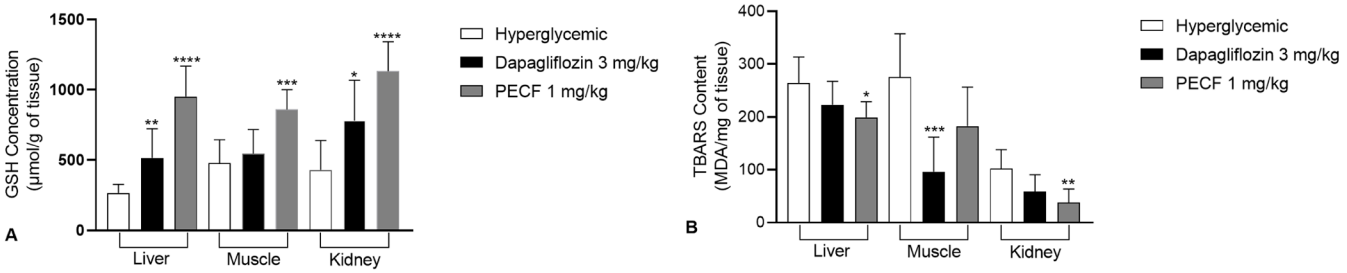

Figure 6. Effect of PECF (1 mg/kg) on the levels of oxidative stress biomarkers in hepatic, renal, and muscular tissues from C57B/6 mice. (A.) GSH concentration. (B) TBARS content. *Each value represents the mean ± SEM of seven determinations. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$, ****$p < 0.0001$.

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The PECF-treated group reduced the content of TBARS in the liver (24%) and kidneys (63%) compared to the hyperglycemic group, suggesting protection against oxidative stress. This effect is beneficial to diabetic patients, who are exposed to renal damage due to protein glycation in the nephrons.[77] However, there was no significant difference between the PECF-treated group (33%) and the hyperglycemic group for muscle tissue, while dapagliflozin showed a 64% reduction (Figure 6B).

Earlier, a study involving volunteers showed that the consumption of cashew juice led to an improvement in oxidative stress status, presenting decreased levels of malondialdehyde (MDA) and increased activities of antioxidant enzymes in the plasma.[78] Indeed, cashew juice contains many phenolic compounds found in its fiber, such as quercetin 3-*O*-rhamnoside and myricetin 3-*O*-rhamnoside.[79] Our results indicate that treatment with PECF can assist in reducing oxidative stress and improving glucose control, offering potential benefits for diabetic patients.

3.3.5. GLUT-4 Gene Expression. The results presented in Figure 7 indicate that treatment with 0.1 mg/kg dexamethasone resulted in a significant reduction in GLUT-4 gene expression, as evidenced by the decrease in relative expression compared to the control group. Indeed, dexamethasone has a side effect of inducing insulin resistance, a condition in which GLUT-4 expression is typically reduced in insulin-sensitive tissues, such as skeletal muscle. This decrease in GLUT-4 expression contributes to lower glucose uptake by cells, exacerbating hyperglycemia and worsening glycemic control.[80]

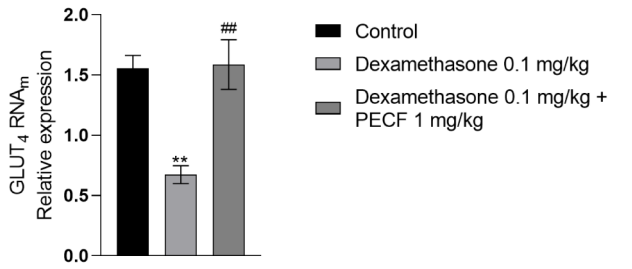

Figure 7. Effect of PECF (1 mg/kg) on relative gene expression of GLUT-4 in muscle cells of C57Bl/6 mice subjected to insulin tolerance test. *Each value represents the mean ± SEM of seven determinations. **;##$p \leq 0.01$.

On the other hand, the group treated with the combination of dexamethasone 0.1 mg/kg and PECF 1 mg/kg showed significantly higher GLUT-4 expression compared to the group treated only with dexamethasone. This increase suggests that PECF possesses a protective or restorative effect capable of counteracting the adverse effects of dexamethasone on GLUT-4 expression. This result indicates that PECF may improve insulin sensitivity by restoring GLUT-4 expression and thereby enhancing the glucose uptake capacity of the target tissues. The ability of PECF to elevate GLUT-4 expression in the context of dexamethasone-induced insulin resistance points to its potential as a therapeutic agent in conditions related to type 2 diabetes mellitus and other associated metabolic disorders. The restoration of GLUT-4 expression is a key factor for improving glucose uptake.[81] These data suggest that PECF may play a significant role in modulating GLUT-4 expression, with important therapeutic implications for conditions of insulin resistance.

In conclusion, we have demonstrated the hypoglycemic effect of PECF using low doses (1.0 mg/kg) through short-term acute and chronic preclinical tests. In glucose tolerance test and insulin sensitivity, its hypoglycemic effect appears to be due to the synergistic action of its phenolic compounds, mainly gallic acid, anacardic acids, and flavonol glycosides. The mechanism of action of PECF seems to be related to its inhibitory activity on α-glucosidase and its antioxidant properties by increasing glutathione and reducing TBARs in the liver and kidneys, besides increasing GLUT-4. Thus, since cashew fiber has proven to be a good source of glycemia-lowering phenolic compounds, its flour or extract (PECF) could be used as functional ingredients in plants-based products and nutraceuticals to aid in the prevention and control of diabetes and other associated comorbidities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsfoodscitech.5c00074.

Fig. S1. UPLC-HRMS chromatogram of the PECF extract; Table S1. Compounds from PECF extract characterized by NMR analysis; (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

PECF, phenolic-rich extract from the cashew fiber; DM2, Type II diabetes mellitus; GLUT-4, glucose transporter 4

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