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Article

Investigating the Hypoglycemic Potential of Phenolic-Rich Extracts for Upcycling into Sugary Processed Foods

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ABSTRACT: Phenolic compounds can act in different stages of glucose metabolism; however, the mechanisms involved in the interactions with glucose have yet to be fully elucidated. The aim of this study is to take advantage of the availability of bioactive compounds in waste from large food production chains, to evaluate the interaction between phenolics and glucose, and to reduce its glycemic impact. The impact of emerging technologies to promote glucose/phenolics interactions was never evaluated. Microwaves and ultrasound did not represent an advantage under the conditions tested to increase the phenolics-glucose interaction. The green coffee (GCE) and peanut skin (PSE) extracts lowered 30% of free glucose content at concentrations of 6.83 and 5.40 mg/mL, in addition to additive effects between these extracts in the decrease of free glucose. PSE showed a higher potential for α-glucosidase and α-amylase inhibition. Therefore, PSE exhibits higher hypoglycemic potential due to its chemical complexation capacity and digestive enzymes inhibition.

KEYWORDS: *phenolic compounds, bioactive extracts from residues, low glycemic index, green coffee, orange residues, peanut skin*

1. INTRODUCTION

Diabetes mellitus is one of the most prevalent metabolic diseases worldwide, affecting around 537 million adults, and approximately 90% of these cases correspond to type 2 diabetes mellitus (T2DM); the prediction for 2045 is up to 783 million people diagnosed, despite the characteristic under-reporting of this disease.[1] Interventions aimed at treating T2DM have the main goal of controlling postprandial glycemia.[2] Metformin and acarbose are widely used in the treatment of T2DM; however, their continued use is often associated with gastrointestinal disturbance, such as flatulence, diarrhea, and nausea, which has an impact on patient adherence to treatment.[3] For all that, screening for natural compounds that can interfere with the glycemic response without triggering side effects is of paramount importance.

Phenolic compounds are a large class of secondary metabolites targeted at plant defense and their main characteristic is the presence of aromatic rings containing hydroxyl groups in their chemical structure.[4] They can be divided into phenolic acids, such as hydroxycinnamic acids and hydroxybenzoic acids; flavonoids, including the classes of flavones, flavonols, flavanones, flavan-3-ols (catechins), isoflavones, and anthocyanidins; stilbenes, represented mainly by resveratrol; lignans; and tannins, such as condensed and hydrolyzable tannins.[5]

The wide availability of polyphenols in nonedible parts of vegetables, usually discarded during industrial processing, provides an opportunity to upcycle these agroindustrial residues, since discarding is not only associated with environmental degradation but also leads to the loss of byproducts with biotechnological and economic potential.[6] Considering the urgent demands set out in the Sustainable Development Goals (SDGs), the recovery of food industry waste for the extraction of high value-added compounds becomes an ideal choice capable of combining the promotion of sustainable production and the benefits of establishing a circular economy.[7] In this sense, agroindustrial byproducts can be used to recover molecules of interest, such as phenolic compounds with great antioxidant power, for incorporation into foods, cosmetics, and pharmacological products.[8] Previous studies have reported high levels of flavonoids in orange byproducts,[9−11] phenolic acids such as chlorogenic acid and caffeic acid in green coffee beans[12,13] and procyanidins and catechins in peanut skins,[14,15] indicating that these byproducts present distinct classes of phenolic compounds, which could result in different bioactivity response, since each class of phenolic compound could interact with others molecules, such as glucose, in different ways.

Some phenolic compounds can act in different stages of glucose metabolism, thus, impacting the glycemic response. In studies where the intake of anthocyanins or flavonoids was combined with glucose or maltose, the phenolic compounds were able to lower postprandial glycemia in mice and diabetic rats.[16,17] However, the mechanisms involved in the interactions

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of phenolic compounds and glucose have yet to be fully elucidated, and this hypoglycemic effect observed is more often related to the inhibition of digestive enzymes than to the chemical interactions themselves.[18,19]

Despite that, it is known that some phenolic compounds can interact with macronutrients, such as carbohydrates, mainly through hydrophobic, covalent, and hydrogen bonds.[20] Most studies that evaluated the combined intake of different types of carbohydrates and polyphenols have observed a lower absorption of this macronutrient.[21] In a study analyzing the *in vitro* codigestion of bread and raspberry extract, it was possible to observe that this combination led to a dose-dependent decrease in starch digestibility.[22] Besides, the formation of hydrophobic and hydrogen bonds between starch and polyphenols is thought to be the cause of resistance to the action of intestinal enzymes.[23] Bioactive compounds such as procyanidins and anthocyanins can interact with pectin, cellulose, and dietary fibers, mainly through hydrogen bonds between the hydroxyl groups of the polyphenols and the oxygen atoms of the polysaccharides.[24]

One hypothesis that had to be tested was whether the ability of complexation between phenolic compounds and simple carbohydrates could be increased by the use of processing technologies such as microwave and ultrasound. In the specific case of lotus seed starch and green tea polyphenols, these technologies have promoted V-type complexes between amylose and phenolic compounds, resulting in a lower release of glucose molecules by digestive enzymes.[25] As far as we know, there are no studies involving the application of these processing technologies in glucose and polyphenols interaction. For this reason, our hypothesis is that the interaction between glucose and phenolics can be promoted by the application of physical methods using emerging technologies. To this purpose, the evaluation of extracts featuring different classes of phenolic compounds can elucidate the mechanisms by which these interactions happen.

Therefore, this study aims to understand how phenolic compounds mainly from coffee, orange, and peanut industrial coproducts may interact with glucose (investigating whether, or not, the application of emergent processes such as microwaves and ultrasound could affect these chemical interactions to reduce glucose bioavailability) and the capacity of these phenolics to inhibit carbohydrate digestive enzymes, also reducing glucose bioavailability.

2. MATERIALS AND METHODS

2.1. Chemicals and Reagents. Milli-Q water with a resistivity of 18.2 MΩ·cm (EMD Millipore Corporation, Merck, Darmstadt, Germany), gallic acid, tannic acid, trolox, AAPH (2,2′-Azobis (2-methylpropionamidine) dihydrochloride), fluorescein sodium salt, porcine pancreatic α-amylase, α-glucosidase from *Saccharomyces cerevisiae*, para-nitrophenyl-α-D-glucopyranoside, and reduced glutathione were purchased from Sigma-Aldrich (Darmstadt, Germany). The reference standards p-coumaric acid and epigallocatechin gallate were also purchased from Sigma-Aldrich. The standards chlorogenic acid, caffeic acid, caffeine, narirutin, hesperidin, hesperetin, tangeretin, gallic acid, procyanidin B1, procyanidin B2, catechin, epicatechin, and epicatechin gallate were acquired from Extrasynthese (Genay, France).

Ethanol (99.5%), glucose, sodium carbonate, soluble starch, and Folin-Ciocalteu reagent were obtained from Dinâmica (São Paulo, Brazil). Potassium phosphate monobasic anhydrous, sodium chloride, and formic acid were purchased from Synth (São Paulo, Brazil). Methanol (99.9%, HPLC grade) was obtained from JT Baker (Bridgewater, USA). The glucose quantification kit was acquired from Bioclin (Belo Horizonte, Brazil).

2.2. Sample Preparation. Low-quality green coffee grains, orange juice industrial byproducts, and peanut skin from industrial peanuts plants were obtained from the following companies: Minasul Coperative (Varginha, Minas Gerais, Brazil), Cutrale (Araraquara, São Paulo, Brazil), and Coplana Coperative (Jaboticabal, São Paulo, Brazil), respectively. The samples of green coffee nonconforming grains are from the *Coffea arabica* species and include mostly immature and broken beans. The orange juice byproducts (*Citrus sinensis*) are derived from the extraction of juice consisting of peels, seeds, and pomace. The peanut skin samples are from the *Arachis hypogaea* species and Runner variety from the industrial blanching processing of the peanuts.

The green coffee residues were milled in a knife and hammer granulator mill (Treu, model 740646, Rio de Janeiro, Brazil). The orange byproducts and peanut skin were received in pellets and were milled in a blender. All samples were sieved on 10 mesh (W.S Tyler, Wheeling). After processing, the samples were stored frozen until further analysis.

2.3. Production of Phenolic-Rich Extracts. The green coffee extract (GCE), orange byproducts extract (OBE), and peanut skin extract (PSE) were obtained in hydroalcoholic solution containing 50% of ethanol (v/v), according to the method of Nakajima et al.[9] with slight modifications. In an Erlenmeyer flask, 10g of the solid byproduct was added with 250 mL of hydroalcoholic solution and submitted to an ultrasound bath with a frequency of 40 kHz at 30 °C for 15 min, followed by stirring in an orbital shaker at 200 rpm and 25 °C for 15 min. The extracts were vacuumed and taken to a rotavapor evaporator (Rotavapor RE, Büchi, Switzerland) at 50 °C for approximately 90 min to remove the solvent. The concentrated extracts were freeze-dried and stored for further analysis. The extraction yield was calculated as the mass of dry extract (g) divided by the mass of solid byproduct (g) from three extractions on different days, and the result was expressed in percentage.

2.4. Determination of Total Phenolic Compounds. The quantification of total phenolic compounds present in the extracts was based on the Folin-Ciocalteu method.[26] The assays were reproduced in triplicate, with results expressed in μg of gallic acid equivalents per milligram of dry extract (μg of GAE/mg of DE).

2.5. Identification and Quantification of Major Phenolic Compounds by High-Performance Liquid Chromatography (HPLC). The phenolic compounds present in the extracts were analyzed by High-Performance Liquid Chromatography using a Dionex Ultimate 3000 HPLC system (Dreiech, Germany) with DAD detector and C18 column (3 μm, 120 Å, 4.6 mm × 150 mm) for separation at 30 °C.

The GCE was diluted in a methanol:water solution (50:50, v/v), centrifuged at 5000 rpm/10 min and filtered using a 0.45 μm syringe filter (PVDF, Millipore, Massachusetts). The filtered extract was analyzed according to Santana and Macedo.[27] The mobile phases (A) water/formic acid 99.9:0.1 v/v and (B) methanol/formic acid 99.9:0.1 v/v were used in a linear gradient mode: 90% A (0−15 min), 90% A (15−25 min), 80% A (25−35 min), 80% A (35−40 min), 74% A (40−55 min), and 90% A (55−60 min). The eluent flow rate was 0.5 mL/min. The standard compounds used for comparison were chlorogenic acid, caffeic acid, and caffeine.

The OBE was diluted in a methanol:water solution (70:30, v/v), centrifuged at 5000 rpm/10 min, and filtered with a 0.45 μm membrane (PTFE, Millipore, Massachusetts) to be submitted to chromatographic analysis. The condition for separating the compounds were described by Barbosa et al.[11] The mobile phases (A) water/formic acid 99.9:0.1 v/v and (B) methanol/formic acid 99.9:0.1 v/v were used in a linear gradient mode: 90% A (0−5 min), 90% A (5−80 min), 20% A (80−85 min), 20% A (85−90 min), and 90% A (90−95 min). The flow rate was set at 0.6 mL/min. The standard compounds used for identification were narirutin, hesperidin, hesperetin, and tangeritin.

As for PSE, the extract was diluted in water and centrifuged at 5000 rpm/10 min. The supernatant was ultrafiltered through a 10 kDa

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membrane (Amicon, Millipore, USA) at 4000 g/60 min and then filtered by using a 0.45 μm syringe filter (PVDF, Millipore, Massachusetts) for chromatographic analysis. The filtered extract was analyzed according to Fernandes et al.[15] The compounds were identified using the mobile phases (A) water/formic acid 99.9:0.1 v/v and (B) methanol/formic acid 99.9:0.1 v/v were used in a linear gradient mode: 92% A (0−5 min), 92% A (5−13 min), 85% A (13−45 min), 75% A (45−67 min), 57% A (67−77 min), 50% A (77−95 min), 35% A (95−97 min), and 92% A (97−107 min). The flow rate was 0.5 mL/min. The standard compounds used for identification were gallic acid, procyanidin B1, procyanidin B2, catechin, epigallocatechin gallate, epicatechin, epicatechin gallate, and p-coumaric acid.

The individual compounds were identified by comparing their retention time and absorption spectrum under the same conditions as the standards. The absorption spectra and chromatograms were obtained at 280 and 330 nm for GCE; 260 and 280 nm for OBE; and 280 and 320 nm for PSE. The analysis was performed in triplicate, and the results were expressed in μg/mg of dry extract.

2.6. Determination of the Antioxidant Activity. The antioxidant activity of the extracts was determined by the ORAC method described by Dávalos et al.[28] and adapted by Macedo et al.[29] The experiment was performed in triplicate, and the results were expressed in μmol of Trolox equivalents per mg of dry extract (μmol Trolox equivalent/mg DE).

2.7. Evaluation of Different Processes (Microwaves and Ultrasound) on the Complexation of Glucose and Phenolic Compounds. Aqueous solutions of glucose (10 mg/mL) were prepared with the addition of the analytical standards of phenolic compounds: gallic acid and tannic acid, separately and at concentrations ranging from 0 to 10 mg/mL. The analytical standards were chosen for this assay to represent phenolic acids with low or high molecular weight, respectively. Glucose quantification was assayed using a glucose oxidase-peroxidase method kit (Bioclin, Belo Horizonte, Brazil), following the manufacturer's instructions, to assess a possible decrease in free glucose content in the solutions after the phenolic acid addition.

Based on the results of the glucose content of the solutions, a concentration of 1 mg/mL gallic acid was chosen to evaluate the probable effect of different processes on the availability of glucose. To verify the influence of microwaves on the complexation of glucose and gallic acid, the solutions were subjected to microwave at 100 W for 120 and 180 s or 200 W for 30, 60, and 90 s. The time intervals at each potency were defined by the maximum exposure time to the microwave without causing evaporation losses. As for the influence of ultrasound, the solutions were subjected to an ultrasound bath at 30 W and a frequency of 40 kHz for 10 or 20 min. After exposure to the different processes, the glucose content was quantified according to the method aforementioned.

2.8. Complexation Potential between Glucose and Phenolic-Rich Extracts. Glucose solutions (10 mg/mL) were prepared by adding different concentrations of the GCE, the OBE, and the PSE separately. The glucose content in the different solutions was quantified using the glucose oxidase-peroxidase method (Bioclin, Belo Horizonte, Brazil). The results were expressed as the EC30 values, relative to the effective phenolic-rich extract concentration to achieve a 30% decrease in free glucose compared to glucose solutions, through nonlinear regression.

To evaluate the effect of the combination of GCE and PSE, glucose solutions (10 mg/mL) were prepared with the extracts added in different proportions (3:1, 1:1, and 1:3) and concentrations based on the EC30 of each extract individually, followed by glucose quantification according to the method previously described. After the determination of the EC30 values of the combined extracts, it was possible to define the effect of this interaction by isobolographic analysis.[30]

2.9. Inhibition of α-Glucosidase and α-Amylase Activity. The enzymatic activity of α-glucosidase from *Saccharomyces cerevisiae* (Sigma-Aldrich, Germany) was determined according to the manufacturer's method. This method is based on the hydrolysis of the substrate para-nitrophenyl-α-D-glycopyranoside by α-glucosidase and the consequent release of para-nitrophenol. Enzymatic activity was calculated in units per milligram of enzyme (U/mg), where one unit of activity corresponds to the capacity to release one μmol of para-nitrophenol per minute of enzymatic reaction.

The effects of the GCE, OBE, and PSE on the inhibition of α-glucosidase activity were determined according to the method of He and Lu[31] with modifications. 500 μL of the extract was added to potassium phosphate buffer (67 Mm; pH 6.8), 20 μL of reduced glutathione (3 mM) and 20 μL of the α-glucosidase enzyme (0.6 U/mL). After incubation in a water bath at 37 °C for 10 min, 50 μL of the substrate para-nitrophenyl-α-D-glycopyranoside (10 mM) was added and the reaction medium was kept at 37 °C for 20 min. For colorimetric determination, 200 μL of the reaction medium was added to 800 μL of sodium carbonate (100 mM) and the absorbance was read at 400 nm on a spectrophotometer (UV-5100, Metash, China).

The inhibition of porcine pancreatic α-amylase activity was determined as described by Kwon et al.[32] A total of 500 μL of the extracts in different concentrations or deionized water for the control was incubated with 500 μL of α-amylase solution (1.3 U/mL) at 25 °C for 10 min. After preincubation, 500 μL of 1% starch solution in sodium phosphate buffer (20 mM with 6.7 mM NaCl, pH 6.9) was added in each reaction tube and incubated at 25 °C for 10 min. The enzymatic reaction was stopped with 1 mL of DNS (3,5-dinitrosalicylic acid) reagent followed by a boiling water bath for 5 min and addition of 10 mL of deionized water in each tube for dilution. The absorbance was measured at 540 nm on a spectrophotometer (UV-5100, Metash, China).

The results of both assays were expressed as a percentage of inhibition relative to the control according to the following equation:

$$\text{Inhibition}(\%) = \left(1 - \frac{\text{Abs sample} - \text{Abs blank sample}}{\text{Abs control} - \text{Abs blank}}\right) \times 100$$

From the inhibition values at different concentrations of each extract, the IC50 (mean inhibitory concentration) of the extracts was calculated by nonlinear regression.

2.10. Statistical Analysis. The results were expressed as the mean ± standard deviations. Analysis of variance (one-way ANOVA) and the Tukey *post hoc* test were performed to determine statistically significant differences ($p < 0.05$). EC30 and IC50 determinations were calculated by nonlinear regression. These analyses were carried out using GraphPad Prism 8.0 software (San Diego, California, USA). The isobolographic analysis was performed using Origin 8.0 software (Northampton, Massachusetts, USA).

3. RESULTS AND DISCUSSION

3.1. Characterization of the Agroindustrial Byproduct Extracts. The yield, the phenolic content, and the antioxidant capacity of the extracts are provided in Table 1. OBE had the highest yield compared to the other extracts, and this is probably due to its total carbohydrate content, as shown in the centesimal composition (Table S1). Given that sugars have a high affinity for the solvents used in the extraction process, it is

Table 1. Yield, Total Phenolic Content and Antioxidant Capacity of the Agroindustrial Byproduct Extracts[a]

Extracts	Yield (%)	Total phenolic content (μg GAE/mg DE)	ORAC (μmol Trolox equivalent/mg DE)
GCE	14.07% ± 1.89[b]	105.96 ± 8.05[b]	2964.9 ± 163.40[b]
OBE	25.91% ± 0.96[a]	17.43 ± 2.62[c]	960.5 ± 104.50[c]
PSE	15.37% ± 0.20[b]	401.08 ± 21.31[a]	3737.9 ± 246.30[a]

[a]Values expressed as mean ± standard deviation. Different letters represent significant differences between extracts ($p < 0.05$).

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expected that these could have been carried into the final extract.[33]

Regarding the total phenolic content of the extracts (Table 1), the PSE had the highest phenolic content corresponding to 401.08 ± 21.31 μg GAE/mg DE, followed by the GCE extract with 105.96 ± 8.05 μg GAE/mg DE and the OBE extract with the lowest phenolic content of 17.43 ± 2.62 μg GAE/mg DE. This same trend was observed when assessing the antioxidant capacity of the extracts through the ORAC assay (Table 1), given the significant correlation of antioxidant activity and phenolic compounds.[34] When analyzing the phenolic content of peanut skin extract, Fernandes et al.[15] found higher values (444.92 μg GAE/mg of extract) than those reported in the present study; however, the antioxidant capacity by ORAC was slightly lower, corresponding to 3099.06 μmol Trolox equivalent/mg of extract. The same was observed in the study by De Matos et al.[14] where they found 538 μg GAE/mg of extract and antioxidant capacity by the ORAC method of 3163 μmol Trolox equivalent/mg of extract. These results highlight the strong ability to recover phenolic compounds with antioxidant potential from peanut byproducts. For green coffee extract, Dias et al.[13] found a lower antioxidant capacity than the present study, corresponding to 832.5 μmol Trolox equivalent/mg of hydroethanolic extract, probably because the use of ultrasound in our extraction process contributed to the release of compounds with greater antioxidant potential.[35,36]

The phenolic profiles of the agroindustrial byproduct extracts were assessed by HPLC method (Table 2) and it showed that chlorogenic acid and caffeic acid are the main phenolic compounds in GCE, representing 141.527 ± 2.984 e 9.826 ± 0.258 μg/mg DE, respectively, corresponding to the profile seen in other studies with green coffee extracts.[13,37] In addition, high levels of caffeine were detected, as expected in coffee byproducts.,[35,37,38] The OBE was characterized by the presence of glycosylated flavanones, with hesperidin (15.387 ± 1.876 μg/mg DE) and narirutin (3.159 ± 0.154 μg/mg DE) as the main phenolic compounds identified. Similar to the present work, other studies also identified these flavanones as the major phenolic compounds in orange byproducts.[10,11] As for the PSE, compounds such as epicatechin and epicatechin gallate were the primary phenolic compounds detected, followed by catechin and procyanidins B1 and B2. These compounds were also found in peanut skin extract by Fernandes et al.[39] Cordeiro-Massironi et al.[40] were able to identify high levels of epigallocatechin gallate, ellagic acid, and epicatechin in aqueous extracts of peanut skin.

Table 2. Phenolic Profile of the Agroindustrial Byproduct Extracts[a]

Extracts	Compounds (μg/mg DE)	
GCE	Chlorogenic acid	141.527 ± 2.984
	Caffeine[b]	59.863 ± 2.206
	Caffeic acid	9.826 ± 0.258
OBE	Hesperidin	15.387 ± 1.876
	Natirutin	3.159 ± 0.154
	Tangeretin	0.200 ± 0.033
	Hesperetin	0.135 ± 0.031
PSE	Epicatechin	7.831 ± 0.199
	Epicatechin gallate	1.024 ± 0.010
	Catechin	0.538 ± 0.014
	Procyanidin B1	0.431 ± 0.011
	Procyanidin B2	0.353 ± 0.012
	Epigallocatechin gallate	0.204 ± 0.009
	Gallic acid	0.170 ± 0.007
	p-Coumaric acid	0.074 ± 0.000

[a]Values expressed as mean ± standard deviation. [b]Not a phenolic compound.

3.2. Complexation between Glucose and Isolated Phenolic Compounds and the Influence of Different Processes. The addition of gallic acid to glucose solutions had a dose-dependent effect on decreasing the free glucose content (Figure 1A). The EC30 value—relating to the effective concentration of gallic acid to decrease free glucose by up to 30% - was 1.03 mg/mL ± 0.12. Complexation between tannic acid and glucose (Figure 1B) also led to a decrease in free glucose with an EC30 of 2.78 mg/mL ± 0.65, i.e., tannic acid had less effect on decreasing free glucose compared to gallic acid, requiring the addition of higher doses to promote an equivalent chemical interaction. Concentrations above 2 mg/mL of both gallic and tannic acid did not result in statistically significant differences in the decrease of free glucose, suggesting a possible saturation of the interactions between glucose and phenolic acid.

Gallic acid is a low molecular weight phenolic acid with a simple structure that can interact with glucose molecules through hydrogen bonds from its hydroxyl groups.[20] On the other hand, the chemical structure of tannic acid, a high molecular weight phenolic acid, is composed of conjugated glucose and gallic acid molecules,[24] and this may have influenced its lower ability to complex with the glucose molecules present in the solution. Nonetheless, it is important to consider the critical role of enzymes in glucose quantification methods, and the observed effect may be attributable to enzymatic inhibition, underscoring a key limitation of this approach.

Due to the higher ability of gallic acid to interact with glucose, it was chosen for further tests at a fixed concentration of 1 mg/mL, to evaluate the influence of microwave and ultrasound applications on the decrease of free glucose. However, the use of microwaves and ultrasound to promote complexation between gallic acid and glucose was not able to influence the amount of free glucose (Table 3), since there was no statistically significant difference in the content of free glucose between microwave, ultrasound, and simple mixture.

The use of technologies such as microwaves and ultrasound in the complexation of phenolic compounds with starch was able to influence the increased interaction of polyphenols with the structure of amylose.[25] This interaction is associated with the formation of resistant starch, which has an impact on limiting the activities of digestive enzymes. The use of microwaves in solutions containing glucose can promote agitation of the hydroxyl groups of the glucose molecule, which can lead to changes in its conformation and promote the interaction of glucose with other molecules through hydrogen bonds. Nevertheless, this effect can only be observed with the establishment of high-intensity electric fields, requiring powers that exceed the capacity of industrial and domestic equipment.[41] The treatment with ultrasound probably did not have the expected effect, because it was also used at a lower power and frequency than necessary to promote the interaction between glucose and phenolic compounds.

3.3. Complexation between Glucose and Phenolic-Rich Extracts and Availability of Glucose. Regarding the possible complexation between glucose and the phenolic-rich

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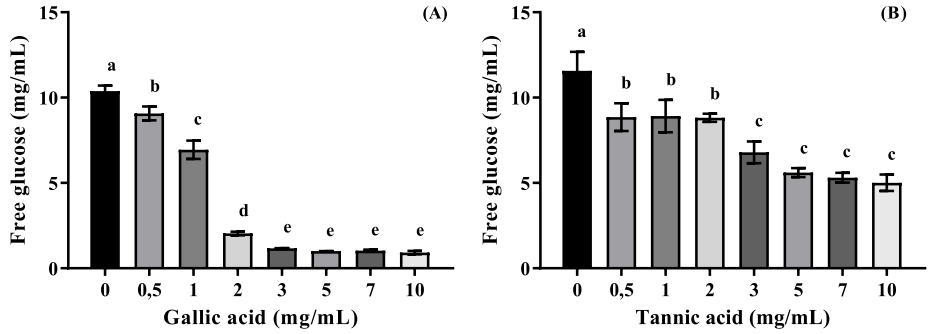

Figure 1. Free glucose content present in glucose solutions (10 mg/mL) added with different concentrations of gallic acid (A) and tannic acid (B). Different letters represent significant differences between extract concentrations ($p < 0.05$).

Table 3. Glucose Content in Solutions of Glucose (10 mg/mL) Added to Gallic Acid (1 mg/mL) Submitted to Different Processes[a]

Processes	Time	Glucose content (mg/mL)
Simple mixture	-	6.95 ± 0.54[a]
Microwave 100 W	120 s	6.93 ± 0.38[a]
	180 s	6.67 ± 0.15[a]
Microwave 200 W	30 s	6.70 ± 0.35[a]
	60 s	6.90 ± 0.62[a]
	90 s	6.90 ± 0.50[a]
Ultrasound 30 W	10 min	7.03 ± 0.21[a]
	20 min	7.63 ± 0.55[a]

[a]The data showed no statistically significant differences using ANOVA and the Tukey test ($p < 0.05$).

extracts (Figure 2), the results show that GCE had a dose-dependent effect on decreasing free glucose, with no significant differences at concentrations above 30 mg/mL. PSE had a greater effect when added at intermediate concentrations, between 15 and 20 mg/mL, and OBE had no impact on the decrease in free glucose at the concentrations tested. The EC30 values, i.e., the effective concentrations for a 30% decrease in free glucose compared to glucose solutions free of phenolic-rich extracts, were 5.40 mg/mL ± 0.16 and 6.83 ± 0.69 mg/mL for PSE and GCE, respectively.

GCE showed a greater complexing capacity with glucose and this may be related to the presence of specific phenolic acids in this extract, such as chlorogenic acid and caffeic acid,[35,38] as evidenced by the dose-dependent response similar to that observed with the addition of gallic acid. The prevalence of high molecular weight condensed tannins in peanut skin extracts, such as procyanidins and epicatechins,[39,40] may be related to the lower complexing capacity of PSE, as seen in the complexation between glucose and tannic acid.

OBE did not have the expected effect, leading to an increase in free glucose. According to the centesimal composition of the orange byproducts (Table S1), a high content of total carbohydrates was observed. In addition, the use of water

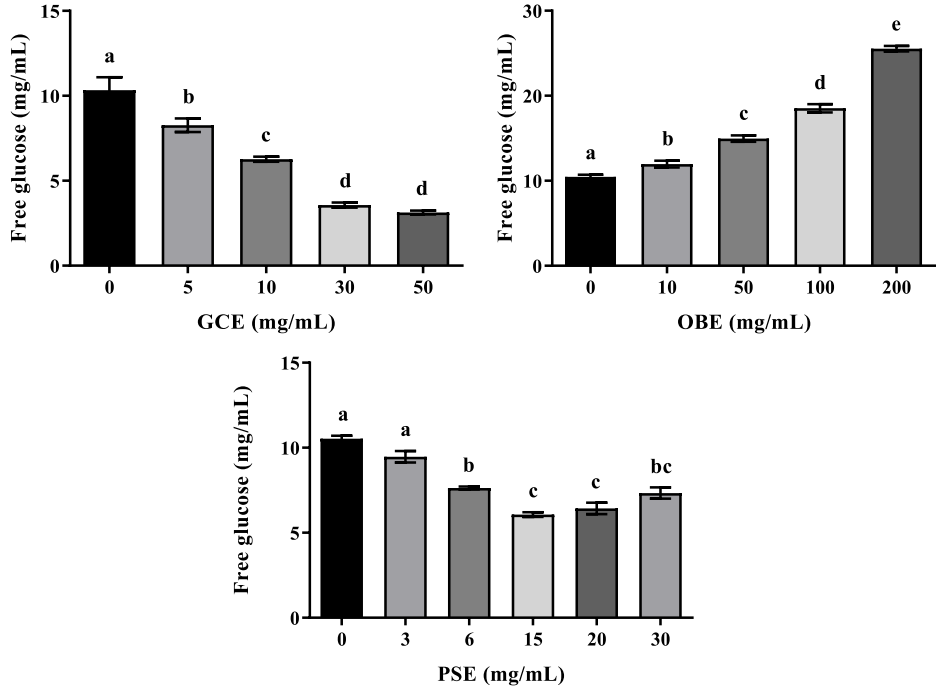

Figure 2. Free glucose content (mg/mL) in solutions with different concentrations of phenolic-rich extracts from agroindustrial byproducts. GCE: Green coffee extract; OBE: Orange byproducts extract; PSE: Peanut skin extract. Different letters represent significant differences between extract concentrations ($p < 0.05$).

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and ethanol to produce the extracts allowed for the solubilization of medium- and high-polarity compounds present in the sample.[33] The use of these solvents to obtain the OBE likely favored the extraction of these sugars along with the phenolic compounds of interest due to their high solubility in water. The phenolic profile of the OBE, characterized by the presence of glycosylated flavanones,[9,11] may also be related to their lower ability to interact with the glucose molecules in the solution.

Based on the EC30 values of the GCE and PSE, an attempt was made to evaluate the effect of combining these extracts on the decrease in free glucose. To do this, a new range of concentrations (20, 10, 5, and 2.5 mg/mL) was considered, covering the EC30 of the two extracts individually. When evaluating the effect of combining the two extracts in 3:1, 1:1, and 1:3 ratios, the EC30 of each ratio corresponded to 6.56, 6.06, and 6.54 mg/mL, respectively. These values were compared with the EC30 of the isolated extracts, which correspond to the theoretical curve plotted on the isobologram graph (Figure 3).

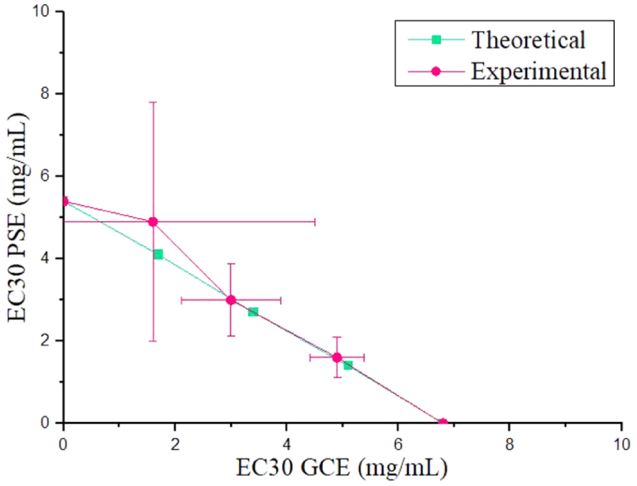

Figure 3. Isobologram shows the effect of the combination of green coffee extract (GCE) and peanut skin extract (PSE) on the decrease in free glucose.

Isobolographic analysis makes it possible to understand whether the effect of the combination is antagonistic or synergistic, when there is no overlap between the theoretical and experimental curves, and additive when these curves overlap.[30] As shown in Figure 3, the effect of combining GCE and PSE is additive for decreasing free glucose, showing that both extracts could be used together, in different proportions, without the action of one interfering with the other.

A possible interaction between the glucose molecules and the phenolic compounds present in the extracts may have led to a decrease in the availability of this monosaccharide, but the mechanism of action by which this interaction occurs is still uncertain.[21] This interaction probably has an effect on glucose absorption by decreasing the concentration of free glucose in the intestinal lumen.[19]

The absorption of polyphenols in enterocytes may depend on the chemical structure and glycosidic portion of the compounds. The enzyme lactase-phlorizin hydrolase, which acts on the apical side of the enterocytes, can hydrolyze these phenolic compounds conjugated to glucose, making them available for intestinal absorption.[21] In addition, glycosylated polyphenols can be transported into enterocytes via sodium-dependent glucose transporter 1 (SGLT-1).[42] Although it is possible that the complexation between some phenolic compounds and glucose may prevent the action of these enzymes and transporters, leading to metabolization by the microbiota in the colon and lowering postprandial glycemia, this could have a possible impact on the glycemic index of foods containing these extracts rich in phenolic compounds as ingredients.

3.4. Inhibitory Effect of Phenolic-Rich Extracts on α-Glucosidase and α-Amylase Enzyme Activity. Considering that the different classes of phenolic compounds can interfere with carbohydrate metabolism in several stages, phenolic-rich extracts were evaluated for their ability to inhibit the digestive enzyme α-glucosidase and α-amylase. It was possible to see that PSE exhibited a positive dose-dependent effect in inhibiting the activity of α-glucosidase, with an increase in enzyme inhibition proportional to the extract concentration (Figure 4). When assessing the inhibitory effect of the extract at concentrations ranging from 2.5−0.05 μg/mL, the IC50 value was 0.70 ± 0.36 μg/mL, indicating the concentration capable of inhibiting 50% of the enzyme activity.

PSE also showed a higher capacity to inhibit α-amylase (Figure 5) with an IC50 of 0.39 ± 0.03 mg/mL. This greater inhibitory activity against digestive enzymes may be attributed to the presence of epicatechins and procyanidins type B in the extract.[15] These flavonoids can inhibit digestive enzymes through the interaction with the active site of the enzyme, in a competitive and noncompetitive manner, reducing their hydrolytic activities.[43] PSE showed the highest inhibitory activity even when used in very low concentrations, an effect that was also observed by Cordeiro-Massironi et al.[40] when evaluating peanut skin extracts subjected to the *in vitro* digestion process.

The OBE also showed a dose-dependent effect in inhibiting the activity of α-glucosidase, although higher concentrations had to be applied compared to the PSE. The IC50 value of the OBE was 12.46 ± 2.01 mg/mL, so the PSE extract showed a stronger potential for inhibiting α-glucosidase than the OBE. However, when assessing the ability of the OBE to inhibit α-amylase, no inhibitory effect was observed at the concentrations tested (1−50 mg/mL; data not shown). When evaluating the phenolic-rich extract of citrus byproducts in the inhibition of α-glucosidase, Fernandes et al.[44] observed a high inhibitory potential of the extract at a concentration of 10 mg/mL against α-glucosidase, as for α-amylase, the same concentration of extract was able to inhibit less than 25% of the enzyme's activity. The flavonoids, hesperidin and narirutin, present in the OBE may be responsible for this effect, as these compounds may interact with digestive enzymes through hydrogen bonds between the chemical structures of these flavonoids and the amino acid residues of the enzyme's active site.[45]

GCE did not have a significant inhibitory effect on the α-glucosidase and α-amylase (data not shown) enzymes. Chlorogenic acid, the main phenolic compound identified in GCE, probably has no effect on inhibiting digestive enzymes, and its antihyperglycemic activity is generally related to a decrease in glucose absorption via SGLT-1 and GLUT2 transporters.[46,47]

Controlling carbohydrate absorption by inhibiting digestive enzymes can have a positive impact on lowering postprandial glycemic levels and preventing hyperglycemia.[48] Phenolic

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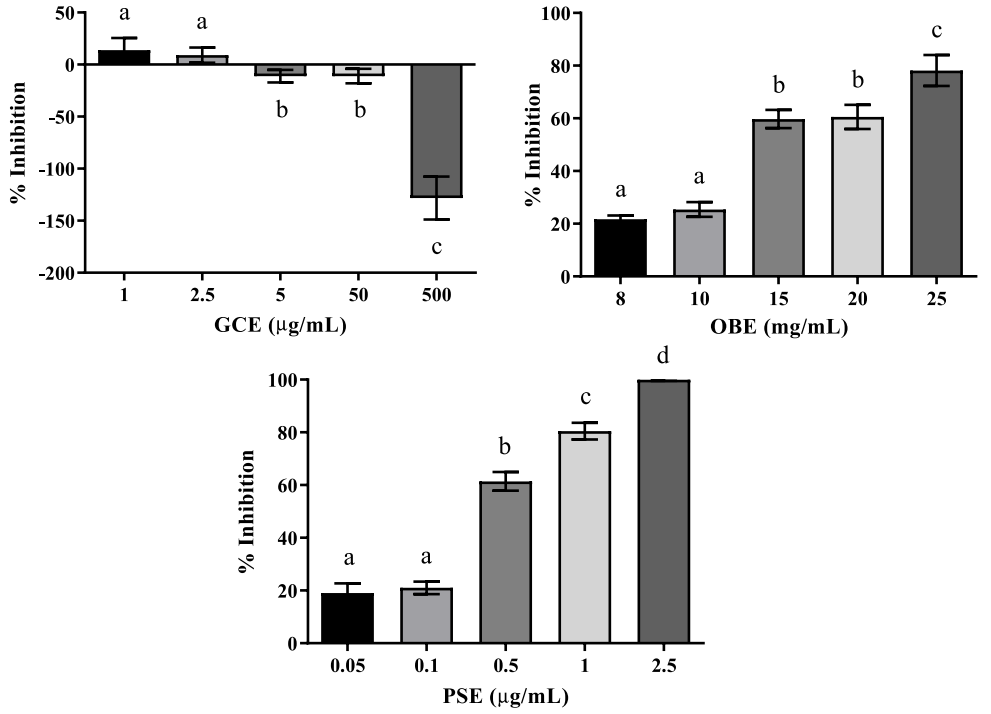

Figure 4. Percentage of inhibition of the α-glucosidase according to the different concentrations of agroindustrial byproduct extracts. GCE: Green coffee extract; OBE: Orange byproduct extract; PSE: Peanut skin extract. Different letters represent significant differences between extract concentrations ($p < 0.05$).

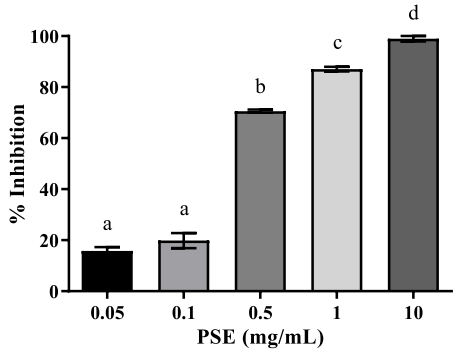

Figure 5. Percentage of inhibition of the α-amylase according to the different concentrations of peanut skin extract (PSE). Different letters represent significant differences between extract concentrations ($p < 0.05$).

compounds are related to their potential to inhibit the α-glucosidase enzyme, resulting in a decrease in the hydrolysis of oligosaccharides and preventing the release of glucose molecules. This mechanism is responsible for slowing down the digestion of carbohydrates in the apical portion of enterocytes and therefore contributing to a lower glycemic index.[49]

Phenolic compounds can probably interfere with the bioavailability of glucose in the intestinal lumen, decreasing the activity of digestive enzymes and possibly intestinal absorption. The PSE showed a high capacity for inhibiting digestive enzymes (α-glucosidase and α-amylase) and complexing with glucose molecules, while the GCE showed a greater capacity for complexing with glucose but without affecting the activity of digestive enzymes. The OBE extract was unable to decrease glucose availability and inhibit α-amylase, and its α-glucosidase inhibition effect was lower than that of PSE.

Compared to the other extracts analyzed, PSE showed a greater antihyperglycemic effect, due to its higher capacity of enzyme inhibition associated with the potential for chemical complexation with glucose. Although the results have demonstrated the potential for important use of these extracts in upcycling, for ingredients with a reduced glycemic index, further tests with other possible reduction mechanisms are still needed. Intestinal absorption *in vitro* studies using intestinal cell lines may be required to understand the action of these phenolic compounds in reducing glucose transport through the SGLT-1 and GLUT2 proteins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsfoodscitech.4c00811.

Table S1 (Centesimal composition of agroindustrial byproducts), Figure S1 (Chromatograms with detected polyphenols from green coffee extract), Figure S2 (Chromatograms with detected polyphenols from orange byproduct extract), Figure S3 (Chromatograms with detected polyphenols from peanut skin extract) (PDF)

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS

T2DM, Type 2 diabetes mellitus; GCE, Green coffee extract; OBE, Orange byproduct extract; PSE, Peanut skin extract; GAE, Gallic acid equivalents; DE, Dry extract; SDGs, Sustainable Development Goals

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