Cambuí (Myrciaria floribunda (West ex Willd.) O. Berg): A potential nutritional supplement for inhibition of COVID-19 infections

Cambuí (Myrciaria floribunda (West ex Willd.) O. Berg): Um potencial suplemento nutricional para a inibição de infecções por COVID-19

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ABSTRACT

In the present study, we suggest that the Myrciaria floribunda (West ex Willd.) O. Berg fruit (cambuí) is a natural source of potential molecules against COVID-19. Extracts from orange and purple cambuí were obtained by using pressurized hot water extraction (PHWE). Extraction overall yield was 39.66 ± 1.62% and 33.00 ± 8.44% for the extracts of purple and orange cambuí, respectively. All analyzed extracts showed high total phenolic contents, especially those of purple fruits (3870.37 ± 353.09 mg GAE/100g). The total flavonoid content was 693.16 ± 180.09 and 770.08 ± 103.62 mg RE/100g for purple and orange fruit extracts, respectively. The secondary metabolite profile exhibited ellagic acid, ellagitannins, and derivatives of caffeic acid and ellagic acid. PHWE showed a good alternative for molecules separation from cambuí with promising potential for further in vitro and in vivo evaluation against Covid-19 infections.

Keywords: COVID-19, Myrciaria floribunda (West ex Willd.) O. Berg, Myrtaceae, Phenolic compounds, Pressurized hot water extraction.

RESUMO

No presente estudo, sugerimos que a Myrciaria floribunda (West ex Willd.) O. Berg (cambuí) é uma fonte natural de moléculas potenciais contra a COVID-19. Os extratos de cambuí laranja e roxo foram obtidos através da extração com água quente pressurizada (EAQP). O rendimento geral da extração foi de 39,66 ± 1,62% e 33,00 ± 8,44% para os extratos de cambuí roxo e laranja, respectivamente. Todos os extratos analisados mostraram alto teor de compostos fenólicos totais, especialmente os extratos de cambuí roxo (3870,37 ± 353,09 mg GAE/100g). O conteúdo total de flavonóides foi 693,16 ± 180,09 e 770,08 ± 103,62 mg ER/100g para extratos de frutas púrpura e laranja, respectivamente. O perfil do metabolito secundário apresentou ácido elágico, elagitaninos e derivados de ácido cafeico e ácido elágico. EAQP mostrou uma boa alternativa para a separação de moléculas de cambuí com potencial promissor para avaliação in vitro e in vivo contra infecções por Covid-19.

Palavras-chave: COVID-19, Myrciaria floribunda (West ex Willd.) O. Berg, Myrtaceae, compostos fenólicos, extração com água quente pressurizada.

1 INTRODUCTION

The COVID-19 (coronavirus disease 2019) has been a public health emergency of global concern (Elizabeth *et al.*, 2021; Santos and Hanna, 2020). This pandemic has ongoing significant morbidity and mortality rates, which cause millions of cases leading to thousands of deaths. Hence, has been become an immediate need for the scientific community to find treatment and/or prevention for COVID-19 infections (Chojnacka *et al.*, 2020; Joshi *et al.*, 2021; Paraiso, Revel and Stevens, 2020).

The trend in food industries has been to the utilization of food additives due to enabling healthier life to the consumers (Galanakis, 2018). The consumption of functional foods containing bioactive molecules can provide an immunological and phytochemical strike against viruses (Galanakis, 2021).

Several molecules present in plant extracts such as phenolic compounds can be potential agents to COVID 19 treatment and prevention (Chojnacka *et al.*, 2020). For this, polyphenolic substances can inhibit COVID 19 enzymes, which are necessary to promote its replication and infection (Chojnacka *et al.*, 2020). The phenolic substances have been the potential to develop formulations for inhibiting coronavirus proteases. Associated with this, these natural molecules have been high safety for people due to their low side effects (Chojnacka *et al.*, 2020).

Plants from the family Myrtaceae produces fruits that have attracted significant the attention of the scientific community, due to their nutritional and functional properties for beneficial effects on human health (Seraglio *et al.*, 2018). Cambuí (*Myrciaria floribunda* (West ex Willd.) O. Berg) is the Myrtaceae native to Brazil, with globose fruits orange or purple. They can be consumed raw, or processed for the production of juices, jellies, or fermented products. Cambuí fruit is rich in vitamin C (129.43 mg of ascorbic acid/100 g) (Sirqueira Nascimento, Muniz and Cruz Silva, 2020), and contains high concentrations of phenolic compounds such as flavonoids (Santos *et al.*, 2020).

Pressurized Liquid Extraction (PLE) has been considered an efficient extraction process due to the use of liquid solvents under high pressure provide the increase of the solvent penetration into the plant-material matrix, hence, enhancing the overall extraction yield (Barbosa *et al.*, 2019; Burin *et al.*, 2022; Santos *et al.*, 2018).

Water can be used as a solvent-free of damage to the environment due to it being non-toxicity, as well as being naturally abundant and available at low cost. Moreover, pressurized hot water extraction (PHWE) is an efficient process for phenolic compound separation from vegetable matrices (Flórez, Conde and Domínguez, 2015; Plaza and

Turner, 2015). The present study aimed to separate polyphenols from cambuí by using PHWE for obtaining potential agents to studies against COVID 19 infections.

2 MATERIALS AND METHODS

2.1 PLANT MATERIAL

Orange and purple cambuí were collected in the fall seasons from in situ germplasm, in Itaporanga d'Ajuda, Sergipe State, Brazil (lat -11.116585º, long -37.186742º, 28m). They were then kept in a hot-air circulation oven at 60 ºC until about 5% humidity. After this, cambuí containing its seeds were crushed in a high-speed industrial blender to obtain particles ranging in size from 1.0 to 0.5 mm, stored in a refrigerator at 4 ºC, and protected from light until extraction occurred.

2.2 REAGENTS AND EXTRACTION METHODS

The main reagents and solvents used were Acetonitrile, Aluminum Nitrate PA (Synth), Sodium Carbonate Anhydrous PA (Dynamics), Dimethylsulfoxide PA (Synth), Folin Ciocauteau (Dynamic), methanol, Potassium Acetate (Synth), Formic Acid ≥ 95% (Sigma - Aldrich), Gallic Acid Monohydrate PA (Neon), Hydrated rutin ≥ 94% (Sigma - Aldrich), Water Milli-Q were used as received.

2.3 PRESSURIZED HOT WATER EXTRACTION

Pressurized water extractions were performed by using 2 g of dry cambuí and distilled water extraction at a temperature of 60 °C, 100 bar pressure, and a constant flow rate of 1 mL/min^{-1} for 60 min. After extraction, samples were dried in a hot air circulating oven until a constant weight was obtained, after which they were stored in a refrigerator at 4 ºC and protected from light until the moment of chemical characterization.

2.4 DETERMINATION OF TOTAL PHENOLIC COMPOUNDS

Phenolic compounds from the cambuí extracts were analyzed with the Folin-Ciocalteu colorimeter method (Perioto *et al.*, 2022). In a test tube, 0.5 ml of extract (100 µg/ml) was mixed with 0.5 ml of distilled water and 2.25 ml of Folin-Ciocalteu (7% w/v), and 1.75 ml of carbonate sodium (7.5% w/v). Then, the tubes containing the solution were incubated for 20 min at 45 ºC and following kept for 10 min at room temperature for reading at 765 nm in a spectrophotometer (721G Visible Spectrophotometer). Gallic acid was used as a standard for the calibration curve (5-140 µg/mL), and phenolic compound concentrations were expressed as milligram of gallic acid equivalent per 100 g of dry extract (mg GAE/100 g) (Barbosa *et al.*, 2019).

2.5 DETERMINATION OF TOTAL FLAVONOID CONTENTS

Total flavonoids were quantified with a colorimetric method, using a 10% (m/v) aluminum nitrate solution, where 0.5 ml of the cambuí extract solution (100 µg/ml) was used mixed with a 0.1 ml solution of 10% aluminum nitrate (w/v) and 0.1 ml of 1M potassium acetate. The final volume was completed with 4.3 ml of methanol. Samples were homogenized at room temperature, and readings were taken with a spectrophotometer (721G Visible Spectrophotometer) at 425 nm absorbance. A calibration curve was prepared with a standard rutin solution (5-140 µg/mL), with the values obtained expressed as milligrams of rutin equivalent per 100 g of dry extract (mg RE/100 g) (Barbosa *et al.*, 2019).

2.6 ANALYSIS BY UPLC-QTOF-MS^E

Analyzes were performed with an Acquity UPLC chromatography (Waters, USA) coupled to Quadrupole and Time-of-Flight (QTOF, Waters) mass spectrometers. Bioactive compounds were separated using a Waters Acquity BEH UPLC column (150 mm x 2.1 mm I.D., 1.7 µm) at 40° C. The mobile phase was graduated, using water with 0.1% formic acid (A) and acetonitrile with 0.1% formic acid (B), eluting with 2%-95% B (0-15 min); 100% B (15.1 to 17 min), and equilibrating with 2% B (17.1 to 19.1 min) at a flow of 0.4 mL/min^{-1}, and a sample volume injection of 5.0 µL. Ionization was performed by electrospray (the negative mode - ESI), using a range of 110-1180 Da, with source temperature set at 120 °C, desolvation temperature at 350° C, desolvation gas flow rate of 500 Lh^{-1}, 0.5 V cone extraction, and 2.6 kV capillary voltage. Encephalin leucine was used as a blocking mass. An MS acquisition mode was used. The instrument was controlled with Masslynx 4.1 (Waters Corporation) software (Sousa *et al.*, 2016).

2.7 DATA ANALYSIS

All analyzes were performed in triplicate. Data were presented as mean values ± standard deviation. To identify significant differences between the means, analysis of variance (ANOVA) was used, followed by the Tukey test using GraphPad Prism 5.0 software. Differences between the means at the 5% level ($p < 0.05$) were considered significant (Santos and Hanna, 2020; Santos *et al.*, 2018).

3 RESULTS AND DISCUSSION

According to Borges et al., 2014, the *Myrciaria* genus is a source for obtaining biomolecules with relevant potential for food and pharmaceutical applications due to its several properties biological such as antioxidant, anti-inflammatory, antimicrobial, antiproliferative, and anti-*Plasmodium* (Borges, Conceição and Silveira, 2014). The edible fruit of plants from the Myrtaceae family has been medicinal properties due to their bioactive molecules such as phenolic compounds (Reynertson *et al.*, 2008). The COVID-19 pandemic has increased the search for immune-boosting food supplements and nutraceuticals. Several studies have indicated the phenolic compounds as potential inhibitors of COVID-19 infection, particularly the flavonoids (Galanakis *et al.*, 2020).

Table 1 are summarized the Overall extraction yield, total phenolic compounds, and total flavonoid contents of cambuí extracts obtained by using PHWE. PHWE showed a significant difference in the overall extraction of molecules from orange (39.66 ± 1.62%) and purple cambuí (33 ± 8.44%). Likewise, the total phenolic compounds showed variation in the fruits. Into purple cambuí, the obtained total phenolic compounds value (3870.37 ± 353.09 mg GAE/100 g) was higher than that from orange cambuí (2679.01 ± 161.33 mg GAE/100). As can also be seen in Table 1, the total flavonoid contents for orange and purple cambuí extracts obtained in this present study were 770.08 ± 103.62 mg RE/100 g and 693.16 ± 180.09 mg RE/100 g, respectively.

Table 1. Results for overall PHWE yield (%), total phenolic compounds (mg GAE/100g), and total flavonoid content (mg RE/100 g). PHWEGP (Pressurized Hot Water Extraction Cambuí Purple); b) PHWEGO (Pressurized Hot Water Extraction Orange). The values are reported as a mean and standard deviation

Extract	Overall yield	Total phenolics	Total flavonoid
PHWEGP	39.66 ± 1.62[a]	2679.01 ± 161.33b	770.08 ± 103.62[a]
PHWEGP	33 ± 8.44[a]	3870.37 ± 353.09a	693.16 ± 180.09[a]

Equal lower case in the same column indicates that there is no significant difference ($P < 0.05$)

The difference in the phenolic compound contents in fruits of the same species can be explained by genetic diversity (Nascimento *et al.*, 2019; Santana *et al.*, 2016), as well as the existence of compounds of various chemical forms, ranging from simple substances to highly polymerized versions, including different proportions of phenolic acids, anthocyanins, tannins, and others. They can also be found in complex states with carbohydrates, proteins, organic acids, and other plant components, thus forming high molecular weight phenolic compounds, which can affect the quantity and concentration of biomolecules obtained in the extracts (Côté *et al.*, 2010).

Santos et al., (2020) reported the presence of 62.28 (mg GAE/g) of total phenolic compound in the cambuí extract obtained using water under room pressure. However, the study reported above did not find flavonoid contents (mg QE/g) in the cambuí aqueous extract (Santos *et al.*, 2020). Hence, we can suggest that the use of water under high pressure in the first step of extraction provides the obtaining relevant amount of flavonoid contents and other phenolic compounds, as can be seen in table 1. de Oliveira et al. (2018) obtained 78.56 ± 0.01 mg RE/100 g from cambuí extracts (Oliveira, de *et al.*, 2018), hence, they confirmed total flavonoid contents presence. PHWEGP phenolic compounds values (mg GAE/100g) were higher than those found by Rufino et al. (2010) in aqueous pulp extracts from Myrtaceae families such as *Myrciaria cauliflora* (3584 ± 90.9), *Syzygium cumini* (1117 ± 67.1), *Eugenia pyriformis* (1930 ± 129), and *Blepharocalyx salicifolius* (2055 ± 75.7) (Rufino *et al.*, 2010).

Polyphenols have been exhibiting effects on different steps of the SARS-CoV-2 replication. These biomolecules are efficient to inhibit the binding of SARS-CoV-2 spike protein to the host-cell receptors, preventing viral entry into the host cell, and disrupting viral replication (Paraiso, Revel and Stevens, 2020). Molecules inhibiting viral proteases have been suggested to be potential candidates to block the coronavirus life cycle (Dai *et al.*, 2020; Paraiso, Revel and Stevens, 2020).

The combuí extracts obtained by using PHWE have a variety of phenolic compounds, which are synergistic combinations that can be effective against coronavirus diseases, in Figure 1 and Table 2 can be seen the profile and molecules from cambuí extracts.

The UPLC-QToF_MS^E analysis of cambuí extracts showed no difference in chromatogram profile (Figure 1). Thus, differences between each extract are in the intensity of the secondary compounds. The compounds tentatively identified are summarized in Table 2.

Figure 1. Chromatogram of cambuí extracts analyzed by UPLC-QToF-MS^E: a) PHWEGP (Pressurized Hot Water Extraction Cambuí Purple); b) PHWEGO (Pressurized Hot Water Extraction Cambuí Orange)

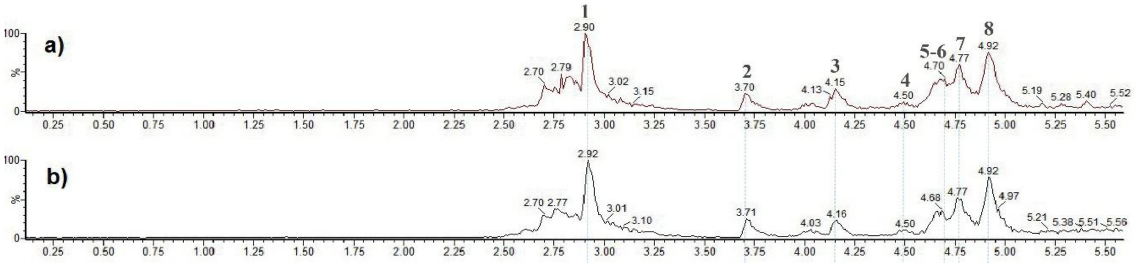

Table 2. Compounds from cambuí extracts were tentatively identified using UPLC-QToF-MS

Peak	Rt	[M H] (*m/z*)	[M-H]$^-$Cal (*m/z*)	MS/MS	Molecular ion	ppm(error)	Compound
1	2.90	353.0872	353.0873	191	$C_{16}H_{17}O_9$	-0.3	5-caffeoylquinic acid
2	3.71	515.1204	515.1190	353, 317, 191, 173	$C_{25}H_{23}O_{12}$	2.7	4,5-caffeoylquinic acid
3	4.15	933.0641	933.0634	915, 631, 300	$C_{41}H_{25}O_{26}$	0.8	Vescalagine or Castalagine isomer
4	4.46	433.0396	433.0304	300	$C_{19}H_{13}O_{12}$	-2.5	Ellagic acid pentoside
5	4.50	447.0555	447.0564	300	$C_{20}H_{15}O_{12}$	-2.0	Ellagic acid rhamnoside
6	4.66	300.9978	300.9984	257, 229	$C_{14}H_5O_8$	-2.0	Ellagic acid
7	4.76	617.1133	617.1143	300	$C_{28}H_{25}O_{16}$	-1.6	Ellagic acid derivative
8	4.92	631.1295	631.1299	300	$C_{29}H_{27}O_{16}$	-0.6	Ellagic acid derivative

Different phenolic compounds, such as derivatives of caffeic acid (mono- and caffeoylquinic acid), ellagic acid, and its conjugated and ellagitannin derivatives, were identified. In the absence of standards, the different compounds were tentatively identified through high-resolution analysis using the UPLC-QToF-MS^E considering their molecular ions, fragmentation patterns, and in comparison, with data described previously in the literature (Table 2).

Comparison of the observed fragmentation patterns and molecular ions with those described in the literature using high-resolution mass spectrometers such as QToF-MS^E provides important structural information on several types of chemical compounds to be obtained, so allowing the structural identification of such compounds (Gašić *et al.*, 2014).

Compounds derived from caffeic acid, 5-caffeoylquinic acid (peak 1), and 4,5-caffeoylquinic acid (peak 2) presented, respectively, molecular ions at *m/z* 353 and 515. In these analyzes, product ions were observed at *m/z* 191 for 5-caffeoylquinic acid, *m/z* 353, 317, 191, and 173 for 4,5-caffeoylquinic acid. These results are in line with those obtained by Ruiz et al. (2015) for fruits of the *Rubus* and *Ribes* genera (Ruiz *et al.*, 2015).

In the experimental conditions used, the fragmentation pattern observed for peak 3, molecular ion in *m/z* 933, and product ions in *m/z* 915, 631, 300, indicated the presence of the ellagitannins vescalagine or castalagine isomers, not being distinguished by mass spectrometry. This is the first report of the presence of vescalagine (or its isomer, castalagine) in cambuí fruit extracts.

Peaks 4, molecular ions in *m/z* 433, and 5 molecular ions in *m/z* 447 showed fragments in *m/z* 300, corresponding to the product ion of ellagic acid. These compounds have been proposed as ellagic acid pentoside (4) and rhamnoside, respectively, previously reported in Myrtaceae species (Neves *et al.*, 2018).

Ellagic acid was identified by standard comparison. In addition, two ellagic acid derivatives (peaks 7 and 8) were detected, which showed molecular ions at *m/z* 617 (7) and *m/z* 631 (8), and which produced fragments in *m/z* 300 (ellagic acid). In a study conducted by Reynertson et al. (2008), ellagic acid was also found in eleven of the fourteen edible Myrtaceae fruits analyzed, which demonstrates that this acid is present in many fruits of this family (Reynertson *et al.*, 2008).

According to the docking results reported by Shah et al. (2021), the 3,5-Dicaffeoylquinic acid is a promising inhibitor of the SARS-CoV-2 Mpro (Shah *et al.*, 2021). As reported by Pandey et al. (2020) ellagic acid and other flavonoids can inhibit the viral proteases will down-regulate the Covid-19 replication process (Pandey and Verma, 2020). Based on a study performed by Suručić et al. 2021, with the protein targets SARS-CoV-2 spike glycoprotein, angiotensin-converting enzyme 2, furin, and transmembrane serine protease 2, the ellagic acid exhibited a significant role against the process of the entry of coronavirus into a host cell (Suručić *et al.*, 2021).

The development of nutraceuticals products to health care and recovery of COVID-19 patients can become popular, as well as will be an important alternative against the potential occurrence of future viral pandemics caused by SARS-CoV-2 (Galanakis *et al.*, 2021). The cambuí extracts obtained in the present study, by using PHWE are promising potential candidates for further in vitro and in vivo evaluation against Covid-19 infections due to having bioactive molecules with antiviral activity.

4 CONCLUSIONS

The cambuí extracts had a high total polyphenol content. However, purple extract cambuí was the richest in total phenolic compounds. The phytochemical profiles of the two fruits are similar, regardless of their color. Different phenolic compounds were tentatively identified, such as 5-caffeoylquinic acid, 4,5-Dicafeoylquinic acid, ellagic acid, ellagic acid pentoside, and ellagic acid raminoside. In addition, the presence of an elagitanine (vescalagine or the castalagine isomer) and two derivatives of conjugated ellagic acid is suggested. PHWE is an appropriate alternative for obtaining total flavonoids and other phenolic compounds from cambuí fruits. These biomolecules are potential candidates for in vitro and in vivo evaluation against COVID-19 infections.

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