Food Chemistry 309 (2020) 125735

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Jabuticaba residues (*Myrciaria jaboticaba* (Vell.) Berg) are rich sources of valuable compounds with bioactive properties

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ARTICLE INFO

Keywords:
Anthocyanins
Hydrolysable tannins
Anti-proliferative
Antimicrobial
Antioxidant activity

ABSTRACT

Jabuticaba (*Myrciaria jaboticaba* (Vell.) Berg) is a Brazilian berry, very appreciated for *in natura* consumption. However, its epicarp is not normally consumed due to its stiffness and astringent taste, and in manufacture of products from jabuticaba fruit, it is responsible for the generation of large amounts of residues. The exploration of by-products is becoming important for the obtainment of valuable bioactive compounds for food and pharmaceutical industries. In this context, jabuticaba epicarp was studied regarding its chemical composition, namely in terms of phenolic compounds, tocopherols, and organic acids, and its bioactive properties, such as antioxidant, anti-proliferate, anti-inflammatory, and antimicrobial activities. A total of sixteen phenolic compounds, four tocopherols and six organic acids were identified in jabuticaba epicarp. Regarding bioactive properties, it showed high antioxidant activity, also presenting moderate anti-inflammatory, anti-proliferative, and antimicrobial activities. The extract did not present hepatotoxicity, confirming the possibility of its applications without toxicity issues.

1. Introduction

Myrciaria jaboticaba (Vell.) Berg, belonging to the Myrtaceae family, is a native species to Brazil, namely from Atlantic Rainforest biome, but also widely growing in the whole country, it blooms between March and October (de Neves, Stringheta, Gómez-Alonso, & Hermosín-Gutiérrez, 2018; Oliveira, Angelotti-Mendonça, Tanaka, da Silva, & Scarpare Filho, 2019). Its fruits, commonly known as jabuticaba or Brazilian berries, are small berries with a diameter of 3–4 cm that contain between one and four small seeds, with thick green to dark violet skin, depending on the ripening stage, that is not commonly consumed. On the other hand, the fruit gelatinous pulp presents a sweet and astringent taste due to its high content of sugars and acids, being very appreciated for *in natura* consumption or as fruit pulp preparation (Oliveira et al., 2019). The consumption of jabuticaba has been associated with diverse health benefits that are linked to its chemical composition with great polyphenol abundance (Donado-Pestana et al., 2018; Wu, Hung, Shin, Wang, & Huang, 2016).

However, the commercialization of this kind of berry is difficult due to its high perishability, which justifies its application in the production of jam, syrups, liqueur, and other alcoholic beverages. Nevertheless, the residues (epicarp and seeds) inherent to the production of such foodstuff and beverages represent about 50% of the total processed volume (Morales et al., 2016), and the fact is that jabuticaba epicarp residue is rich in phenolic compounds, such as anthocyanins and ellagic acid derivates (Morales et al., 2016; Neri-Numa, Soriano Sancho, Pereira, & Pastore, 2018). These characteristics have been attracting the attention of academia and food industry that consider its use as a food additive or ingredient, for example, some studies have reported the application of this by-product to improve sensory characteristics of meat products (Almeida et al., 2015; Baldin et al., 2016, 2018), and also to increase the nutritional value, namely carbohydrate and fibre content, of bakery products (Marquetti et al., 2018). Besides, the addition of *M. jaboticaba* to food products also conferred them increased antioxidant activity (Almeida et al., 2015; Baldin et al., 2016; Marquetti et al., 2018) and antimicrobial action (Baldin et al., 2016). Moreover, *M. jaboticaba* epicarp has also been explored by some authors for the prevention of cardio, neurodegenerative, and chronic diseases, with these benefits possibly ascribed to its antioxidant and anti-inflammatory potential (Plaza et al., 2016; Zhao et al., 2019). However, its chemical composition is still poorly elucidated, and the characterization of such residues can play crucial roles in the valorization of natural resources that

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https://doi.org/10.1016/j.foodchem.2019.125735
Received 10 June 2019; Received in revised form 16 October 2019; Accepted 16 October 2019
Available online 21 October 2019
0308-8146/

are usually discarded, contributing to the creation of more economically and socially sustainable productive chains (Ravindran & Jaiswal, 2016). With that in mind, the present work aims to provide detailed data concerning the chemical composition of *M. jaboticaba* epicarp, namely in terms of organic acids, tocopherols, and phenolic compounds. Furthermore, the bioactive potential of the hydroethanolic extracts was also assessed in terms of cytotoxicity, hepatotoxicity, antioxidant, anti-inflammatory, and antimicrobial properties.

2. Material and methods

2.1. Sample preparation

Jabuticaba (*Myrciaria jaboticaba* (Vell.) Berg) fruits were acquired in CEAGESP – Brazil from a farm producer "Unidos". The fruits were washed and the epicarp was manually separated from the pulp. The epicarp was frozen at −18 °C and lyophilized by the Instituto Mauá de Tecnologia (Brazil). The dried epicarp was sent to Centro de Investigação de Montanha (CIMO), located at the Polytechnic Institute of Bragança (IPB), Portugal, where it was reduced to a fine and homogeneous powder and stored at −20 °C until the analyses were performed.

2.2. Chemical characterization

2.2.1. Phenolic compounds

2.2.1.1. Non-anthocyanin compounds. The powdered sample (5 mg) was extracted with 65 ml of an ethanol:water solution (80:20 v/v) under stirring for 1 h, the mixture was then filtered through filter paper (Whatman No. 4) and the epicarp residue was re-extracted for 1 additional hour. The combined filtrates were evaporated under reduced pressure at 40 °C (rotary evaporator Büchi R-210, Flawil, Switzerland) until total removal of ethanol and were subsequently frozen and lyophilized.

For further identification of the compounds, a purification step was performed using a C-18 SepPak® Vac 3 cartridge (Phenomenex, Torrance, CA, USA), activated with 5 ml of ethanol followed by 5 ml of water. Then 5 ml of re-dissolved lyophilized extract in water (40 mg/ml) was loaded into the cartridge. The removal of compounds that may interfere with the analysis of phenolic compounds (such as sugars) was done with 5 ml of water. The purified extract was then recovered with 5 ml of ethanol. Afterwards, the solvent was evaporated under reduced pressure at 35 °C, the extract was dissolved in 2 ml of ethanol:water (80:20, v/v), and filtered through a 0.22 μm nylon filter.

The purified extract was analysed by high performance liquid chromatography (Dionex Ultimate 3000 UPLC, Thermo Scientific, San Jose, CA, USA), with a diode-array detector (280, 330, and 370 nm wavelengths) linked to an electrospray ionization mass spectrometry working in negative mode (Linear Ion Trap LTQ XL, Thermo Scientific, San Jose, CA, USA) as described by Bessada, Barreira, Barros, Ferreira, and Oliveira (2016).

Data were collected and analysed using the Xcalibur® program (ThermoFinnigan). Results were expressed as mg per g of extract and mg per g of epicarp dry weight (dw).

2.2.1.2. Anthocyanin compounds. The powdered sample (1 mg) was extracted with 30 ml of an ethanol:water solution (80:20 v/v) acidified with 0.1% citric acid (1 μM), by stirring for 1 h protected from light. After filtration through filter paper (Whatman No. 4), the residue was re-extracted (1 h) and the combined filtrates were evaporated under reduced pressure at 40 °C and subsequently lyophilized.

The lyophilized extract (10 mg) was re-dissolved in 2 ml of ethanol:water (80:20 v/v) and filtered through a 0.22 μm disposable filter disk into an amber vial for HPLC analysis. The analysis was made using a Dionex Ultimate 3000 HPLC (Thermo Scientific) system equipped with a quaternary pump, an automatic injector (at 5 °C), a degasser, and an automated thermostat column compartment. The detection of the compounds was carried out with a DAD, using wavelengths of 520 nm and coupled to a mass spectrometry detector (HPLC-DAD-ESI/MS), operating under the conditions thoroughly described by Gonçalves et al. (2017). Data were collected and analysed using the Xcalibur® program (Thermo Finnigan). Results were expressed as mg per g of extract and mg per g of epicarp dry weight (dw).

2.3. Organic acids

Organic acids were extracted from the freeze-dried epicarp using a methodology previously described by Barros et al. (2013) with some modifications. Samples (1.5 g) were extracted by stirring with 25 ml of meta-phosphoric acid (25 °C at 150 rpm) for 25 min protected from light and subsequently filtered through Whatman No. 4 paper. Before analysis, samples were filtered through 0.22 μm nylon filters. The analysis was performed following the methodology described by Barros et al. (2013). The results were expressed in mg per 100 g of epicarp dry weight (dw).

2.4. Tocopherols

For tocopherols analysis, a methodology previously described by Barros et al. (2013) was followed, using a high performance liquid chromatography system coupled to a fluorescence detector (HPCL-FL; Knauer, Smartline system 1000, Berlin, Germany). Authentic standards of tocopherol isoforms (α-, β-, γ-, and δ-) (Sigma, St. Louis, MO, USA) and tocol (Matreya, Pleasant Gap, PA, USA) were used for quantification. Data were collected and analysed using the Clarity 2.4 software (DataApex, Prague, Czech Republic). The results were expressed in mg per 100 g of dry weight (dw).

2.5. Evaluation of bioactive properties

2.5.1. Cell-based antioxidant activity

2.5.1.1. Inhibition of lipid peroxidation through thiobarbituric acid reactive species (TBARS). The lipid peroxidation inhibition in porcine (*Sus scrofa*) brain homogenates was evaluated by measuring the formation of thiobarbituric acid reactive substances (TBARS), according to a previously described methodology Corrêa et al. (2015). The result was expressed as EC_{50} value, which correspond to the extract concentration that provides 50% of antioxidant activity (μg/ml). Trolox was used as positive control.

2.5.1.2. Oxidative haemolysis inhibition assay (OxHLIA). The anti-haemolytic activity of jabuticaba epicarp extract was evaluated by the oxidative haemolysis inhibition assay (OxHLIA), as described in detail by Lockowandt et al. (2019). The results were expressed as IC_{50} values (μg/ml), meaning the extract concentration able to promote a Δt haemolysis delay of 120 and 180 min. Trolox was used as positive control.

2.5.2. Anti-inflammatory activity

The anti-inflammatory activity was evaluated by LPS-induced nitric oxide (NO) production by mouse macrophages RAW 264.7, following the procedure described by Corrêa et al. (2015). Negative control was prepared without the addition of LPS to observe their possible effect on the basal levels of NO. For the positive control, Dexamethasone (50 μM) was used. The results were expressed as IC_{50} value (μg/ml), which correspond the concentration that induces 50% of inhibition of the NO production.

2.5.3. Anti-proliferative activity and hepatotoxicity

The cytotoxic activity of the jabuticaba epicarp extract was performed on four human tumor cell lines: NCI-H460 (lung carcinoma);

MCF-7 (breast carcinoma); HepG2 (hepatocellular carcinoma); and HeLa (cervical carcinoma); and one non-tumor liver cells primary culture obtained from porcine liver (PLP2). The analysis was performed for each of the dilutions of the extract following the Sulforodamine B (SRB) assay, as previously described by Corrêa et al. (2015). The results were expressed as GI_{50} value (μg/ml), which correspond to the concentration of extract that inhibited 50% of cell proliferation.

2.5.4. Antimicrobial activity

For the antimicrobial activity, the jabuticaba epicarp extract was tested against five Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Morganella morgannim*, *Proteus mirabilis*, and *Pseudomonas aeruginosa)* and three Gram-positive bacteria (*Enterococcus faecalis*, *Listeria monocytogenes*, and Methicillin-resistant *Staphylococcus aureus* (MRSA)). The bacteriostatic action of the jabuticaba extract was established following a methodology described by Pires et al. (2018) and the results were expressed as MIC (mg/ml), which correspond to the minimal inhibitory concentration for cell multiplication. The bactericidal action was determined according to Corrêa et al. (2015) and the results were expressed as MBC value (mg/ml), meaning the minimal bactericidal concentration. Ampicillin was used as negative control for all bacteria while Imipenem was used for all Gram-negative bacteria and for *L. monocytogenes*, and Vancomycin was used only for *E. faecalis* and MRSA.

3. Results and discussion

3.1. Chemical characterization

3.1.1. Phenolic compounds

The phenolic profile, chromatographic characteristics (Rt, λmax, and mass spectral data), tentative identifications, and quantification of jabuticaba epicarp is shown in Table 1. The purified hydroethanolic extract presented sixteen phenolic compounds, being fourteen non-anthocyanins (thirteen ellagitannins and one quercetin derivate) and two anthocyanin compounds. According to the mass spectral data presented in the Table 1, peaks **1** and **2** showed the same pseudomolecular ($[M-H]^-$ at *m/z* 783) and released two MS^2 fragment at *m/z* 481 (−302 u, loss of an HHDP unit) and *m/z* 301 (ellagic acid) presenting a further loss a hexose (−180 u). Plaza et al. (2016) and Morales et al. (2016) also detected a similar fragmentation behavior in aqueous extract from *M. jaboticaba* epicarp from the Southeast part of Brazil and in methanolic extract of jabuticaba pomace (epicarp, seed and residual pulp) obtained from licour and juice processing of *Myrciaria cauliflora* Mart, obtained from the Central Region of Brazil, being these compounds tentatively identified as bis-HHDP-glucose isomers. Peaks **3** and **4** ($[M-H]^-$ at *m/z* 951) also presented compound isomers with two MS^2 fragment at *m/z* 907 and *m/z* 783, these compounds were associated to trigalloyl-HHDP-glucose isomers. These identifications were performed taking into account previous reported studies using an acidified methanolic extract obtained from epicarp of *Myrciaria trunciflora* (a different jabuticaba species) from the southern region of Brazil (Quatrin et al., 2019) and an acetonic extract from the edible part (epicarp and pulp) of Araça (*Psidium guineense* Sw.), from the Amazon Region and also belonging to the Myrtaceae family (Gordon, Jungfer, Da Silva, Maia, & Marx, 2011). Peaks **5** and **7** ($[M-H]^-$ at *m/z* 935) had the same MS^2 fragments at *m/z* 917 (−18 u, loss of a water molecule), *m/z* 783 (−152 u, loss of a galloyl group), *m/z* 633 (−302 u, loss of an HHDP group) and *m/z* 301 (−332 u galloyl-glucose moieties); thus the identification of these compounds was galloyl-bis-HHDP-glucose isomers, being also confirmed with literature data to *M. jaboticaba* (Plaza et al., 2016). Peak **6** ($[M-H]^-$ at *m/z* 633) released a MS^2 fragmentation patter at *m/z* 481 (−152 u, loss of a galloyl moiety), *m/z* 463 (−170 u, loss of a gallic acid) and *m/z* 301 (−162 u, loss of a glucosyl residue), being assigned as a galloyl-HHDP-glucose. This compound was also previously described by Morales et al. (2016) in the methanolic extract obtained from jabuticaba *(M. cauliflora)* pomace. The same pseudomolecular ion at $[M-H]^-$ at *m/z* 785, and MS^2 fragmentation patter at *m/z* 633 and 483, revealing two successive losses of galloyl moieties (−152 u) and *m/z* 301 corresponding to ellagic acid (−162 u loss of hexose residue), were found for peaks **8** and **9**, and according with data reported in literature, these compounds were tentative identified as digalloyl-HHDP-glucose isomers (Morales et al., 2016; Wu, Long, & Kennelly, 2013). Peaks **10** and **11** ($[M-H]^-$ at *m/z* 933) presented the same MS^2 fragment ions at *m/z* 915, 633, 451 (loss of a trigalloyl unit) and 301, and were tentatively assigned to castalagin/vescalagin isomers, due the similar characteristic spectral data found from other Brazilian Myrtaceae fruits (Gordon et al., 2011); however to the best of our knowledge this was the first time this compound was identified in *M. jaboticaba*. Peak **12** ($[M-H]^-$ at *m/z* 937) presented four MS^2 fragments at *m/z* 767, 637, 467 and 301, being coherent with a trigalloyl-HHDP-glucose, already reported in *M. jaboticaba* epicarp aqueous extract (Plaza et al., 2016; Wu, Dastmalchi, Long, & Kennelly, 2012). Peak **13** ($[M-H]^-$ at *m/z* 939) revealed a MS^2 fragmentation pattern at *m/z* 787, 769 and 301 tentatively identified as pentagalloy glucose (Plaza et al., 2016).

Peak **14** ($[M-H]^-$ at *m/z* 447) was the only flavonoid present in the extract and was tentatively identified as quercetin-3-*O*-rhamnoside (quercitrin), taking into account previous findings reported for jabuticaba residues (Morales et al., 2016; Plaza et al., 2016).

Concerning, the total phenolic non-anthocyanin content (7.48 ± 0.03 mg/g and 3.59 ± 0.01 mg/g of ethanolic extract and dryer jabuticaba epicarp, respectively), hydrolyzed tannins (ellagitannins) were the main group of molecules present (~98% of the TFC non-anthocyanin), this is in accordance with data reported by other authors (Morales et al., 2016; Plaza et al., 2016). This group of compounds has been largely studied due to their great bioactive proprieties, such as antimicrobial, anti-proliferative and anti-inflammatory activity (Lipińska, Klewicka, & Sójka, 2014). Trigalloyl-HHPD-glucose was the major compound (1.408 ± 0.003 mg/g dw), followed by pentagalloyl glucose (0.51 ± 0.02 mg/g dw). These values were higher than those found by Plaza et al. (2016). However, the amount of quercetin-3-*O*-rhamnoside (quercitrin) detected in our work was relatively lower than those reported by these authors (0.051 mg/g dw against 0.61 mg/100 g dw, respectively). These differences could be due to several factors, such as a different kind of extraction method and solvents used (Naczk & Shahidi, 2004), as well as different stages of maturation (Betta et al., 2018; Oliveira et al., 2019).

Jabuticaba also displayed two anthocyanins as presented in Table 1. Peak **15** ($[M+H]^+$ at *m/z* 463) depict a unique MS^2 fragment at *m/z* 303, corresponding to a delphinidin, bearing the loss of a hexose moiety (−162 u), being assigned as delphinidin-3-*O*-glucoside (D3G) (de Neves et al., 2018; Morales et al., 2016; Plaza et al., 2016). Peak **16** ($[M+H]^+$ at *m/z* 449) was identified as cyanidin-3-*O*-glucoside (C3G), in comparison to the chromatographic and MS characteristics to the standard compound, as also with previous reported literature (de Neves et al., 2018; Morales et al., 2016; Plaza et al., 2016). The main anthocyanin present in the epicarp was C3G (19.45 ± 0.07 mg/g dw), being the total anthocyanin content found in the jabuticaba epicarp of 50.1 ± 0.1 mg/g of extract and 24.54 ± 0.05 mg/g dw. The proportion between C3G and D3G was similar with those found by Inada et al. (2015) in an acidified methanolic extract from *M. jaboticaba* epicarp, 12.61 and 2.69 mg/g dw, respectively. However, these results differ in terms of proportion and quantity with those reported by Plaza et al. (2016) for *M. jaboticaba* epicarp extract obtained by pressurized hot water, where the amount of C3G was about eight times higher than D3G, 28.66 and 35.63 mg/g dw, respectively. In these studies, the authors used different solvents and extraction methods, which can influence over the result obtained in each work (Naczk & Shahidi, 2004). Moreover, these differences may also be caused by the different ripening stages and cultivation conditions of *M. jaboticaba* (Betta et al., 2018; Oliveira et al., 2019).

Table 1
Phenolic compounds composition of *M. jaboticaba* epicarp.

Peak	Rt	λmax	$[M+H]^+/[M-H]^-$	MS^2	Tentative identification	References	Quantification	
	(min.)	*(nm)*	*(m/z)*	*(m/z)*			Extract	Epicarp
							(mg/g extract)	(mg/g dw)
Non-anthocyanins compounds								
1	4.3	240,270	783	481(60),301(100)	Bis-HHDP-glucose isomer	(Morales et al., 2016; Plaza et al., 2016)	0.17 ± 0.01	0.079 ± 0.003
2	4.5	241,268	783	481(56),301(100)	Bis-HHDP-glucose isomer	(Morales et al., 2016; Plaza et al., 2016)	0.262 ± 0.003	0.126 ± 0.002
3	5.0	241,267	951	907(100),783(10)	Trisgalloyl-HHPD-glucose isomer	(Gordon et al., 2011; Quatrin et al., 2019)	0.37 ± 0.02	0.18 ± 0.01
4	5.5	230,272	951	907(100),783(10)	Trisgalloyl-HHPD-glucose isomer	(Gordon et al., 2011; Quatrin et al., 2019)	0.18 ± 0.01	0.084 ± 0.005
5	5.8	228,280	935	917(100),783(5),633(10),301(5)	Galloyl-bis-HHDP-glucose isomer	(Fracassetti, Costa, Moulay, & Tomás-Barberán, 2013; Plaza et al., 2016)	0.157 ± 0.001	0.075 ± 0.005
6	6.1	228,280	633	481(3),463(10),301(100)	Galloyl-HHDP-glucose	(Morales et al., 2016; Plaza et al., 2016)	0.19 ± 0.01	0.093 ± 0.005
7	6.5	234,276	935	917(50),783(10),633(100),301(5)	Galloyl-bis-HHDP-glucose isomer	(Fracassetti et al., 2013; Plaza et al., 2016)	0.70 ± 0.03	0.33 ± 0.01
8	7.5	224,280	785	633(22),483(100),301(78)	Digalloyl-HHDP-glucose isomer	(Morales et al., 2016; Plaza et al., 2016)	0.283 ± 0.002	0.136 ± 0.001
9	8.7	223,275	785	633(20),483(100),301(40)	Digalloyl-HHDP-glucose isomer	(Morales et al., 2016; Plaza et al., 2016)	0.200 ± 0.004	0.096 ± 0.002
10	10.9	230,274	933	915(10),633(33),451(100),301(10)	Castalagin/vescalagin	(Fracassetti et al., 2013; Gordon et al., 2011)	0.592 ± 0.002	0.284 ± 0.001
11	12.8	229,270	933	915(10),633(28),451(100),301(10)	Castalagin/vescalagin	(Fracassetti et al., 2013; Gordon et al., 2011)	0.29 ± 0.01	0.139 ± 0.003
12	16.6	233,275	937	767(100),637(18),467(37),301(23)	Trigalloyl-HHDP-glucose	(Plaza et al., 2016; Wu et al., 2012)	2.93 ± 0.01	1.408 ± 0.003
13	19.0	220,275	939	787(15),769(100),301(3)	Pentagalloyl glucose	(Plaza et al., 2016)	1.06 ± 0.04	0.51 ± 0.02
14	20.4	350	447	301(100)	Quercetin-3-*O*-rhamnoside (quercitrin)	(Morales et al., 2016; Plaza et al., 2016)	0.11 ± 0.01	0.051 ± 0.004
					THT		**7.38 ± 0.03**	**3.543 ± 0.016**
					TF		**0.11 ± 0.01**	**0.051 ± 0.003**
					TPC–non-anthocyanin		**7.48 ± 0.03**	**3.59 ± 0.01**
Anthocyanins compounds								
15	16.7	523	463	303(100)	Delphinidin-3-O-glucoside	(de Neves et al., 2018; Morales et al., 2016; Plaza et al., 2016)	10.39 ± 0.04	5.09 ± 0.02
16	20.0	515	449	287(100)	Cyanidin-3-O-glucoside	(de Neves et al., 2018; Morales et al., 2016; Plaza et al., 2016)	39.7 ± 0.1	19.45 ± 0.07
					TA		**50.1 ± 0.1**	**24.54 ± 0.05**

Phenolic compound used for quantification: ellagic acid (y = 26719x − 317255, R^2 = 0.999); quercetin-3-*O*-glucoside (y = 34843x − 160173, R^2 = 0.999); cyanindin-3-*O*-glucoside (y = 134578x − 3000000, R^2 = 0.999). THT- total hydrolysable tannins; TF – total flavonoids; TPC – total phenolic compounds; TA – total anthocyanins

Table 2
Organic acids and tocopherols composition of *M. jaboticaba* epicarp.

ORGANIC ACIDS	*mg/100 g dw*
Oxalic acid	0.481 ± 0.009
Quinic acid	0.554 ± 0.002
Malic acid	1.66 ± 0.01
Shikimic acid	0.125 ± 0.008
Citric acid	18.8 ± 0.1
Fumaric acid	tr
Total organic acids	21.67 ± 0.09
TOCOPHEROLS	*mg/100 g dw*
α-tocopherol	0.301 ± 0.002
β-tocopherol	0.194 ± 0.005
γ-tocopherol	0.56 ± 0.01
δ-tocopherol	0.66 ± 0.02
Total tocopherols	1.71 ± 0.03

tr- traces.

In comparison to other brazilian fruit residues, the total content of anthocyanins in jabuticaba epicarp extract is relatively higher than those found in extract obtained from grape skin and juçara residue (7.9 and 11.54 μg/g of extract, respectively) (Garcia et al., 2019; Peixoto et al., 2018). Interestingly, the major anthocyanin present in *M. jaboticaba* epicarp, C3G, has presented positive effects against lipolysaccharides (LPS)-induced inflammation on human rheumatoid fibroblast (Sun & Li, 2018).

3.1.2. Organic acids

The composition in organic acids of jabuticaba epicarp is presented in Table 2. Six organic acids were detected in this by-product, with a clear predominance of citric acid (18.8 ± 0.1 mg/100 g dw), but it also presented malic acid in a lower concentration, followed by quinic and oxalic acids (1.66 ± 0.01, 0.554 ± 0.002, and 0.481 ± 0.009 mg/100 g dw, respectively). Shikimic (0.125 ± 0.008 mg/100 g dw) and fumaric acids were the least abundant organic acids found in the sample, with the latter only detected in a residual quantity. The results obtained highlight the importance of recovering this kind of residues given their high concentration in compounds such as those reported. Indeed, citric acid is well used in several industrial fields for different purposes, being mainly used in food processing, where it can be applied as an acidifying or preserving agent or even to enhance foodstuff flavour and aroma, but it can also find application in the pharmaceutical industry as an antioxidant for vitamins, a pH corrector and other functions (Ciriminna, Meneguzzo, Delisi, & Pagliaro, 2017). The results found herein are similar to those described by Morales et al. (2016) in a study that involved jabuticaba pomace generated from juice and wine processing, mainly composed of epicarp, pulp, and seeds.

3.1.3. Tocopherols

Table 2 presents the tocopherols profile of jabuticaba epicarp. The isoforms α, β, γ, and δ-tocopherol were identified in this sample, with δ and γ -tocopherol being the major isomers detected (0.66 ± 0.02 and 0.56 ± 0.01 mg/100 g dw, respectively). To the best of our knowledge, this is the first report regarding tocopherols composition in this part of the *M. jaboticaba* fruit. Morales et al. (2016) determined the total tocopherols content of jabuticaba pomace and the results reported were significantly higher than those obtained in the present study (3.3 and 3.2 mg/100 g of dry pomace of wine and juice, respectively), which can be justified by the presence of pulp and seeds in the pomaces. Comparing the tocopherols concentration of jabuticaba epicarp with those found in other matrices, such as grape skin (~0.014 mg/g dw) or grape pomace (~0.0147 mg/g dw), this by-product presented greater amounts (Gülcü et al., 2018). The benefits of tocopherols consumption, also known as lipid-soluble vitamin E, are widely recognized and described, being that this essential micronutrient is associated with the prevention of several diseases due its anti-inflammatory and antioxidant properties (Jiang, Christien, Shigenaga, & Ames, 2001).

Table 3
Cell-based antioxidant activity of *M. jaboticaba* epicarp.

	OxHLIA (IC_{50} values; μg/ml)		TBARS (IC_{50} values; μg/ml)
	$\Delta t_{120\ min}$	$\Delta t_{180\ min}$	
M. jaboticaba epicarp	0.82 ± 0.03	1.2 ± 0.1	2.07 ± 0.03
Trolox	41.1 ± 0.8	63 ± 1	5.8 ± 0.6

3.2. Bioactive proprieties of jabuticaba epicarp extract

3.2.1. Cell-based antioxidant activity

The hydroethanolic extract prepared from jabuticaba epicarp was evaluated in terms of its ability to prevent lipid peroxidation of porcine brain tissues and haemolysis of sheep blood cells. The results are presented in the Table 3. Regarding the TBARS assay, jabuticaba epicarp extract showed a great antioxidant activity, presenting an IC_{50} value of 2.07 ± 0.03 μg/ml, which represents a higher activity than Trolox (5.8 ± 0.6 μg/ml), the positive control. In fact, previous studies carried out with jabuticaba epicarp extracts assessing its antioxidant activity in Bologna-type sausages, revealed that the presence of this extract led to the formation of lower amounts of TBARS after 35 days of storage (Almeida et al., 2015). Similar results were obtained by Baldin et al. (2018), which incorporated microencapsulated extracts from jabuticaba residue (epicarp and seeds) in mortadella sausages to evaluate their capacity to inhibit lipid peroxidation with 56 days of storage. In the referred studies, the authors suggest that the antioxidant properties showed by the extracts are mainly ascribed to their anthocyanin composition (Almeida et al., 2015; Baldin et al., 2016). With this by-product, the antioxidant activity achieved is higher than those obtained through the application of residues from grape and juçara in similar food products (Garcia et al., 2019; Peixoto et al., 2018).

In the OxHLIA assay, the extract concentrations needed to protect half of the erythrocyte population from the haemolytic action caused by an oxidative agent for 120 min (0.82 ± 0.03 μg/ml) and 180 min (1.2 ± 0.1 μg/ml) were more than 50 times lower than those required for the artificial antioxidant, Trolox (41.1 and 63 μg/ml, for 120 and 180 min, respectively). Once again, these results highlight the great antioxidant activity of the extract and corroborate the huge potential to be applied for antioxidant purposes, for instance, in food industry. There are several methods to evaluate the antioxidant capacity of an extract, but most of them are chemical methods based on the scavenging of free radicals, notwithstanding, the OxHLIA method is cell-based and has the main advantage of inducing erythrocyte haemolysis by two ways in aqueous systems: 1) by the action of hydrophilic radicals generated from the thermal decomposition of APPH (2,20-azobis(2-methyl-propionamidine) that attack the erythrocytes membrane; and 2) by lipophilic radicals generated by the oxidation of the erythrocyte membrane; thus promoting similar conditions to *in vivo* systems (Prieto & Vásquez, 2014). In an *in vivo* study conducted by Plaza et al. (2016) with volunteers, the consumption of jabuticaba epicarp powder strengthened the serum antioxidant capacity against peroxyl radicals, which can be mainly explained by its composition of phenolic compounds, namely anthocyanins and ellagitannins (Plaza et al., 2016; Zhao et al., 2019). In comparison to other residues, the jabuticaba epicarp extract was notoriously more efficient on retarding the erythrocytes haemolysis than juçara residues extract ($IC_{50(120min)}$ = 107 μg/ml) (Garcia et al., 2019).

3.2.2. Anti-inflammatory activity

The anti-inflammatory potential of the jabuticaba epicarp extract

Table 4
Anti-inflammatory and cytotoxic activity of *M. jaboticaba* epicarp.

Anti-inflammatory activity IC_{50} (μg/ml)	*M. jaboticaba* epicarp	Dexamethasone
RAW 264.7	299 ± 13	16 ± 1
Anti-proliferative activity **GI_{50} (μg/ml)**		**Ellipticine**
MCF-7 (breast carcinoma)	300 ± 17	0.91 ± 0.04
NCI-H460 (non-small cell lung carcinoma)	> 400	1.0 ± 0.1
HeLa (cervical carcinoma)	278 ± 7	1.91 ± 0.06
HepG2 (hepatocellular carcinoma)	258 ± 5	1.1 ± 0.2
Hepatotoxicity **GI_{50} (μg/ml)**		
PLP2	> 400	3.2 ± 0.7

was evaluated and the results are presented in Table 4. The extract exhibited anti-inflammatory activity, inhibiting the growth of RAW 264.7 mouse macrophages in a concentration of 299 ± 13 μg/ml, which, despite being higher than the one exhibited by the positive control, Dexamethasone (16 ± 1 μg/ml), was obtained with a by-product extract, justifying its consideration as a natural alternative. In a previous study, jabuticaba epicarp also presented anti-inflammatory activity for chronic obstructive pulmonary disease (Zhao et al., 2019), which has been associated with the presence of certain phytochemicals. For instance, the jabuticaba tree and its whole fruit are reported as sources of jaboticabin (methyl 2-[(3,4-dihydroxybenzoyloxy)-4,6-dihydroxyphenyl] acetate), being that this compound mostly present in the epicarp (Zhao et al., 2019). This molecule was identified for the first time in jabuticaba fruits in 2006 (Adachi et al., 2006) and belongs to the depsides class, which are polyphenols with two or more aromatic rings linked by an ester bond, known by their bioactive properties, such as antibiotic, anti-HIV, and antiproliferative activity.

3.2.3. Anti-proliferate activity and hepatotoxicity

Cancer is one of the diseases that causes the greatest number of deaths worldwide. Phytochemicals and functional foods have been reported as crucial agents in preventing the development of these abnormal cells (Kotecha, Takami, & Espinoza, 2016; Li, Wang, Luo, Zhao, & Chen, 2017). The potential of jabuticaba epicarp in inhibiting tumor cell growth was evaluated in four different tumor cell lines and the results obtained are presented in Table 4. The extract revealed anti-proliferate activity in all tumor cells assessed in concentrations ranging from 258 ± 5 (in HepG2) to 300 ± 17 (in MCF-7) μg/ml, except for NCI-H460 (GI_{50} value > 400 μg/ml). On the other hand, it did not reveal toxicity for PLP2, a non-tumor liver cell primary culture, which corroborates the possibility of its application in food matrices without risks of toxicity. The anti-proliferative activity of jabuticaba epicarp against non-small lung cancer cells was previously described by Leite-Legatti et al. (2012), in a study where the authors found GI_{50} values of 28 and 209 μg/ml for non-polar (extraction with dichloromethane) and polar (extraction with 80% ethanol) extracts, respectively. In addition, jabuticaba epicarp also showed inhibitory activity in the tumour cells of glioma (U251), melanoma (UACC-62), kidney (786-0), leukemia (k-562), and prostate (Leite-Legatti et al., 2012). The chemoprotective properties revealed by these anthocyanin rich matrices against several types of cancer cells have been previously reported (Li et al., 2017).

3.2.4. Antimicrobial activity

The results of the antibacterial activity of the tested ethanolic extract are presented in Table 5. *M. jaboticaba* epicarp extract was active against all the tested microorganisms, inhibiting their growth at concentrations of 10 and 20 mg/ml (MIC values), in the case of Gram-positive and Gram-negative bacteria, respectively. Nevertheless, it did not present bactericidal properties at the studied concentration (20 mg/ml). In *M. morganii*, the MIC value presented by the extract was the same as the one presented by the positive control Ampicillin, and in *P. aeruginosa*, the extract presented even higher activity than this antibiotic. The potential of growth inhibition against *E. coli*, *S. aureus*, and *L. monocytogenes* found in this study is in agreement with the results obtained by Machado et al. (2018). In what concerns the addition of jabuticaba epicarp extract to food matrices, no positive nor negative effects were verified in different types of sausages in terms of microbial characteristic (aerobic bacteria count) of the products along with storage time (Almeida et al., 2015; Baldin et al., 2016).

4. Conclusion

With this study, it was possible to characterize a food industry by-product, jabuticaba epicarp, and contribute to its valorisation as source of compounds with great interest for different industries, such as food or pharmaceutical, among others. To our best knowledge, this is the first study describing the tocopherol profile of *M. jaboticaba* epicarp. In addition, the results of the present work showed that jabutibaca epicarp is rich in anthocyanins and ellagitannins, which were considered the main responsible compounds for the great bioactive properties presented by its extract.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 5
Antibacterial activity of *M. jaboticaba* epicarp.

	M. jaboticaba epicarp		Ampicillin (20 mg/ml)		Imipenem (1 mg/ml)		Vancomycin (1 mg/ml)	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Gram-negative bacteria								
Escherichia coli	20	> 20	< 0.15	< 0.15	< 0.0078	< 0.0078	nt	nt
Klebsiella pneumoniae	20	> 20	10	20	< 0.0078	< 0.0078	nt	nt
Morganella morganii	20	> 20	20	> 20	< 0.0078	< 0.0078	nt	nt
Proteus mirabilis	20	> 20	< 0.15	< 0.15	< 0.0078	< 0.0078	nt	nt
Pseudomonas aeruginosa	20	> 20	> 20	> 20	0.5	1	nt	nt
Gram-positive bacteria								
Enterococcus faecalis	10	> 20	< 0.15	< 0.15	nt	nt	< 0.0078	< 0.0078
Listeria monocytogenes	10	> 20	< 0.15	< 0.15	< 0.0078	< 0.0078	nt	nt
MRSA	10	> 20	< 0.15	< 0.15	nt	nt	0.25	0.5

MRSA – Methicillin resistant *Staphylococcus aureus*; MIC – minimal inhibitory concentration; MBC – minimal bactericidal concentration; nt – not tested.

Acknowledgements

The authors are grateful to the Foundation for Science and Technology (FCT, Portugal) and FEDER under Programme PT2020 for financial support to CIMO (UID/AGR/00690/2019); national funding by FCT, P.I., through the institutional scientific employment program-contract for M.I. Dias, L. Barros, and R.C. Calhelha contracts; C. Pereira contract though the celebration of program-contract foreseen in No. 4, 5 and 6 of article 23° of Decree-Law No. 57/2016, of 29th August, amended by Law No. 57/2017, of 19th July; and B. Albuquerque (SFRH/BD/136370/2018) PhD grant; to FEDER-Interreg España-Portugal programme for financial support through the project 0377_Iberphenol_6_E; the European Regional Development Fund (ERDF) through the Regional Operational Program North 2020, within the scope of Project NORTE-01-0145-FEDER-023289: DeCodE and project Mobilizador Norte-01-0247-FEDER-024479: ValorNatural®. The authors thank Dra. Cyanthia J. Kunigk (Instituto Mauá de Tecnologia, Brazil) for her collaboration.

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