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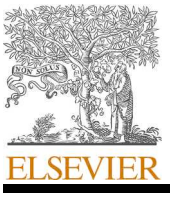

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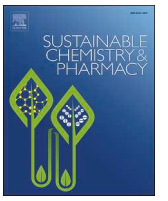

The effect of ultrasound on improving the extraction of tannins from the *Stryphnodendron adstringens* bark

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ABSTRACT

Stryphnodendron adstringens (*Barbatimão*) barks is one of the plants listed in the national list of medicinal plants of interest to the Brazilian health system and in the Brazilian pharmacopeia. Its extracts have been used in commercial products and popular medicine due to their phenolic compound's composition. Reported works dealing with *Barbatimão* and ultrasound-assisted extraction (UAE) does not cover all possible variables to be studied. Also, there is a gap in understanding the ultrasound phenomena's effect on the extract composition and biological properties of the *Barbatimão*. This work aimed to apply the UAE, using hydroethanolic solution (50 wt%) as the solvent to recover phenolic compounds from *Barbatimão* barks. Amplitude (0–40%), solvent-to-feed mass ratio (5-25), and extraction time (2–12 min) were evaluated. Ferric-reducing antioxidant capacity (FRAP), antioxidant cell activity, and cytotoxicity were also evaluated. The results showed that UAE parameters play significant roles in obtaining higher yields of phenolic compounds compared to other processes including conventional techniques. It was identified that the ultrasound waves contribute to enhancing the tannin extraction through mechanisms that only ultrasound, among the tested techniques, can provide. The extract obtained by UAE promoted cell viability higher than 80%, while the extracts obtained by the conventional method did not demonstrate this activity. UAE showed an efficient technique to obtain a tannins-rich extract from *Barbatimão*barks.

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1. Introduction

Stryphnodendron adstringens (Mart.) Coville, popularly known as *Barbatimão*, is a medicinal plant from the Brazilian savanna (*Cerrado*) and the arid biome from Northesteam (*Caatinga*) (Bieski et al., 2015; Brandão et al., 2008, 2008d; de Albuquerque et al., 2007a, 2007be Albuquerque et al., 2007b). The stem barks of this species are listed in the national list of medicinal plants of interest to the Brazilian health system and in the pharmacopeia (ANVISA, 2019). It has been used to treat inflammation, poor blood circulation, wound healing, and cleaning uterine wounds (Bieski et al., 2015; Brandão et al., 2008, 2008d; de Albuquerque et al., 2007a, 2007be Albuquerque et al., 2007b). In addition, *Barbatimão* presents secondary metabolites such as phenolic compounds, alkaloids, terpenes, and steroids. Among the phenolic compounds, tannins receive the most attention (Lima et al., 2016) since the concentration in the extract ranges from 8% (ANVISA, 2019) to 39% (Corrêa et al., 2012). Tannins are water soluble molecules that can create insoluble complexes by binding with macromolecules such as proteins, besides alkaloids, and metal ions (Haslam, 1996). Moreover, they are used as raw materials in several industrial processes, such as leather, adhesives, coating, beverage, food packaging, pharmaceutical, paper, mining, water treatment, and foams (Pizzi, 2019; Shirmohammadli et al., 2018; Singh and Kumar, 2019). Therefore, finding new production routes using sustainable techniques is of great interest to the chemical industry.

Extraction processes are a feasible strategy to recover bioactive compounds from plant materials. Ultrasound-assisted extraction (UAE), applying high-intensity and low-frequency ultrasound (16–100 kHz), has been efficiently used to produce extracts from a wide range of plants barks: *Eucommia ulmodies* (Li et al., 2005), *Hymenaea courbaril* (Veggi et al., 2013), *Acer saccharum* (St-Pierre et al., 2013), *Betula alleghaniensis* (St-Pierre et al., 2013), *Cassia auriculata* (Sivakumar et al., 2014), *Picea abies* (Chmelová et al., 2020; Lazar et al., 2016). The UAE apply ultrasound waves that, in a liquid medium, generate physicochemical phenomena induced by acoustic cavitation (collapse of microbubbles), such as mechanical agitation, microjets, shear forces, microextraction, heating, and shock waves, that can be advantageous in extraction processes (Ashokkumar, 2015; Chemat et al., 2017). In addition to these phenomena, when ultrasound waves interact with plant material, it alters its physicochemical properties, and cavitation allows for more release of compounds by changing the structure of the cell wall (Chemat et al., 2017). Because of such mechanisms, the extraction yield may be increased, and the extraction time is reduced due to high mass transfer coefficients. Other advantages of the UAE are applying green solvents that are less harmful to the environment and human health (such as ethanol and water) and the need for a smaller amount of solvent and energy than other conventional extraction techniques like maceration, percolation, turbo-extraction, infusion, and decoction (Azmir et al., 2013; Belwal et al., 2018). UAE can also be integrated with other extraction techniques, such as a high-pressure process to increase the extraction yield with reduced process time (Zabot et al., 2021). Among the disadvantages is the lack of selectivity compared to, for instance, supercritical fluid extraction (Picot-Allain et al., 2021), the need for post-extraction processes to filter the extract (Vinatoru et al., 1997), and high heat transfer that causes an increase in temperature, which could degrade thermosensitive compounds (Martínez et al., 2020), and prolonged use may damage the probe (Esclapez et al., 2011). It is also worth noting that ultrasound can generate reactive oxygen through sonolysis, degrading or altering some compounds (Belwal et al., 2018). Therefore, works that identify the beneficial effects and mitigate the disadvantages of this technique are desirable.

Despite its rich composition in phenolic compounds and applications, studies on the UAE from *Barbatimão* barks are scarce (de Souza Ribeiro et al., 2022). Sousa et al. (2014) used an ultrasound bath system and evaluated the extraction time, solid-liquid ratio, and the ethanol content in the hydroalcoholic solvent. Nascimento et al. (2020) also applied an ultrasonic bath to evaluate the sample granulometry, pH of the 50% hydroalcoholic solvent, and temperature influence. Despite recent studies using the UAE technique to obtain extracts from *Barbatimão*, there are still gaps regarding the application of this technique. The main demands are understanding the effects of amplitude and power of high-intensity and low-frequency ultrasound and identifying the main UAE mechanisms. It is worth mentioning that among the phenolic compounds found in *Barbatimão*, the flavonoids also stand out (Mello et al., 1996a). Therefore, studying the influence of the process parameters on the total flavonoid content is also very welcome (de Souza Ribeiro et al., 2022). Given this background, this work aimed to evaluate the effect of UAE variables, in a probe system, on the extraction yields of target compounds from *Barbatimão* barks. UAE was compared to Soxhlet and mechanical agitation (MA) to identify the mechanisms acting in the extraction of the *Barbatimão* bark. In addition, the antioxidant activity and cytotoxicity of the extracts were evaluated to understand the correlation of these activities with the phenolic composition and to verify possible applications of the extract obtained.

2. Material and methods

2.1. Chemicals and raw material

Ethyl alcohol, methyl alcohol (Dinamica, Indaiatuba, SP, Brazil), and distilled water were used as the solvents. Folin-Denis and sodium carbonate anhydrous (Dinamica, Indaiatuba, SP, Brazil) were used to determine total phenolic and tannin content. Tannic acid (Synth, Diadema, SP, Brazil) was used as a reference in total phenolic content analysis. Casein (Dinamica, Indaiatuba, SP, Brazil) and pyrogallol (Sigma-Aldrich, San Luis, MO, EUA) were used as reagents in total tannin analysis. Sodium nitrite, aluminum chloride (Dinamica, Indaiatuba, SP, Brazil), micro-pearls sodium hydroxide (Synth, Diadema, SP, Brazil), and Quercetin (HPLC ≥95%, Sigma-Aldrich, San Luis, MO, EUA) were used to evaluate the total flavonoids content. Hydrochloric acid (Synth, Diadema, SP, Brazil), 2,4,6-tris(2-pyridyl)-*s*-triazine – TPTZ, 6-hydroxy-2,5,7,8-etramethylchromane-2-carboxylic acid – Trolox (Sigma-Aldrich, San Luis, MO, EUA), ferric chloride, sodium acetate (Dinamica, Indaiatuba, SP, Brazil), glacial acetic acid (Nuclear, Diadema, SP, Brazil) were used for the antioxidant capacity (FRAP). (Epi)catechin (Sigma-Aldrich, San Luis, MO, EUA) was used for electrospray ionization mass spectrometry analysis. DMEM (Dubelcco's Modified Eagle's Medium) high glucose, fetal bovine serum, L-Glutamine, antibiotic solution (10,000 UI/mL of penicillin, 10 mg/mL of streptomycin, and 1 mg/mL of amphotericin B) (Vitrocell, Campinas, SP, Brazil), Neu-

tral Red (NR, Sigma-Aldrich, San Luis, MO, EUA), glacial acetic acid and sodium chloride (Synth, Diadema, SP, Brazil), potassium phosphate, sodium phosphate (Dinamica, Indaiatuba, SP, Brazil) were used for cytotoxicity tests. DCFH-DA (2′,7′-dichlorofluorescein diacetate), hydrogen peroxide, NAC (N-Acetyl-L-cysteine suitable for cell culture, Sigma-Aldrich, San Luis, MO, EUA), and resveratrol (DSM, Heerlen, Limburg, Netherlands) were used for antioxidant cell capacity tests.

Barbatimão (*Stryphnodendron adstringens*) barks were donated by the company Kampo de Ervas (Ribeirão Preto, SP, Brazil) in March of 2019 (batch number: 08032019) after shade-dried at room temperature and packed in plastic bags, the raw material presented a moisture content of 13.15 ± 0.07 g/100 g. The dry barks were crushed (Lippel, Agrolândia, SC, Brazil) and then ground in a knife mill (Marconi, Piracicaba, SP, Brazil). The mean particle size of the raw material was 0.50 ± 0.02 mm, determined using the sieving method on Tyler series sieves of 10, 14, 18, 35, 45, and 60 mesh (Bronzinox, São Paulo, SP, Brazil) (Romero et al., 2019). The real density was 1465 ± 1 kg/m^3, determined by helium gas pycnometer (Micromeritics, Norcross, GA, USA). The bulk density was 541.6 ± 12.7 kg/m^3, determined by measurement in graduated glassware.

2.2. Extraction processes

2.2.1. High-intensity ultrasound-assisted extraction (UAE)

UAE was performed in an ultrasound (VC 505, Sonics & Materials, Newtown, CT, USA) equipped with a ½" diameter probe with 500 W nominal power at 20 kHz. Hydroethanolic solution (50 wt%) was used as the extraction solvent and was selected based on our previous studies. For each UAE run, the raw material and solvent were weighed, manually mixed for 1 min, and applied to the ultrasound. After UAE, the extract was vacuum filtered, and the final volume was measured in graduated glassware. UAE was performed in duplicate, and the extract was stored without light at −18 °C for future analysis.

The effects of UAE variables were studied by applying a univariate experimental design. First, the effect of ultrasound amplitude (20, 30, and 40%) was evaluated, keeping constant the solvent-to-feed mass ratio (S/F; 5 g/g) and extraction time (6 min). The minimum amplitude was chosen based on the mechanical limitation of the equipment used, while the maximum amplitude was the highest amplitude allowed to prevent ethanol evaporation. Then, after an ultrasound amplitude was selected, the S/F was evaluated (5, 10, 15, 20, and 25) at 6 min. In this step, the solvent's total mass was maintained not to change the system's energy density (Table 1). Afterward, the extraction time (2, 4, 6, 8, 10, and 12 min) was accessed, keeping constant the ultrasound amplitude (30%) and the S/F (20). Each extraction with the different conditions was performed in duplicate.

2.2.2. Conventional extraction methods

Extraction by Soxhlet was selected as an exhaustive extraction method. Mechanical agitation (MA) was performed to compare the results with UAE to understand the mechanism of extraction. Soxhlet was carried out for 6 h in triplicate using approximately 3 g of the raw material using ethanol (SE) and methanol (SM). For extraction by MA, 4.76 g raw material and 95 g solvent (S/F = 20; 50 wt% ethanol) were submitted to agitation (713D, Fisatom, São Paulo, SP, Brazil) in a beaker (250 mL) positioned inside a heat beath (69 °C). Agitation was maintained at 20 rpm for 8 min, and the process was repeated in duplicate. After, the extract was separated from the solid raw material through vacuum filtration. Extracts were stored without light at −18 °C for future analysis.

2.2.3. Global yield (X_0)

The global extraction yield (X_0) of all extraction processes was analyzed according to the methodology adapted from Viganó et al. (2020). A volume of 2.5 mL of extract was dried in an oven (Ethik Technology, Vargem Grande Paulista, SP, Brazil) at 105 °C until reaching constant mass to calculate the solid content. The ratio between the dry extract mass (m_{ext}) and the dry raw material mass (m_s) was obtained according to Equation (1). The m_{ext} was calculated by multiplying the solid content by the volume of the liquid extract recovered from each extraction run.

$$X_0 = \frac{m_{ext}}{m_s} \times 100 \quad (1)$$

Table 1
Composition of the extraction medium and energy density used in the UAE.

S/F	Raw material mass (g)	Solvent mass (g)	Total mass (g)	Energy density (kJ/g)[a]
5	10.0059	50.0912	60.0971	0.1138[a]
	10.0060	50.2202	60.2262	0.1136[a]
10	5.0811	50.2697	55.3508	0.1236[a]
	5.0974	50.2674	55.3648	0.1235[a]
15	3.3010	50.0587	53.3597	0.1282[a]
	3.3098	50.1243	53.4341	0.1213[a]
20	2.5046	50.3327	52.8373	0.1226[a]
	2.5052	50.4834	52.9886	0.1291[a]
25	2.0265	50.0272	52.0537	0.1245[a]
	2.0237	50.0654	52.0891	0.1313[a]

[a] Different lowercase letters in the same column indicate significant difference ($p < 0.05$).

2.3. Extract evaluation

2.3.1. Total phenolics content (TPC)

The TPC was determined according to the Folin-Denis method (Campos et al., 2005) with some modifications. First, in test tubes, 0.2 mL of diluted extract or standard, 3.5 mL of distilled water, and 0.25 mL of Folin-Denis reagent were added. The mixture was shaken vigorously with the tube shaker (Gehaka, São Paulo, SP, Brazil) and left to stand for 3 min. Then, 0.5 mL of saturated aqueous sodium carbonate solution and 0.55 mL of distilled water was added and left to stand for 30 min in the dark and at room temperature. Absorbance was read at 730 nm using a UV–Vis spectrophotometer (Thermo Fisher Scientific, Waltham, MA, EUA). Tannic acid (0.05–0.40 mg/mL) was used as a standard. The reaction was performed in duplicate for the extracts and triplicate for the standard. The results were expressed in mg of equivalent tannic acid (ETA) per g of dry RM (raw material).

2.3.2. Total tannins content (TTC)

The TTC was determined according to Soares and Assunção Ferreira (2020) with some modifications. This indirect quantification method performs the complexation and precipitation of tannins with casein. The phenolic compounds content in the filtrate and the initial solution without precipitation were analyzed. The tannin content was obtained from the difference between these values. This analysis is divided into two steps: quantifying total polyphenols (TP) and the non-tanning fraction (NTF). For the TP, in the test tube, 0.25 mL of diluted extract, 0.25 mL of Folin-Denis reagent, and 2 mL of aqueous saturated sodium carbonate solution were added. It was left to stand for 2 min in the dark and at room temperature. Absorbance was read at 730 nm using a UV–Vis spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). As a standard curve, pyrogallol (0.010–0.045 mg/mL) was used. The reaction was performed in duplicate for the extracts and triplicate for the standard. The results were expressed in mg of equivalent pyrogallol (EP) per g of dry RM. For NTF, before the reaction, 20 mL of extract was placed to stir with 0.3 g of casein in a magnetic stirrer (IKA, Staufen, BW, Germany) for 1 h. Then, the mixture was filtered. A volume of 0.25 mL filtrate was submitted to the TP analysis. The TTC was determined according to Equations (2)–(5). $A^{1\%}$ is the specific absorbance of the reference solution, A_3 is the measured absorbance for the reference substance (pyrogallol), C is the concentration of the standard solution (pyrogallol curve points), TP is total polyphenols, FD is dilution factor, A_1 is measured absorbance for precipitable tannins, p is raw material mass (g), m is the raw material moisture (g), $\underline{A^{1\%}}$ is the mean specific absorbance of the reference solution, NTF is the non-tanning fraction, and A_2 is measured absorbance for the non-precipitable fraction.

$$A^{1\%} = \frac{(A_3 \bullet 10)}{C} \tag{2}$$

$$TP\ (wt.\%) = \frac{(FD \bullet A_1)}{[(p-m) \bullet \underline{A^{1\%}}]} \tag{3}$$

$$NTF\ (wt.\%) = \frac{(FD \bullet A_2)}{[(p-m) \bullet \underline{A^{1\%}}]} \tag{4}$$

$$TTC\ (wt.\%) = PT - FNT \tag{5}$$

2.3.3. Total flavonoids content (TFC)

The TFC was determined according to the colorimetric assay (Kim et al., 2003) with some modifications. In test tubes, 2 mL of distilled water, 0.5 mL of extract or standard, and 0.15 mL of 5% $NaNO_2$ were added. After 5 min of rest, 0.15 mL of 10% $AlCl_3$ was added, and after 1 min of rest, 1 mL of 1 M NaOH and 1.2 mL of distilled water were added. The mixture was then shaken vigorously with the tube shaker (Gehaka, São Paulo, SP, Brazil), and absorbance was read at 510 nm using a UV–Vis spectrophotometer (Thermo Fisher Scientific, Waltham, MA, EUA). As a standard curve, quercetin (0.19–0.95 mg/mL) was used. The reaction was performed in duplicate, and the results were expressed in mg of equivalent quercetin (EQ) per g of dry RM.

2.3.4. Ferric reducing ability power (FRAP)

The antioxidant capacity was analyzed by FRAP based on Benzie and Strain (1996) with some modifications. The FRAP solution was prepared using 100 mL of 0.3 M acetate buffer (pH 3.6), 10 mL of 10 mM TPTZ in 40 mM HCl solution and 10 mL of 20 mM $FeCl_3$. The solution was prepared immediately before the analysis of the extract and was warmed at 37 °C. A volume of 0.35 mL of diluted extract in duplicates was added to 2.45 mL of FRAP solution in test tubes and kept in the dark for 30 min at 37 °C. Next, the absorbance was measured at 595 nm in a UV–Vis spectrophotometer (Thermo Fisher Scientific, Waltham, MA, EUA). The Trolox standard curve was obtained (0.005–0.035 mg/mL). Results were expressed in mg equivalent Trolox (TE) per g of dry RM.

2.3.5. Electrospray ionization mass spectrometry fingerprinting

Flow injection analysis (FIA) was performed using a Thermo Fisher Scientific ion trap mass spectrometer (San Jose, CA, USA) equipped with an electrospray ionization source. MS and MS/MS analyses were performed in negative ionization mode after calibration, infusing a standard solution of (epi)catechin (1 μg/mL in methanol) at a flow rate of 5 μL/min under the following conditions: capillary voltage 35 V, spray voltage 5 kV, tube lens offset 100 V, capillary temperature 290 °C, sheath gas (N_2) flow rate 8 (arbitrary units). Negative ion mass spectra were recorded in m/z 180–2000 Da. The first event was a full-scan mass spectrum to acquire data on ions in the m/z range, followed by a second scan (MS^2) experiment performed using a data-dependent vscan on deprotonated mole-

cules from the compounds at a collision energy of 25–30% and activation time of 30 ms. Data were acquired and processed using the Xcalibur software (version 2.2 SP1.48).

2.3.6. Cytotoxicity

UAE and MA extracts were subjected to cytotoxicity evaluation at different concentrations (0.015–2.000 mg/mL, prepared by dissolving the dry extract in the culture medium). In 96-well plates, the immortalized human keratinocyte lineage (HaCat) was seeded, where the cultured cells were distributed over 60 wells of the microplate, with each well containing 20,000 cells, and D10 culture medium (DMEM with high glucose, supplemented with 10% (v/v) fetal bovine serum, 1% (v/v) L-Glutamine and 1% (v/v) antibiotic solution) was added. They were then incubated in an oven at 37 °C and 5% CO_2 with controlled humidity (model 3425, Thermo Scientific, Waltham, MA, USA) for 24 h. Next, the culture medium was removed, the wells were washed with PBS (Phosphate Buffer), aspirated, and 100 μL of the extracts previously diluted in the culture medium were added. The plates were incubated again, and after 48 h, after the extracts were aspirated, 100 μL of the NR solution (50 μg/mL) in DMEM was added. Next, the cells were incubated at 37 °C in a humidified atmosphere and 5% CO_2 for 3 h. After the NR solution was removed, the wells were washed with the PBS solution and aspirated. Then, 150 μL of the desorb solution composed of 49% (v/v) of ultra-purified water, 50% (v/v) of ethanol, and 1% (v/v) of glacial acetic acid were added. Subsequently, protected from light, the microplate was shaken for 15 min until total extraction of NR from the cells. The absorbance reading of the microplates after staining was performed in the microplate reader (model Synergy HT, Biotek, Winooski, VT, USA) at a wavelength of 540 nm. Cell viability was calculated according to Equation (6), where abs_s is the absorbance of the sample and abs_{cc} is the absorbance of the control.

$$Cell\ viability\ (\%\ cell/cell) = \frac{abs_s}{abs_{cc}} \bullet 100 \tag{6}$$

2.3.7. Antioxidant cell activity

UAE and MA extracts at different concentrations (0.02 and 2.00 mg/mL, prepared by dissolving the dry extract in the culture medium) were subjected to Antioxidant cell activity. First, 100,000 HaCat cells/well were plated in a black microplate with a transparent bottom. After 24 h, the media were removed, and the wells were washed twice with PBS (pH 7.4), and 50 μL of DCFH-DA (2′,7' – dichlorofluorescein diacetate, 60 μM) were added to all wells, except for the side wells, then the microplate was incubated at 37 °C for 30 min. Subsequently, 50 μL of H_2O_2 (hydrogen peroxide, 2 mM) was added to the wells intended to apply to the cells. Next, in the wells designated for the positive control of hydrogen peroxide, 100 μL of the NAC solution (N-acetylcysteine, 10 μL) was added to each well to evaluate the antioxidant activity of the positive control; then, 100 μL of resveratrol solution at each station for the evaluation of the antioxidant activity of the second positive control, finally the extracts diluted in culture medium were added to their respective microplate column and incubated for 30 min. Next, the plates were removed from the oven, the wells aspirated, 100 μL of PBS was added, and the plate was shaken for 10 min on the plate shaker. Then, the fluorescence reading was performed in a spectrophotometer with excitation at 485 nm and emission at 538 nm (model Synergy HT, Biotek, Winooski, VT, USA). Antioxidant cell activity (ACA) was calculated according to Equation (7), with abs_s being the absorbance of the sample and $abs_{H_2O_2}$ of the oxidizing reagent.

$$ACA\ (\%) = 100 - \frac{abs_s}{abs_{H_2O_2}} \bullet 100 \tag{7}$$

2.3.8. Statistical analysis

The results were statistically evaluated in the software Statistica® 13.5.0.17 version (TIBCO Software Inc, Palo Alto, CA, EUA) by one-way analysis of variance (ANOVA) with a statistical significance level of 5%, followed by Tukey's test.

3. Results and discussion

3.1. Electrospray ionization mass spectrometry fingerprinting

The*Barbatimão* bark extract obtained by SE and SM was analyzed by mass spectrometry (Table 2). Both extracts showed similar chemical composition, based on flavonoids, tannins, quinic acid, and its derivatives. Caffeoylquinic acid and dicaffeoylquinic acid were identified for the first time in *Barbatimão* bark extracts, whereas condensed tannins are usually detected for this species (Mello et al., 1996b, 1999). Among the flavonoid group, only (epi)gallocatechin and (epi)gallocatechin-*O*-gallate were found, which agrees with the flavonoids found for this species (Mello et al., 1996a; Pellenz et al., 2018). However, the literature points to the presence of other flavonoids for this species, such as gallocatechin, 4′-*O*-methylgallocatechin, epigallocatechin-3-*O*-(3,5-dimethyl)gallate, epigallocatechin-3-*O*-(3-methoxy-4-hydroxy)benzoate (Mello et al., 1996a), delphinidin (Santos et al., 2002), catechin, rutin, quercetin, and kaempferol (Pellenz et al., 2018). Phenolic composition differences between this study with the literature may be related to the extraction process differences and the geo-climatic conditions to which the species was subjected. Based on these results, the extraction processes were evaluated regarding the quantification of TPC, TTC, and TFC.

3.2. Effect of UAE amplitude and S/F

The influence of amplitude and S/F was evaluated on X_0 and TPC (Tables 3 and 4). The increase in ultrasound amplitude (0–30%) increased the X_0 from 7.58 to 22.2% and TPC from 64 to 197 mg ETA/g dry RM, representing an increase of 193% and 207%, respectively (Table 3). Such behavior is explained by the increase in the collapse of the bubbles (cavitation) produced by the increase in the

Table 2
Chemical profile of ethanolic and methanolic extracts obtained by refluxing solvent in Soxhlet from *Stryphnodendron adstringens* (Mart.) Coville obtained by FIA-ESI-IT-MS/MS.

Id.	Compound	$[M-H]^-$ (*m/z*)	MS^2
1	Quinic Acid	191	–
2	(Epi)gallocatechin	305	179 $[M-H-126]^-$, 221 $[M-H-84]^-$, 261 $[M-H-44]^-$, 287 $[M-H-18]^-$
3	Caffeoylquinic acid	353	191 $[M-H-162]^-$
4	(Epi)gallocatechin-*O*-gallate	457	305 $[M-H-152]^-$, 169 $[M-H-288]^-$, 125 $[M-H-332]^-$
5	Dicaffeoylquinic acid	515	353 $[M-H-162]^-$, 191 $[M-H-324]^-$
6	(Epi)catechin-(epi)catechin	577	289 $[M-H-288]^-$, 125
7	(Epi)catechin-(epi)gallocatechin	593	575 $[M-H-18]^-$, 425 $[M-H-168]^-$, 305 $[M-H-288]^-$
8	(Epi)gallocatechin-(epi)gallocatechin	609	423 $[M-H-186]^-$, 305 $[M-H-304]^-$
9	(Epi)catechin-3′-*O*-galloyl-(epi)gallocatechin	745	423 $[M-H-322]^-$, 305 $[M-H-440]^-$, 287$[M-H-458]^-$
10	(Epi)gallocatechin-(epi)gallocatechin-*O*-gallate	761	609 $[M-H-152]^-$, 453 $[M-H-308]^-$, 423 $[M-H-338]^-$
11	(Epi)catechin-(epi)catechin-(epi)gallocatechin	881	423 $[M-H-458]^-$, 287 $[M-H-594]^-$
12	(Epi)gallocatechin-(epi)gallocatechin-(epi)gallocatechin	913	609 $[M-H-304]^-$, 305 $[M-H-608]^-$, 303 $[M-H-610]^-$
13	(Epi)gallocatechin-*O*-gluco-(epi)gallocatechin-*O*-gallate	923	473 $[M-H-450]^-$, 609 $[M-H-314]^-$, 423 $[M-H-500]^-$
14	(Epi)gallocatechin-*O*-gallate-(epi)gallocatechin-(epi)gallocatechin	1065	1001 $[M-H-64]^-$, 879 $[M-H-186]^-$, 727 $[M-H-338]^-$, 483 $[M-H-582]^-$
15	Tetramer of (epi)gallocatechin	1217	1199 $[M-H-18]^-$, 1049 $[M-H-168]^-$, 745 $[M-H-472]^-$, 609 $[M-H-608]^-$, 423 $[M-H-724]^-$
16	(Epi)gallocatechin-*O*-gallate-(epi)gallocatechin-(Epi)gallocatechin-(epi)gallocatechin	1369	1183 $[M-H-186]^-$, 1065 $[M-H-304]^-$, 895 $[M-H-474]^-$, 709 $[M-H-660]^-$, 589 $[M-H-780]^-$, 465 $[M-H-904]^-$
17	(Epi)gallocatechin-*O*-gallate-(epi)gallocatechin-*O*-gallate-(epi) gallocatechin-(epi)gallocatechin	1521	–

Table 3
Influence of UAE amplitude on X_0 and TPC at S/F equal to 5 and extraction time of 6 min.

Amplitude (%)	X_0 (%wt)[a]	TPC (mg ETA/g dry RM)[a]
0	7.58 ± 0.04^{a}	64 ± 2^{a}
20	16.87 ± 0.02^{b}	158 ± 3^{b}
30	22.2 ± 0.2^{c}	197 ± 6^{c}
40	21.8 ± 0.1^{c}	211 ± 16^{c}

[a] Different lowercase letters in the column indicate significant difference ($p < 0.05$).

Table 4
Influence of S/F and US application on X_0 and TPC at 30% amplitude and extraction time of 6 min.

S/F	With US[a]		Without US[a]	
	X_0 (%wt)	TPC (mg ETA/g dry RM)	X_0 (%wt)	TPC (mg ETA/g dry RM)
5	$14.1 \pm 0.4^{a,B}$	$83 \pm 6^{a,B}$	10.4 ± 0.8^{A}	37 ± 4^{A}
10	$19.0 \pm 1.2^{b,B}$	$99 \pm 6^{a,A}$	13.7 ± 0.3^{A}	83 ± 9^{A}
15	$23.0 \pm 0.5^{c,B}$	$165 \pm 14^{b,B}$	17.6 ± 1.2^{A}	101 ± 12^{A}
20	$29.7 \pm 1.2^{d,B}$	$303 \pm 30^{c,B}$	17.9 ± 1.4^{A}	182 ± 14^{A}
25	$28.9 \pm 1.3^{d,B}$	$234 \pm 9^{d,B}$	18.2 ± 0.6^{A}	113 ± 5^{A}

[a] Different lowercase letters in the same column indicate significant difference ($p < 0.05$), and different capital letters in the same line indicate significant difference ($p < 0.05$) between the extraction with and without ultrasound (US) application.

ultrasound dissipated power (Fig. 1SM(A), Supplementary Material). Increasing the amplitude/power, the size of the bubbles increases, and consequently increases the possibility of the implosions, as well as the accumulation of energy to be released in the collapse (Kumar et al., 2021). However, minimum power is required for this phenomenon to occur (Niemczewski, 1980). The ultrasound cavitation changes the cellular matrix structure, induces mechanical effects by the agitation of the extraction medium (solvent + raw material) (Kumar et al., 2021; Niemczewski, 1980), and produces thermal effects by the compression of the gas inside the bubbles at the moment of collapse, increasing the extraction medium temperature; such effects increase the extraction yields (Carreira-casais et al., 2021; Leighton, 2007; Martínez et al., 2020). The thermal effect produced by the UAE is observed in Fig. 2SM(A) (Supplementary Material); one can figure out that the temperature increased during the extraction process for the three amplitudes, but the increase was higher as the higher amplitudes were applied. This increase in amplitude leads to an increase in the energy accumulated in the bubbles, generating this temperature variation, which favors the mass transfer of the process. The effect of increasing temperature in

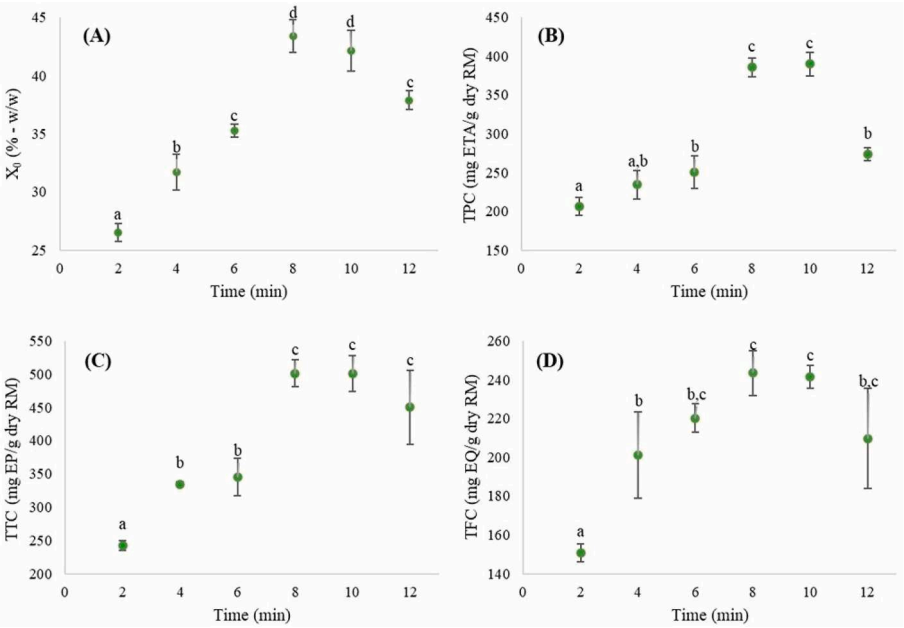

Fig. 1. Effect of UAE time on X_0 (A), TPC (B), TTC (C), and TFC (D) at 30% amplitude and S/F equal to 20. Different letters between markers in the same graph indicate significant differences ($p < 0.05$).

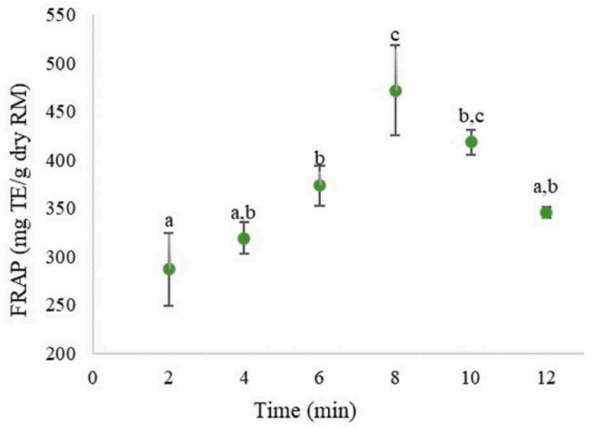

Fig. 2. Effect of UAE time on FRAP. UAE performed at 30% amplitude and S/F equal to 20. Different letters between markers indicate significant differences ($p < 0.05$).

extraction processes is well described in the literature; it is associated with higher desorption and solute solubilization, mainly caused by breaks of molecular bonds, decreasing solvent viscosity, and surface tension (Carreira-casais et al., 2021; Esclapez et al., 2011).

However, increasing the amplitude from 30 to 40% did not generate a significant difference in the yields (Table 3). Four hypotheses could explain this behavior. The first is the excessive increase in bubbles triggered by the increase in amplitude, generating a decrease in the cavitation effect since, from a specific concentration of bubbles, the collision between them, the deformation, and even the non-spherical collapse occurs, reducing the impact of the implosion, which could reduce the extraction process efficiency (Kumar et al., 2021). Another factor that can affect the cavitation effect is the medium's temperature (Nagalingam and Yeo, 2018; Niemczewski, 1980). By increasing the temperature of the medium to close to the boiling point of the solvent, the microbubbles lose the ability to keep the gas inside and implode before being able to increase in size (Nagalingam and Yeo, 2018). According to the process behavior in terms of temperature and power dissipated as a function of amplitude (Fig. 1SM(A) and 2SM(A), Supplementary Material), it is possible that the reduction in the effect of cavitation for the studied process occurred in as a function of the increase in temperature and not just by the increase in amplitude. Because the 40% amplitude presented a higher final temperature than the 30% amplitude (Fig. 1SM(A), Supplementary Material), while the powers dissipated at the end of the process were statistically similar (Fig. 2SM(A), Supplementary Material). The second is the saturation effect, which is the accumulation of bubbles around the probe, making it difficult to transmit energy to the medium (Kumar et al., 2021). The third is the degradation of bioactive compounds affected by the high intensity of ultrasound, which can occur by the action of temperature or by the generation of free radicals (Al-Dhabi et al.,

2017; Kumar et al., 2021; Leighton, 2007). In addition, the energy supplied to the extraction medium at 30% amplitude may be sufficient to achieve the maximum effect in obtaining phenolic compounds. To sum up, establishing an order of importance for the ultrasound effects in reducing the extraction yield with the amplitude increase is challenging even because they could co-occur.

Based on the results obtained, the 30% amplitude was selected to evaluate the effect of S/F, whose results are presented in Table 4. The increases in S/F from 5 to 20 increased X_0 (14.1–29.7%) and TPC (83–303 mg ETA/g dry RM). These findings could result from reducing the viscosity and concentration of the extraction medium, allowing a more significant effect of ultrasound cavitation than the smaller S/F. Consequently, higher S/F enhances the changes in a matrix structure, such as fragmentation, erosion, and pore formation. Moreover, the decrease in the extraction medium concentration caused by a high solvent-to-feed ratio decreases the solute concentration, increasing the diffusivity and dissolution of the solute in the extraction solvent (Al-Dhabi et al., 2017; Kumar et al., 2021).

On the other hand, increasing the S/F from 20 to 25 did not significantly increase the yields, probably because the solvent excess reached the maximum of the described extraction mechanisms, and increments in S/F no longer make a difference. Besides being important in the extraction yields, the S/F plays an essential role in the energy expenditure to evaporate the solvent from the extract (Šibul et al., 2016) and solvent consumption. However, in this case, economic analysis can provide more reliable data to select the most appropriate S/F considering yields and costs of manufacture.

Table 3 also shows the effect of ultrasound application. Extraction runs were reproduced without turning on the ultrasound, and the results are expressed in 0% amplitude. Therefore, the X_0 and TPC are the natural ability of the solvent to solubilize the solutes in the raw material at room temperature, without agitation for 6 min. Note that the yields at 0% were significantly lower than 20% amplitude, reinforcing the above-discussed ultrasound effects. From Table 4, it is also possible to see the effect of ultrasound application in which, regardless of the S/F, the extraction with ultrasound produced significantly higher yields (X_0 and TPC). However, more than that, it is possible to note that increasing the S/F potentiated the ultrasound effect, corroborating with the S/F effect mentioned above discussed; note that the higher differences between extractions with and without ultrasound occurred at S/F of 20 and 25.

3.3. Effect of UAE time

Once the amplitude and S/F (30% and 20, respectively) were defined, the UAE kinetics were accessed by varying the time from 2 to 12 min and evaluating X_0, TPC, TTC, and TFC (Fig. 1). The yields (except TPC) linearly increased with time up to 8 min. After that, all yields did not statistically differ between 8 min and 10 min, but showed a slight tendency to decrease, which was confirmed by the yields produced at 12 min. Therefore, 8 min of UAE was appropriate to produce the higher yields from *Barbatimão* barks (X_0: 43.39%, TPC: 385.40 mg ETA/g dry RM, TTC: 501.25 mg EP/g dry RM, and TFC: 243.33 mg EQ/g dry RM). The UAE, at 30% amplitude, S/F equal to 20, and 8 min achieved 43% of X_0; in other words, almost half of the raw material was converted into the extract.

The application of ultrasound initially increases the extraction yields due to the ultrasound effects. However, prolonged extraction times can lead to degradation of the solute and decrease process yield (Kumar et al., 2021). Therefore, experiments were conducted to evaluate a possible compound degradation induced by the increasing temperature and the formation of free radicals generated by ultrasound energy; for that, ultrasound was applied directly to the extract previously obtained and characterized (TPC, TTC, TFC, and FRAP), simulating the UAE but without solid raw material. Afterward, the extract was analyzed again to verify a possible change in its composition. The results are presented in Fig. 3SM (Supplementary Material) and show, regardless of the analyzed response (TPC, TTC, TFC, and FRAP), that the extract concentration did not change. Thus, the evidence does not suggest extract degradation to explain the yield reduction. Other authors have reported this behavior of reducing UAE yield after a given process time. For instance, Luo et al. (2019) reported that the tannin yield linearly decreased between 2.5 and 4.0 min in the UAE of acorns and associated the behavior with the loss of ultrasonication post-processing. It is important to emphasize that X_0 also decreased after 8 min of UAE (Fig. 1 (A)), which implies that up this process time, there was the mass transfer of extract from the particle to the solvent and, therefore, after 8 min, some transformation occurred in the extract to decrease its solubility in the solvent and allowing its retention in the post-extraction filter element. Moreover, chromatographic analysis could be an alternative to understanding the phenomenon, as it is more specific than applied spectrophotometric methods. Still, it is challenging for samples containing tannins due to their high molecular mass, highly polymerized structure, and association with other constituents, such as carbohydrates (Mouls and Fulcrand, 2015; Shirmohammadli et al., 2018). In these cases, preliminary steps to chromatography are necessary to prepare the extract, such as hydrolysis (Santos et al., 2002), acid catalysis (Watrelot et al., 2018), or depolymerization by thiolysis (Bianchi et al., 2015; Zhou et al., 2011) or thioglycolysis (Mouls and Fulcrand, 2015). However, in these cases, the quantification would be performed regarding flavonoids and not tannins.

3.4. Ferric reducing antioxidant power

The antioxidant capacity of the extracts was accessed through ferric reducing antioxidant power (FRAP), whose results are presented in Fig. 2. One can observe that the FRAP behavior during the UAE kinetic was very similar to that observed in Fig. 1, showing greater antioxidant capacity at 8 min of extraction (472.09 ± 46.66 mg TE/g dry RM) and subsequent stabilization at 10 min and reduction at 12 min (345.90 ± 5.38 mg TE/g dry RM). According to the literature (Ávila-Román et al., 2021; Pandey and Rizvi, 2009), the antioxidant capacity of the extract may be related to its phenolic composition. For the UAE of *Barbatimão* barks, such observation is coherent, in which the antioxidant capacity results coincide with TPC behavior (Fig. 1(B)).

Among the possible analyses to determine the extract's antioxidant capacity, FRAP was chosen due to its particularity in using the iron ion reduction mechanism to measure the level of oxidation (Benzie and Strain, 1996). Tannins, which were the compounds quantified in more significant proportions (Fig. 1(C)), can complex into metal ions (Haslam, 1996). Thus, using the FRAP methodology, it is possible to observe the oxidation of tannins by Fe(III) and the reduction of ferric-tripyridyltriazine (Fe^{3+}-TPTZ) to its ferrous form

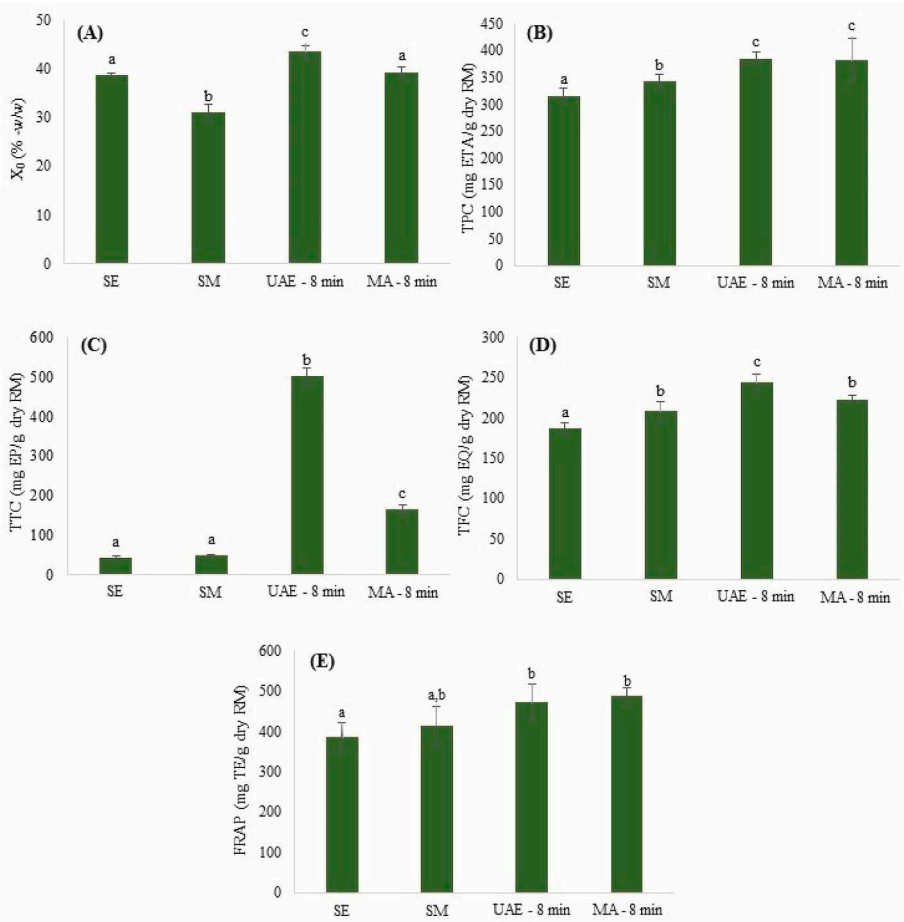

Fig. 3. Effect of different extraction techniques on X_0 (A), TPC (B), TTC (C), TFC (D), and FRAP (E). Different letters between bars indicate significant difference ($p < 0.05$).

(Fe(II)) (Motta et al., 2020). This method makes it possible to verify the relationship between the antioxidant capacity and the tannin content obtained in the extracts.

Regarding antioxidant capacity by FRAP, Sereia et al. (2019) reported 5.79 mmol of TE/g sample, higher than that obtained in this study (1.90 mmol of TE/g dry RM). It should, however, be noted that the authors used a mixture of acetone and water (70%) as the extraction solvent. In this study, a mixture of ethanol and water (50%) was used, which could justify the higher performance of the reference since acetone has a greater affinity for phenolic compounds. Still, it is worth noting that this solvent is not considered sustainable since it presents toxicity. Besides, it is acceptable that the composition could vary between different batches of raw material, impacting the yields and other extract characteristics.

3.5. Comparison between extraction techniques

UAE was compared with other extraction techniques to verify its yields' efficiency and understand the UAE mechanisms acting in*Barbatimão* barks. The selected UAE conditions were 30% amplitude, S/F was equal to 20, and 8 min extraction time. Extraction by solvent reflux in Soxhlet (SE and SM) and the mechanical agitation (MA) was used for comparison. MA was performed at similar UAE conditions (time equal to 8 min, S/F was equal to 20, 50 wt% ethanol as the solvent); the temperature was that one reached at 8 min in UAE (69 °C), and 20 rpm was used to simulate the agitation induced by the ultrasound. The extraction techniques were evaluated and compared regarding X_0, TPC, TTC, TFC, and FRAP (Fig. 3).

UAE resulted in significantly higher yields than extraction by Soxhlet (using ethanol and methanol), and it is carried out in expressive lower time, 8 min against 6 h of the extraction by Soxhlet, which is very welcome for industrial purposes. The better performance of the UAE compared to the Soxhlet is due to the properties related to ultrasound, such as the physical-chemical alteration of the plant cell structure, releasing the compounds of interest to the extractive medium, and the effects of turbulence and agitation of the medium improving the process mass transfer (Chemat et al., 2017). In comparison, in the Soxhlet, the raw material is fixed in the reservoir where the extraction solvent refluxes, thus having none of the effects presented by the sound wave except for the thermal effect (Luque de Castro and García-Ayuso, 1998; Wang and Weller, 2006). Another collaborative factor for the performance of the UAE is the type of solvent used because while in the extraction with the Soxhlet, it is only possible to use pure solvent, due to the boiling

point (Luque de Castro and García-Ayuso, 1998), in the ultrasound, as it is not necessary to reflux the solvent, different mixtures can be used, allowing to obtain different properties and affinities with the compounds of interest, improving the extraction process (Kumar et al., 2021).

The literature describes that a mixture of solvents (ethanol and water) is more efficient than pure organic solvent in extracting phenolic compounds, including tannins and flavonoids (Kumar et al., 2021). Therefore, the results presented in Fig. 3 corroborate the literature since UAE and MA were performed at 50 wt% ethanol. Sousa et al. (2014) reported the mixture of ethanol and water (65 vol%) as optimum for the *Barbatimão* barks extract obtained by UAE. The ethanol content in the extraction solvent positively affects the yield of the phenolic compounds compared to pure water. This behavior is related to the increased solubility and diffusivity of the extracted solutes by decreasing the solvent's dielectric constant (polarity) with increasing ethanol content (Kumar et al., 2021). Another factor that may be related to the better performance in the solvent mixture is the decrease of highly oxidizing species generated from the hemolytic cleavage of water. During the growth of bubbles in the solvent, ethanol also enters the bubbles. Since ethanol is more stable than water in homolytic cleavage, the release of oxidative species to the extraction medium is reduced (Vinatoru et al., 2017). However, the use of pure ethanol, or above a specific concentration, which varies according to the process and the raw material, it can lead to dehydration of the plant cell tissue, in addition to the denaturation of proteins, which makes the yield lower compared to mixtures of ethanol and water at low or medium ethanol concentration (Kumar et al., 2021).

Moreover, we can identify and confirm possible UAE mechanisms by comparing the yields of UAE and MA. Since MA was carried out at the same temperature reached by UAE, time, S/F, and agitation of the extraction medium, it is expected that the UAE has a higher yield than MA due to intensifying ultrasound mechanisms; the difference should be triggered by the mechanisms that only UAE can provide (like fragmentation, erosion, and pore formation). Nevertheless, X_0, TPC, TFC, and FRAP are similar between UAE and MA, sometimes without significant difference (Fig. 3). In this case, the mechanism of UAE to obtain the extract from *Barbatimão* barks can be associated with other ultrasound mechanisms such as turbulence and heating of the extraction medium, which were simulated in MA. Interestingly, the TTC was 3.07-fold higher in UAE than in MA (Fig. 3(C)), confirming for the tannin extraction that UAE provides mechanisms that go beyond thermal and turbulence effects. Some phenomena that may have contributed to the better performance of UAE compared to MA are the disruption effects of the cellular matrix (fragmentation, erosion, and pore formation) and, in parallel, the breaking bonds between tannins and other structures of the plant matrix such as proteins or polysaccharides, releasing these molecules to the extract may have occurred (Muñoz-Labrador et al., 2019).

Faye et al. (2021) also obtained more than a 50% increase in the tannins yield by UAE compared to the conventional technique. The authors pointed to the ability of ultrasound waves to intensify mass transfer in and out of Canadian yellow birch bark pores, facilitating tannin extraction. Wang et al. (2015) conducted an optimization study for ultrasound extraction of tannins from the succulent stem of *Cynomorium songaricum*. The variables studied were ethanol concentration in the extraction solvent, ultrasound power, ratio of raw material to water, and time. According to the authors, ultrasound power had a greater effect on the process than the other variables.

For *Barbatimão,* few works applied the extraction technique with ultrasound (de Souza Ribeiro et al., 2022). Sousa et al. (2014) optimized the UAE of phenolic compounds and tannins from *Barbatimão* bark in an ultrasonic bath system at 40 kHz using a hydroethanolic solution as an extraction solvent. They evaluated the extraction time (15, 30, and 45 min), solid-to-liquid ratio (4, 6, and 8 mg/mL), and ethanol concentration (65, 80, and 95% v/v). The optimized condition was using 30 min process, with a solid to liquid ratio of 4 mg/mL and 65% hydroethanolic solution as extraction solvent. They obtained at the optimized condition 22.95 and 11.95% (w/w) of phenolic compounds and tannins, respectively. Nascimento et al. (2020) also optimized the extraction process of phenolic compounds and tannins from *Barbatimão* bark using an ultrasonic bath system but evaluated sample particle size (0.250, 0.355, and 0.841 mm), the pH (7.9, and 11) of the hydroethanolic solution (50%), and the temperature (30, 40, and 50 °C). At the optimized conditions (temperature of 48 °C, pH of 7, and particle size of 0.841 mm), they obtained 12.76 g of gallic acid equivalent/100 g of sample for phenolic content and 27.91 g of catechin equivalent/100 g of sample for condensed tannins content. As can be observed, both studies presented lower results than those obtained in the present study. It is worth mentioning that the extraction process with the ultrasonic probe is being applied for the first time to this plant species. Moreover, the ultrasonic bath system does not apply direct ultrasound waves on the sample, so it is not a method of high-intensity ultrasound. Moreover, the present work obtained high yields compared to the literature with a shorter process time (8 min).

3.6. Cytotoxicity and antioxidant cell activity

The extract obtained by the selected UAE conditions (30% amplitude, S/F equal to 20, and 8 min of extraction) was evaluated in cytotoxicity and antioxidant cell activity to verify possible pharmacological applications of *Barbatimão* barks extract. In addition, a comparative study was also carried out with the extract obtained by MA at 8 min of extraction. The results are shown in Fig. 4. In terms of cytotoxicity, which evaluated the toxicity of UAE and MA extracts concerning the healthy cells (Fig. 4(A)), it was observed that both extracts at concentrations ranging from 0.015 to 2.0 mg/mL showed cell viability higher than IC50 (value to cause 50% cell death), demonstrating that in this range of extract concentration it is safe to use the *Barbatimão* extracts. The UAE extracts were evaluated at the concentration of highest cell death (2.0 mg/mL) to verify the change in cytotoxicity along with the extraction kinetics (Fig. 4(B)). The results showed cell viability higher than 61%, and no significant difference was observed between UAE times. Therefore, it is appropriate to proceed with studying antioxidant cell activity with the extract with 8 min of extraction time. Pellenz et al. (2018) analyzed the cytotoxicity of the hydroethanolic extract (70%) of *Barbatimão* barks on keratinocytes (HaCaT). According to the results, the extracts obtained by the hydroethanolic solvent did not show cytotoxicity at concentrations from 0.012 to 1.99 mg/mL. Furthermore, in the current study despite not having shown toxicity (cell viability greater than 50% for all concentrations tested), there was a decrease in cell viability as the extract concentration increased.

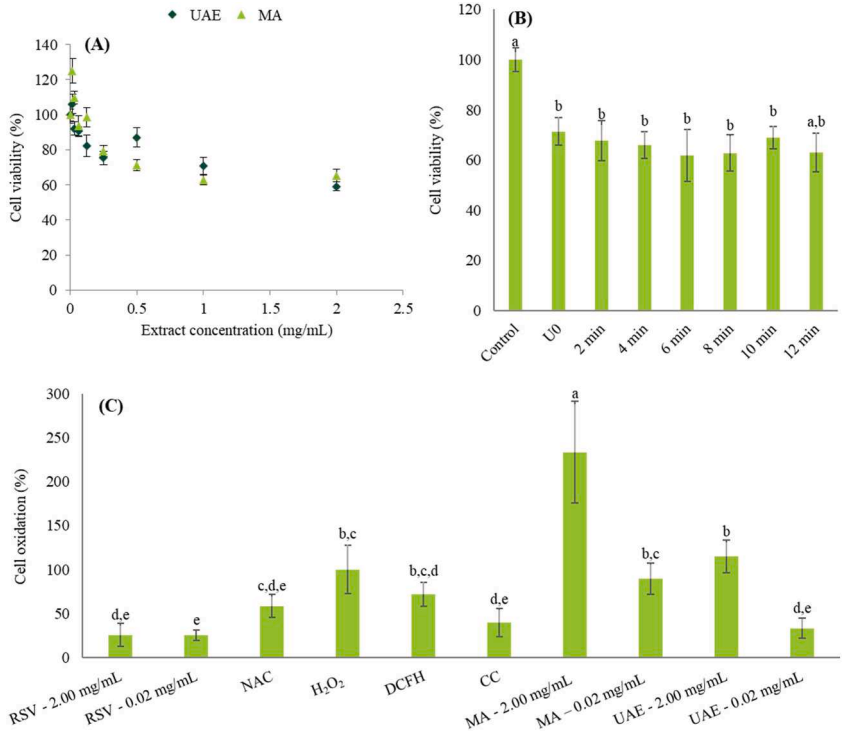

Fig. 4. Cytotoxicity of extracts obtained by UAE (8 min) and MA (8 min) at different concentrations (A). Cytotoxicity of extracts obtained by UAE at different extraction times (B). Antioxidant cell activity of the UAE extract (8 min) and MA (8 min) in two concentrations (0.02 and 2.00 mg/mL) (C). H_2O_2: hydrogen peroxide; RSV: resveratrol; NAC: N-acetylcysteine; DCFH: 2′,7′–dichlorofluorscein diacetate; CC: control. Different letters between bars indicate significant difference ($p < 0.05$).

The antioxidant cell analysis evaluated two extract concentrations obtained by UAE and MA (Fig. 4(C)). Hydrogen peroxide (H_2O_2) was used as the reference for 100% oxidation, resveratrol (RSV) and N-acetylcysteine (NAC) represent the reference of antioxidant substances, 2′,7′–dichlorofluorescein diacetate (DCFH) was used as the fluorescent probe that indicates the occurrence of oxidation, and control (CC) is composed of only cells with the culture medium. According to Fig. 4(C), RSV at the lowest concentration (0.02 mg/mL) showed the highest antioxidant cell activity (77.78%). At the same time, the *Barbatimão* barks extract obtained by MA presented 14.82% against 66.67% of the UAE extract, both at the lowest concentration (0.02 mg/mL). Furthermore, the UAE extract at a concentration of 0.02 mg/mL showed cellular antioxidant activity similar to RSV and NAC standards (44.45%). It was also analogous to CC (60%), demonstrating that it efficiently inhibited cellular oxidation. However, the UAE extract at 2 mg/mL and both concentrations of the MA extract reported greater cellular oxidation than H_2O_2, so instead of showing antioxidant activity, they are propagating to cellular oxidation. The extract's oxidant activity propagation may be related to the higher concentration of phenolic compounds. Instead of inhibiting the oxidation, it would be reacting with other compounds such as metal ions, generating cytotoxic compounds that could be causing this activity in favor of oxidation (Squillaci et al., 2018).

The difference in the antioxidant cell activity between the UAE and the MA extracts may be related to the composition in terms of tannins because among the parameters evaluated, it was the one that presented the more difference between these two extraction techniques (Fig. 3). This hypothesis is supported by the literature, in which Squillaci et al. (2018) verified the protective action against cellular oxidation of extracts obtained from chestnut (*Castanea sativa* Mill.) shells. Furthermore, the authors identified and quantified the presence of tannins (condensed and hydrolysable tannins) and quantified the presence of epicatechin, one of the structural monomers of condensed tannins identified in the *Barbatimão* extracts (Table 2). Furthermore, such authors also observed that extracts with higher concentrations of these compounds showed high antioxidant activities. Sobeh et al. (2018) also observed antioxidant cell activity of extracts from *Syzygium samarangense* leaves. The identified tannins and flavonoids were similar to those identified and presented in Table 2. The authors highlighted the (epi)-catechin gallate, (epi)-gallocatechin gallate, and (epi)-catechin-(epi)-catechin as they strongly collaborate for the free radical's elimination due to the presence of phenolic hydroxyl groups, which will likely be the same for the other compounds identified in this current work.

Pellenz et al. (2018) also analyzed the antioxidant cell activity of the hydroethanolic extract (70%) of *Barbatimão* barks (0.49 and 0.99 mg/mL) in fibroblast cells. According to the results, they also found a decrease in antioxidant activity with increasing concentration, but the highest percentage of protection was higher (87.20%) than 66.67% obtained in the present work. Therefore, antioxidant cell activity may be related to the extract's concentration.

The result obtained from the cellular assays is highly relevant since it demonstrated that in low UAE extract concentration (0.02 mg/mL), antioxidant cell activity was superior to NAC, a substance with proven antioxidant activity. Moreover, such concentra-

tion does not show cytotoxicity (cellular viability from 80 to 100%, Fig. 4(A)). Furthermore, since the extracts obtained via UAE and MA showed similar results in FRAP analyses, it emphasizes the importance of analyzing the antioxidant activity in cellular terms. Still, UAE and MA were distinguished in performance by the antioxidant cell activity. Firstly, considering only the high total tannins content obtained in the *Barbatimão* barks extract, an application could be proposed as a raw material for the leather industry (Das et al., 2020; Pizzi, 2019; Shirmohammadli et al., 2018; Singh and Kumar, 2019) or even for the plastic and adhesive industry (Carvalho et al., 2014a, 2014b, 2015; Das et al., 2020; Pizzi, 2019; Shirmohammadli et al., 2018), as both use tannins in their processes. However, these applications would not take advantage of the pharmacological potential presented in this work. Considering the low cytotoxicity and the antioxidant potential of the tannins, a promising application for the obtained extracts would be the pharmaceutical and cosmetic industries. Several works showed these compounds' antimicrobial properties and other pharmacological properties of interest for maintaining health, such as wound healing and antiviral propriety (Costa et al., 2013; Farha et al., 2020; Fraga-Corral et al., 2021; Oliveira et al., 2021; Pizzi, 2019; Shirmohammadli et al., 2018; Singh and Kumar, 2019; Souza et al., 2007). In addition, these extracts could be applied as an additive in the wine and beverage industry (Pizzi, 2019; Shirmohammadli et al., 2018) and the preparation of food packaging (Das et al., 2020; Nascimento et al., 2021; Shirmohammadli et al., 2018; Singh and Kumar, 2019); both applications would take advantage of the antioxidant properties demonstrated in this study.

4. Conclusions

This work studied the influence of UAE parameters on the yields of phenolic compounds in*Barbatimão* barks extracts. The influence of amplitude, S/F, and extraction time was evaluated, and the performance of UAE was compared with other conventional extraction techniques (Soxhlet and MA). The results indicate UAE as a potential technique to produce *Barbatimão*barks extract rich in phenolic compounds. Various compounds were extracted, including tannins, flavonoids, and phenolic acids, of which tannins were found in more significant amounts. In addition, phenolic acids such as quinic acid and its derivatives (caffeoylquinic and dicaffeoylquinic acids) were identified for the first time for this species.

The best performance conditions of the UAE were with the amplitude of 30%, S/F of 20, and 8 min of extraction. Compared with Soxhlet, mixed solvents are preferred over pure solvents for richer yields. While in comparison with MA, for TPC and TFC, the performance was similar to UAE, indicating that the possible mechanisms of extraction are related to heating and agitation of the extraction medium. On the other hand, for TTC, UAE showed superior performance than MA, indicating that the extraction mechanism was associated with phenomena only ultrasound could provide, such as effects on the structure of the cell-matrix and effects of bond breaking on tannin molecules.

The extract obtained by UAE did not show cytotoxicity at any of the concentrations tested. The lowest concentration of UAE extract showed higher cellular antioxidant activity than the same extract at higher concentration and the MA extract regardless of concentration. This behavior among the extracts may be related to the TTC since the UAE extract had higher tannin content than the MA extract. The lower concentration of UAE extract showed antioxidant activity statistically similar to the antioxidant compounds tested (RSV and NAC) and also to DCFH and CC, indicating that there was no cellular oxidation at this extract concentration.

The presented work indicates that UAE is a fast and effective technique for obtaining hydroalcoholic extracts rich in phenolic compounds from*Barbatimão*barks. In addition, it demonstrated potential for applying the extract as an alternative source of tannins for the wine and beverage, pharmaceutical, cosmetics, and food packaging industries, in addition to its traditional use in the leather, plastics, and adhesives industries. Finally, the authors highlight the importance of conducting economic studies to demonstrate the feasibility of the presented technical processes in large production scales for future works.

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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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scp.2023.101044.

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