

Phenylpropanoid Substituted Flavan-3-ols from *Trichilia catigua* and their *In Vitro* Antioxidative Activity

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O novo flavan-3-ol contendo um substituinte fenilpropanoide apocinina E, juntamente com oito substâncias conhecidas, epicatequina, procianidina B2, procianidina B4, procianidina C1, cinchonafina Ia, cinchonafina Ib, cinchonafina IIB e cinchonafina IIA foram isoladas a partir do extrato acetona-H₂O das cascas secas de *Trichilia catigua*. As substâncias cinchonafina Ib e cinchonafina IIB foram reavaliadas em relação à sua estereoquímica. Todas as substâncias foram caracterizadas por análises espectroscópicas incluindo ressonância magnética nuclear (NMR) 1D e 2D e espectrometria de massa (MS) de seus derivados acetilados. A configuração absoluta do substituinte fenilpropanoide foi determinada por espectropolarimetria de dicroísmo circular (CD) e pela análise do efeito anisotrópico empregando modelo de Dreiding, e por experimento de espectroscopia de efeito nuclear Overhauser (NOESY NMR). As nove substâncias mostraram maior atividade sobre o sequestro de radical livre e poder de redução do que o ácido ascórbico e Trolox frente ao radical livre 2,2-difenil-1-picrilhidrazila e no sistema do teste de redução do ferro (Fe³⁺-Fe²⁺).

The new phenylpropanoid substituted flavan-3-ol apocynin E, together with eight known compounds, epicatechin, procyanidin B2, procyanidin B4, procyanidin C1, cinchonain Ia, cinchonain Ib, cinchonain IIB, and cinchonain IIA were isolated from an acetone-H₂O extract of the air-dried stem bark of *Trichilia catigua*. The cinchonain Ia e Ib were reevaluated to its stereochemistry. All the compounds were characterized by spectroscopic analysis including 1D and 2D nuclear magnetic resonance (NMR) and mass spectrometry (MS) of their peracetate derivatives. The absolute configuration of the phenylpropanoid moiety was determined by circular dichroism (CD) spectra and by analyzing the anisotropic effects in the Dreiding model and nuclear Overhauser effect (NOESY NMR) experiments. The nine isolated compounds showed higher radical scavenging activity and reducing power than ascorbic acid and Trolox in the free-radical 2,2-diphenyl-1-picrylhydrazyl and Fe³⁺-Fe²⁺ reduction assay systems.

Keywords: *Trichilia catigua*, Meliaceae, cinchonains, proanthocyanidins, antioxidative activity

Introduction

Trichilia catigua A. Juss. (Meliaceae), commonly known as “catuaba”, is a plant native to South and

Central America and widely distributed in Brazil.¹ However, the identity of the plant source is often uncertain, and stem barks from several different species of *Erythroxylum* or *Anemopaegma*, all regionally known as “catuaba”, are sold commercially. Marques² described the differences among the species known as “catuaba” and

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determined that *T. catigua* is the main species that is sold as “catuaba” in Brazil. The same conclusion was reached by Kletter *et al.*³ and Daolio *et al.*⁴ The bark of *T. catigua* has been traditionally used as a health and mental tonic, and especially as a sexual stimulant.^{3,5} Some pharmacological studies of this bark have reported antimicrobial, trypanocidal, antinociceptive, vasorelaxant or dopamine-mediated antidepressant-like effects.⁵⁻¹⁰ The bark contains a high concentration of polyphenols (6.96 ± 0.11%; RSD 1.57%) including flavan-3-ols and phenylpropanoid derivatives,^{5,11} as well as tropane alkaloids.³ Other species, *T. clausenii* and *T. lepidota*, were evaluated and yielded sesquiterpenoids.¹² We further investigated the constituents of *T. catigua* bark and isolated nine polyphenolic constituents, including one new compound. The isolated polyphenols showed high radical scavenging and antioxidative activity in DPPH (2,2-diphenyl-1-picryl-hydrazyl) and Fe³⁺-Fe²⁺ assays.

Results and Discussion

Isolation of polyphenols from bark of *Trichilia catigua*

Multiple chromatography on Sigma-Sephadex® LH-20 and high-speed countercurrent chromatography (HSCCC) of the ethyl acetate fraction originating from an acetone/H₂O (7:3) extract of the air-dried stem bark of *T. catigua* yielded eight known compounds together with a new compound. The known compounds were identified as epicatechin (**1**), procyanidin B2 [epicatechin-(4β → 8)-epicatechin] (**2**), procyanidin B4 [catechin-(4α → 8)-epicatechin] (**3**), procyanidin C1 [epicatechin-(4β → 8)-epicatechin-(4β → 8)-epicatechin] (**4**), cinchonain Ia (**5**), cinchonain Ib (**6**), cinchonain IIb (**8**), and cinchonain IIa (**9**) by comparison of the physical and spectral data [¹H nuclear magnetic resonance (NMR), ¹H-¹H correlation spectroscopy (COSY NMR), [α]_D²⁰, mass spectrometry (MS), circular dichroism (CD)] of their peracetates with published data.^{5,13-18} The new compound was isolated as its peracetate **7a** and identified as apocynin E (**7**).

Structure of phenylpropanoid substituted flavan-3-ols

Cinchonain Ia (**5**) and Ib (**6**) were first described by Nonaka and Nishioka¹³ and their structures were revised by Chen *et al.*,¹⁵ based on nuclear Overhauser spectroscopy (NOESY NMR), nuclear Overhauser effect (NOE) and CD data. Several reports have been published with ambiguous stereochemistry of both compounds.^{5,11,16,19,20} The now generally accepted structures for cinchonain Ia and Ib are outlined in Figure 1.

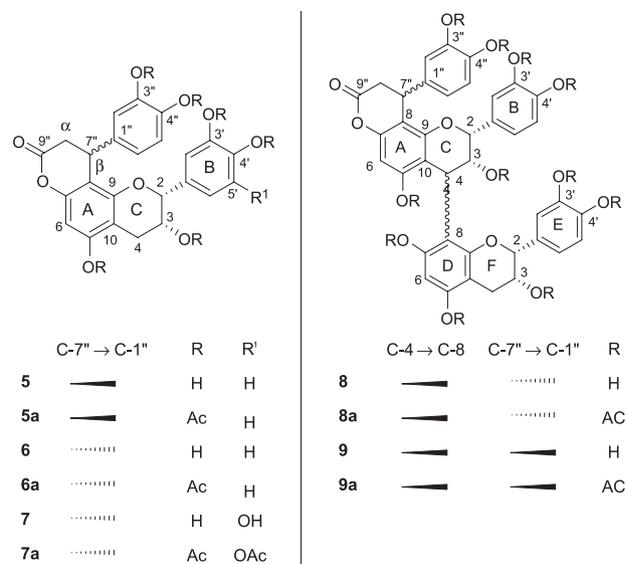


Figure 1. Structures of the compounds isolated from *T. catigua*.

Compounds **5a** and **6a** showed the same [M – H]⁻ signal at *m/z* 451.4 in negative ESI-MS (electrospray ionization mass spectrometry). The presence of a basic flavan-3-ol skeleton in each molecule was readily confirmed by the observation of AMX₂-type resonances at δ 5.20 (brs) and 5.43 (m), 5.46 (brs) and 5.46 (m), and between 2.72 and 3.08 (m, 2H), respectively ascribable to H-2, H-3 and H-4, for peracetates **5a** and **6a**. The appearance of an aromatic proton singlet at δ 6.50 for **5a** and δ 6.63 for **6a** indicated the occurrence of a C8 or C6 attached linkage in the flavan A-ring, while the aromatic ABX-type resonances at δ 7.11-7.33, and the chemical shifts and coupling constants were in good agreement with those of the epicatechin peracetate (**1a**) (Table 1). ¹³C NMR spectra revealed the presence of a carbonyl (δ 167.3 and 167.1), a β-methine carbon (δ 35.1 and 34.9), an α-methylene (δ 36.8 and 36.5) and an additional 1,3,4-trisubstituted aromatic ring system for **5a** and **6a**, respectively. This suggests the presence of a phenylpropanoid linked to the A-ring of the epicatechin unit through a carbon-carbon linkage. According to Nonaka and Nishioka¹³ and Tang *et al.*,²¹ the C-8 resonance (δ 111.5 for **5a** and δ 111.1 for **6a**) relative to the C-6 (δ 104.8 for **5a** and δ 104.5 for **6a**) demonstrates the occurrence of a carbon-carbon linkage at the C-8 position for both compounds. The HMBC (heteronuclear multiple-bond correlation spectroscopy) spectra of **5a** and **6a** clearly indicated a strong correlation between H-7'' and C-8 and C-9, H-8'' and C-8, C-9'' and C-1'', and H-6 and C-5, C-7, C-8, and C-10, which would be impossible if the substituent were attached at the C-6 position, and therefore confirmed the position of the phenylpropanoid moiety at C-8.

For compounds **5a** and **6a**, the *S*- or *R*-absolute configuration of the β-methine carbon in the phenylpropanoid

Table 1. ¹H NMR spectral data of the peracetate compounds **1a**, **5a**, **6a** and **7a** (300 MHz, acetone-*d*₆)

H	1a (δ_{H}) (J / Hz)	5a (δ_{H}) (J / Hz)	6a (δ_{H}) (J / Hz)	7a (δ_{H}) (J / Hz)
2	5.39, brs	5.20, brs	5.46, brs	5.48, brs
3	5.52, m	5.43, m	5.46, m	5.45, m
4	2.84, dd (1.5, 17.7) 3.09, dd (4.5, 17.7)	2.72, dd (1.5, 16.2) 2.99, dd (4.5, 16.2)	2.88, dd (1.8, 16.8) 3.08, dd (4.5, 17.7)	3.01, m
6	6.60, d (2.1)	6.50, s	6.63, s	6.63, s
8	6.68, d (2.1)			
2'	7.43, d (1.8)	7.33, d (1.8)	7.03, d (1.8)	7.01, s
5'	7.26, d (9.0)	7.11, d (8.4)	7.14, d (5.4)	
6'	7.42, dd (1.8, 9.0)	7.25, dd (1.8, 8.4)	7.17, m	7.01, s
2''		6.93, d (2.4)	7.14, d (1.8)	7.35, d (2.1)
5''		6.90, d (8.1)	7.04, d (8.4)	7.25, d (8.4)
6''		6.98, dd (2.4, 8.1)	7.25, dd (1.8, 8.4)	7.18, dd (2.1, 8.4)
7''		4.75, brd (6.0)	4.78, brd (6.0)	4.80, brd (4.8)
8''		3.24, dd (7.5, 16.2) 2.90, dd (1.8, 16.2)	3.34, dd (7.5, 16.2) 3.11, dd (1.8, 16.2)	3.34, dd (7.5, 16.2) 3.13, dd (1.8, 16.2)

substituent was determined based on ¹H NMR, 1D- or 2D-NOESY NMR experiments and CD data. The NMR spectrum of **5a** revealed resonances due to the H-2 and the ABX-type B-ring in accordance with those of epicatechin (see Experimental part). On the other hand, in acetone-*d*₆, **6a** displays the H-2 resonance at δ 5.46 and the B-ring proton resonances at δ 7.03 (d, *J* 1.8 Hz, H-2'), δ 7.14 (d, *J* 5.4 Hz, H-5') and δ 7.17 (m, H-6'). The H-2 resonance is shifted downfield, while H-2' and H-6' are shifted upfield compared with those of epicatechin (Table 1). This implies that these protons are anisotropically affected by the aromatic ring in the phenylpropanoid moiety.¹³ Examination of the Dreiding model indicated that in the case of the β -configuration of the methine proton (H-7''), the direction of the B-ring to the aromatic ring of the phenylpropanoid moiety leads to the concentration of the electronic cloud, thus causing a shielding effect at the B-ring protons and an opposite effect at H-2. These effects explain the upfield shift of the B-ring proton resonances and the downfield shift of the H-2 resonance in compound **6a**. CD data for **5a** show strong negative Cotton effects at 234 and 280 nm and a positive effect at 255 nm, whereas **6a** exhibited Cotton effects of opposite signs, indicating that these Cotton effects are mainly affected by the configuration at the β -methine carbon, and are largely unaffected by the asymmetrical flavan C-2 and C-3 atoms; and hence that the absolute configuration at the β -methine carbon in **5a** is *S* and in **6a** is *R*. From the 2D-NOESY NMR experiments, a small effect between the H-7'' and the H-2' and H-6' of the B-ring was observed for compound **5a**. Another important observation is the cross peak between

H-2(C) and H-2'' and H-6''. This could only be the case if the proton 7'' in **5a** is in α -orientation. The compound **6a** with a β -orientation shows in the NOESY NMR spectrum a strong cross peak between H-7'' and the H-2' and H-6' of the B-ring, and H-2'' and H-6'' of the phenylpropanoid moiety. No effect between H-2(C) and H-2'' or H-6'' was observed. This situation was confirmed with a Dreiding model, and established compound **5** as cinchonain Ia and compound **6** as cinchonain Ib.

Compound **7a** showed the [M + Na]⁺ signal at *m/z* 785.4 in the positive ESI-MS. The HR-ESI-MS (positive-ion mode) exhibited a pseudo-molecular ion peak at *m/z* 785.1688 [M + Na]⁺ (calcd. for 785.6561). The ¹H and ¹³C NMR data are almost similar to those of cinchonain Ib (**6a**), with the exception of a two-proton singlet corresponding to the 1,3,4,5-substituted B-ring, and proved that compound **7a** contained an epigallocatechin unit. This was also confirmed by the ¹H-¹H COSY and HMBC spectra. The *R* absolute configuration of the β -methine carbon of **7a** was determined by comparing the ¹H NMR, NOESY NMR and CD data with those of **5a** and **6a**. The H-2 and H-3 resonances of **7a** suggested that the β -methine carbon configuration is the same as **6a**. The Cotton effect in the CD spectrum of **7a** is in perfect agreement with those found for **6a**. Furthermore, the NOESY NMR spectrum shows no effect between the aromatic ring systems, and H-2' and H-7'', confirming the absolute configuration as *R*. Thus, it was concluded that the structure of compound **7** corresponds to apocynin E. To the best of our knowledge, **7** has been isolated for the first time from a natural source.

Structure of phenylpropanoid substituted dimeric flavan-3-ols

Compounds **8** and **9** were shown to be proanthocyanidin dimers substituted by a phenylpropanoid moiety at the A-ring. Both substances showed the same $[M - H]^-$ peak at m/z 739.4 in negative ESI-MS. Compound **9a** exhibited a pseudo-molecular ion peak at m/z 619.1785 [(calcd. for $C_{61}H_{54}O_{26} + 2 NH_4$) $^{2+}$ 619.1789] in the HR-ESI-MS (positive-ion mode), ascribable to molecular formula $C_{61}H_{54}O_{26}$, and showed a peak at m/z 1220.4 $[M + NH_4]^+$ at ESI-MS. The occurrence of two constituent flavan-3-ol units with 2,3-*cis* configuration in **8a** and **9a** and a phenylpropanoid moiety was deduced from the small coupling constants ($J_{2,3} < 2$ Hz) of the heterocyclic H-2 and H-3 protons and additional methylene (δ 2.53 and 3.26) and methine (δ 4.16 and 4.92) proton resonances, respectively. The HMBC spectrum of **8a** and **9a** strongly favored the 4 \rightarrow 8 interflavonoid bond and the existence of a phenylpropanoid substituent linked to the C-8(A) of the "upper" flavan units in both compounds. Furthermore, 2D correlations between H-6(A), H-7", and H-8" and the carbon C-8(A) at δ 110.2 for **8a** and 111.6 for **9a** strongly favored the existence of a phenylpropanoid substituent linked to the C-8 (A) of the "upper" flavan units in **8a** and **9a**.

The relative configuration of **8a** was determined based on anisotropic effects by comparison of 1H NMR data with those of the peracetate of procyanidin B2. The downfield shift of the H-2(C) resonance at δ 5.86 and the upfield shift of the B-ring proton resonances H-2' and H-6' at δ 6.96 (d, J 2.1 Hz) and δ 7.05 (dd, J 2.1 and 8.4 Hz) for **8a**, respectively, in comparison to the equivalent protons in procyanidin B2 supported the *S*-configuration at C-7". In addition, the 4 β \rightarrow 8-linkage and thus the *R*-configuration at C-4(C) was confirmed by the strong positive Cotton effect observed between 220 and 230 nm, and 280 nm in the CD spectrum.²²⁻²⁷ The missing NOE effect between H-2(C) and H-4(C) strongly supported the proposed 4 β orientation of the interflavonoid bond. The high-amplitude positive Cotton effect was caused by the phenylpropanoid substituent with an *S*-configuration at C-7". No NOE effect between H-7" and H-2(C) was observed, confirming the information from the CD data. Thus, it was concluded that the structure of compound **8** corresponds to cinchonain Iib.

The absolute configuration of the β -methine carbon in **9a** was determined based on CD data and NOESY NMR experiments. In general, the 4*S*-linkage between two flavan units produces negative Cotton effects at 220-240 and 275 nm in the CD spectra.²²⁻²⁷ Such negative Cotton effects can be observed in the spectrum of compound

9a, in addition to a positive Cotton effect at 255 nm. The latter effect is (probably) due to the *S*-configuration of the phenylpropanoid substituent. The 4 β \rightarrow 8 interflavonoid-linkage was determined by the NOESY NMR experiment, where no effect between H-2(C) and H-4(C) was observed. Therefore it was concluded that the structure of compound **9** is cinchonain Iia.

Physical data from the well documented **8** and **9** are in good agreement with the literature values.¹⁴

Antioxidative activity of *Trichilia catigua* polyphenols

The antioxidant effects of the polyphenols are mainly due to their redox properties, which allow them to act as reducing agents or hydrogen-atom donors. Thus, natural antioxidants function as free-radical scavengers and chain-breakers, complexers of pro-oxidant metal ions and quenchers of singlet-oxygen formation.²⁸ The radical-scavenging properties of polyphenols can be shown by the effects on DPPH radical as a model compound for lipid radicals or lipid peroxide radicals.^{29,30} The effects of the polyphenols isolated from *T. catigua* bark on the DPPH radical scavenging and their reducing power were therefore examined.

The DPPH radical scavenging activities of all the tested polyphenols were stronger than the effect of ascorbic acid and Trolox (a water-soluble analogue of α -tocopherol), as shown in Table 2. The differences between the monomers cinchonain Ia and Ib and also between the dimers cinchonain Iib and Iia were not statistically significant. This implies that the stereochemistry does not influence the DPPH radical scavenging activity. According to the literature, the radical scavenging activity of polyphenols is mainly due to the number of hydroxyl groups in the molecule.^{18,31} This could be confirmed, in this study, for compounds

Table 2. Radical scavenging activity of compounds isolated from *T. catigua* on the DPPH radical

Sample	Mean EC_{50} / ($\mu\text{mol L}^{-1}$)	RSD / %
Epicatechin	10.12 \pm 0.24 ^a	2.43
Procyanidin B2	7.95 \pm 0.04 ^b	0.51
Cinchonain Ia	7.87 \pm 0.05 ^b	0.63
Cinchonain Ib	7.67 \pm 0.23 ^b	2.98
Cinchonain Iib	5.05 \pm 0.05 ^c	0.98
Cinchonain Iia	5.15 \pm 0.08 ^c	1.61
Procyanidin C1	4.08 \pm 0.01 ^c	0.28
Ascorbic acid	30.11 \pm 1.31	4.36
Trolox	30.10 \pm 0.48	1.59

Equal letters indicate absence of significant difference ($P < 0.05$); different letters indicate significant difference ($P < 0.05$); RSD = relative standard deviation.

containing only flavan-3-ol units in their structures. However, for the phenylpropanoid substituted flavan-3-ols, the capacity of scavenging DPPH radicals of cinchonain monomers does not differ from procyanidin B2 and the activity of the cinchonain dimers does not differ significantly from procyanidin C1. Obviously the number of catechol type B-rings to form quinone intermediates is more responsible for the radical scavenging activity than the number of hydroxyl groups, especially A-Ring hydroxyl groups.

The reducing power of a compound may serve as a significant indicator of its potential antioxidative activity, and therefore can reduce the oxidized intermediates of lipid peroxidation processes, so that they can act as primary and secondary antioxidants.^{32,33} The presence of reducing substances causes the reduction of the Fe^{3+} /ferricyanide complex to the ferrous form. Therefore, Fe^{2+} can be monitored by measuring the formation of Perl's Prussian blue at 700 nm.³⁴ Figure 2 shows the reducing power of the compounds isolated from *T. catigua* compared to Trolox and ascorbic acid. Like the radical scavenging activity, the reducing capacity of these compounds depended on the concentration.

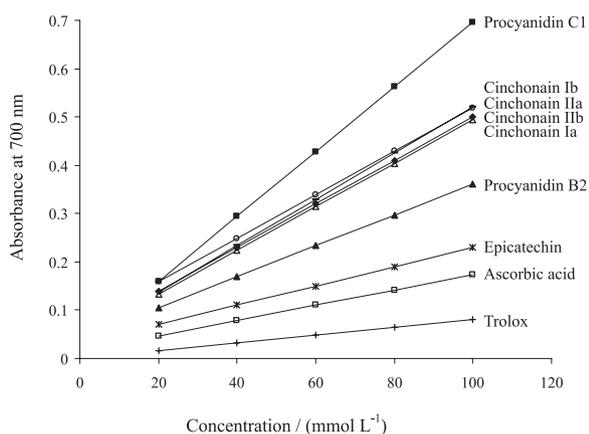


Figure 2. Reducing power of compounds isolated from *T. catigua*.

The absence of a significant difference ($P < 0.05$) between the reducing capacity of the cinchonain monomers and the cinchonain dimers, in contrast to the series of flavan-3-ol analogues, suggests that the reducing ability of substituted phenylpropanoids is largely unaffected by the number of hydroxyl groups or catechol-type B-rings.

Experimental

General experimental procedures

NMR spectra of the peracetates (Varian Mercury 300BB) were recorded in acetone- d_6 or $CDCl_3$ at

ambient temperature with TMS as internal standard. Some compounds were recorded in $CDCl_3$ to confirm the positions of some protons, or to better define them. ESI-MS was carried out on a Quattro LCZ (Waters-Micromass, Manchester, UK) and HR-ESI-TOF-MS (high resolution-electrospray ionization-time-of-flight-mass spectroscopy) on a microTof (Bruker-Daltonics, Bremen, Germany). Optical rotations were measured in acetone and CD data were obtained in MeOH (Jasco 815 spectrometer). Compounds were revealed by spraying with 1% ethanolic $FeCl_3$ solution. Analytical TLC (thin-layer chromatography) was carried out on pre-coated aluminum sheets (Kieselgel 60 F₂₅₄, Merck) with EtOAc/formic acid/ H_2O (18:1:1; system S1). Preparative TLC was performed on silica gel plates (Kieselgel 60 F₂₅₄, 1.0 mm) using toluene/ Me_2CO (7:3; system S2). Acetylations were performed in pyridine/ Ac_2O (1:1) at ambient temperature.

Plant material

Stem bark of *T. catigua* A. Juss. was collected in January 1997 in Caitité City (Bahia State, Brazil) and identified as described elsewhere.³⁵ A voucher specimen is deposited in the Herbarium of the Municipal Botanical Museum of Curitiba City, Paraná State, Brazil (65 901).

Extraction, isolation and identification of compounds

The data of extraction, isolation and identification of all compounds are presented as supplementary information.

Radical scavenging effects of *Trichilia catigua* polyphenols on the DPPH radical

To a DPPH radical solution in MeOH (1 mmol L⁻¹, 0.3 mL), a solution of the test polyphenol in MeOH (3.0 mL) was added, and the reaction mixture was left to stand for 30 min at room temperature. The scavenging activity of each polyphenol at 1, 2, 4, 6, 8 and 10 $\mu\text{mol L}^{-1}$ was estimated by measuring the absorption of the mixture at 517 nm, which reflects the amount of DPPH radical remaining in the solution. The scavenging activity was expressed as the EC_{50} ($\mu\text{mol L}^{-1}$), the concentration of polyphenol required for scavenging 50% of DPPH radical in the solution.²⁸

Reducing power of the polyphenols by $Fe^{3+} - Fe^{2+}$ transformation

Different concentrations of the polyphenols (20, 40, 60, 80 and 100 $\mu\text{mol L}^{-1}$) in 1 mL of distilled water were

mixed with phosphate buffer (2.5 mL, 0.2 mol L⁻¹, pH 6.6) and potassium ferricyanide [K₃Fe(CN)₆] (2.5 mL, 1%). The mixture was incubated at 50 °C for 20 min. Trichloroacetic acid (2.5 mL, 10%) was added to the mixture, which was then centrifuged for 10 min at 1000× g. The upper layer of solution (2.5 mL) was mixed with distilled water (2.5 mL) and FeCl₃ (0.5 mL, 0.1%), and the absorbance was measured at 700 nm. Higher absorbance of the reaction mixture indicated greater reducing power.³⁶

Statistical analysis

Results were assessed by one-way analysis of variance (ANOVA) and represent the mean ± standard deviation of three different measurements. The significant differences were determined by the Tukey test with *P* < 0.05.

Supplementary Information

The data of extraction, isolation and identification of all compounds are presented as Supplementary Information together with 29 spectra referring to the isolated compounds. Supplementary data are available free of charge at <http://jbcs.sbq.org.br> as pdf file.

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