Chemical constituents of *Pseudobrickellia brasiliensis* leaves(Spreng.) R.M. King & H. Rob. (Asteraceae)

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ABSTRACT: *Pseudobrickelliabrasiliensis*is aspecies endemic toBrazil, popularlyknown as “arnica”/ “arnica-do-campo”/ “arnica-do-mato” and used for itsanalgesicand anti-inflammatoryproperties. The objective of this research was thephytochemical studyof the essential oilandhexaneandethyl acetateextracts of the leaves of this species. The essential oilwasextracted byhydrodistillation using a Clevengerapparatusand was analyzed byGC/MS, 25components were identified, with a predominance ofmonoterpenes. The extractswere subjected toclassicalchromatographyand the fractionswere analyzed byGC/MS, 1D ^{1}H-NMR, ^{13}C-NMR and ^{13}C-NMR-DEPT 135.α-amyrin, α-amyrin acetate, β-amyrin, β-amyrin acetate, lupeol, lupeolacetate, pseudotaraxasterol andtaraxasterol (triterpenes), andkaurenoicacid (diterpene) were identified.Theseterpenesarechemo-taxonomicallyrelated to theEupatorieaetribe(Asteraceae) and may be responsible for the anti-inflammatory activity attributed to the plant.

Key words: *Pseudobrickellia brasiliensis*, Asteraceae, medicinal plant, phytochemistry, terpenes.

RESUMO: Constituintes químicos das folhas de *Pseudobrickellia brasiliensis* (Spreng.) R.M. King & H. Rob. (Asteraceae). *Pseudobrickellia brasiliensis* é uma espécie endêmica do Brasil, popularmente conhecida como “arnica”/ “arnica-do-campo”/ “arnica-do-mato” e usada por suas propriedades analgésica e antiinflamatória. O objetivo do trabalho foi o estudo fitoquímico do óleo essencial e dos extratos hexânico e em acetato de etila das folhas dessa espécie. O óleo essencial foi extraído por hidrodestilação em aparato de Clevenger e foi analisado por CG/EM, sendo identificados 25 componentes, com predomínio de monoterpenos. Os extratos foram submetidos a cromatografia clássica, e as frações foram analisadas por CG/EM, 1D ^{1}H-RMN, ^{13}C-RMN e ^{13}C-RMN-DEPT 135. Foram identificados α-amirina, acetato de α-amirina, β-amirina, acetato de β-amirina, lupeol, acetato de lupeol, pseudotaraxasterol e taraxasterol (triterpenos) e o ácido caurenóico (diterpeno). Estes terpenos estão quimiotaxonomicamente relacionados a tribo Eupatorieae (Asteraceae) e podem ser responsáveis pela atividade antiinflamatória atribuída a planta.

Palavras-chave: *Pseudobrickellia brasiliensis*, Asteraceae, planta medicinal, fitoquímica, terpenos.

INTRODUCTION

The “arnica” or “arnica-do-campo” or “arnica-do-mato” plant (*Pseudobrickellia brasiliensis* (Spreng.) R.M. King & H. Rob.) is a shrub or subshrub species, belonging to the Eupatorieae tribe, Asteraceae family. It is endemic to Brazil and is observed in “campo rupestre” and “cerrado” regions in the States of Minas Gerais, São Paulo, Goiás, Mato Grosso, Pernambuco, and Bahia (Almeida et al., 2004; Forzza et al., 2010).

The whole plant or parts of the plant are popularly used as an analgesic and an anti-inflammatory and topical wound healer in a tanned or macerated form in alcohol (Ribeiro et al., 2001; Silva et al., 2015).

Despite its medicinal use, *P. brasiliensis* has not been widely studied until now except two phytochemical studies: a research for the ether extract of its aerial parts, which was reported to

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contain sesquiterpenes (4β-hydroxygermacra-1(10), 5-diene, spathulenol, γ-cadinene, α-cadinol, and oplopanone) and triterpenes (lupeol, isomer Δ^{12} of lupeol, β-amyrin acetate, 11α-hydroxy-α-amyrin, and 11α-hydroxy-β-amyrin) in its composition (Bohlmann et al., 1984) and another study of essential oil was obtained from plants collected in another region (Araçuai-MG) in winter at the beginning of flowering time. In this previous study, the essential oil presents the predominance of monoterpenes with the main ones being terpinen-4-ol, γ-terpinene, α-terpinene, and α-terpineol (Silva et al., 2015).

Therefore, considering the sparse reports of the chemical composition of *P. brasiliensis*, this study was conducted to contribute to the phytochemical study of this species by identifying the chemical components in the essential oil and hexane and ethyl acetate extracts as obtained from its leaves.

MATERIAL AND METHOD

Plant material

The leaves of *Pseudobrickellia brasiliensis* (Spreng.) R.M.King & H. Rob.(Asteraceae) were collected in vegetative stage in the "campo rupestre" located on the JK Campus of the Universidade Federal dos Vales do Jequitinhonha e Mucuri (UFVJM), Municipality of Diamantina, Minas Gerais, Brazil (18°12.164′ S and 43°34.398' W; altitude 1384 m) in April 2010 (autumn). Taxonomic identification was performed by Prof. Dr. Aristônio M.Teles and vouchers were deposited under numbers 1096 and 1296 at the DIAM Herbarium of the UFVJM.

General experimental procedures

Gas chromatography (GC) analyses were performed using a Shimadzu® GC-MS QP2010 model equipment using a mass spectrometer as detector (GC/MS), where the following conditions were employed, depending on the fraction to be analyzed:

A) Analysis of the essential oil - Agilent® DB-5MS capillary column (30 m × 0.25 mm × 0.25 μM); oven temperature program: 60 to 240 °C (3 °C min^{-1}); injector temperature: 250 °C; carrier gas: helium set at a flow rate of 1.33 ml min^{-1} and a pressure of 81.90 kPa; ionization mode: electron ionization at 70 eV.

B) Analysis of the chemical constituents found in the organic extracts (hexane and ethyl acetate extracts) – a) Agilent® DB-5MS capillary column (30 m × 0.25 mm × 0.25 μM); oven temperature program: heated to 280 °C (6 °C min^{-1}) and maintained at 280 °C (20 min); injector temperature: 260 °C; carrier gas: helium set at a flow rate of 1.50 ml min^{-1} and a pressure of 182.20 kPa; ionization mode: electron ionization at 70 eV. Or *b)* Agilent® DB-17MS capillary column (30 m × 0.25 mm × 0.25 μM); oven temperature program: 120 °C to 260 °C (20 °C min^{-1}) maintained at 260 °C for 5 min, increased from 260 ° C to 280 °C (2 °C min^{-1}) maintained at 280 °C for 9 min, increased from 280 °C up to 290 °C (2 °C min^{-1}) maintained at 290 °C for 20 min); injector temperature: 260 °C; carrier gas: helium set at a flow rate of 1.40 mL min^{-1} and a pressure of 114.10 kPa; ionization mode: electron ionization at 70 eV.

The essential oil constituents were identified by comparing the relative retention index (RRI) and the mass spectrum of each constituent with data available in the literature (Adams, 2001; Babushok & Zenkevich, 2009) and the Wiley 7® spectra database, respectively. The minimum similarity index (SI) adopted in the comparison of mass spectra of essential oil components and the spectra database was eighty-nine. RRI calculations were performed by the interpolation of retention times with a homologous series of hydrocarbons (C_9–C_{24})-Alltech®, as proposed by Van Den Dool & Kratz (1963).

In the specific case of the terpenes, 5-α-cholestane (Sigma®) was used as internal standard to calculate the RRIs. The calculated RRIs were compared with those observed for a series of terpene standards, as described in the literature (Gonçalves et al., 2011). The terpene standards used were previously isolated from extracts of various plants and identified by ^{1}H-NMR and ^{13}C-NMR (presented good degree of purity) and are deposited at the Núcleo de Pesquisa em Produtos Naturais e Sintéticos, da Faculdade de Ciências Farmacêuticas de Ribeirão Preto –USP (SP, Brazil).

The relative areas (%) of each individual peak from the GC/MS chromatograms were proportional to the total ion current without standardization.

For the column chromatography (CC), Vetec® silica gel 60 (35 –70 mesh) was used as the stationary phase, and n-hexane, ethyl acetate (EtOAc), ethanol (EtOH), and mixtures of these solvents were used as the mobile phase in an increasing gradient of polarity.

The chromatographic profiles were established by thin layer chromatography (TLC), performed on chromatography plates on an aluminum support and silica gel 60 with a fluorescent indicator (Macherey-Nagel®- UV_{254}) using the eluent systems of various polarities and ultraviolet light (λ 255 and 366 nm), sulfuric vanillin, and/or iodine vapor as developing agents.

Nuclear magnetic resonance spectra (1D ^{1}H-NMR, ^{13}C-NMR, and ^{13}C-NMR-DEPT 135) were recorded on a Bruker® Avance DPX-200 spectrometer, operating at 200 MHz for ^{1}H and 50 MHz for ^{13}C NMR. Chemical shifts (δ_H and δ_C) were

obtained in ppm, with the TMS signal as an internal reference using $CDCl_3$ (Aldrich®) as the solvent.

Essential oil extraction

Previously grated fresh leaves of *P. brasiliensis* (84.49 g) were subjected to hydrodistillation for about 2 h using a Clevenger apparatus. The oil obtained had a lower density than water. The obtained oil was separated from the water, dried (by percolation in a simple filtering system containing anhydrous sodium sulfate Synth®), maintained at − 20 °C, and protected from light until analysis. Distillation yielded 0.002% (v/w) of a slightly yellow oil with a distinctive odor. The yield calculation was performed by relating the obtained oil volume (measured directly in Clevenger apparatus) with the mass of plant material used in the extraction. The chemical composition of the oil was determined by GC/MS.

Obtaining hexane and ethyl acetate extracts and fractionation to identify chemical constituents

P. brasiliensis leaves were desiccated to a constant weight at room temperature while being protected from light. The dried material (184 g) was ground and then successively macerated with n-hexane (by two times) and EtOAc (by two times). In each maceration step, the material was kept in contact with the solvent for 72 h. The extracts were concentrated using a rotary evaporator (40 – 42 °C under reduced pressure) yielding 5.03 g of hexane extract (2.73% yield) and 4.99 g of EtOAc extract (2.71% yield).

The EtOAc extract was then resuspended in a water: EtOH (1:3) mixture was successively partitioned in n-hexane and chloroform ($HCCl_3$), yielding 1.83 g of the hexane phase, 0.92 g of the $HCCl_3$ phase, and 1.41 g of water–alcohol phase after solvent removal.

The hexane extract and $HCCl_3$ phase of the EtOAc extract were fractionated by CC, and similar TLC fractions were pooled.

The fractionation of the hexane extract yielded 107 fractions of 25 mL, which, once pooled, yielded 53 fractions. Of these, the EHE1 fraction (15 mg; eluted with 9:1 n-hexane:EtOAc), the EHE4 fraction (40 mg; eluted with n-hexane:EtOAc 8:2) and the EHE5 fraction (123 mg; eluted with n-hexane:EtOAc 7:3), when treated with n-hexane, yielded colorless solids (by precipitation), which were separated from the solution.

In turn, the fractionation of the $HCCl_3$ phase yielded 234 fractions of 20 mL, which were pooled together totaling 80 fractions. The treatment of the EAE1 fraction (50 mg; eluted with 7:3 n-hexane:EtOAc) with n-hexane provided a colorless solid, which was separated from the solution.

The extracted solids (EHE1, EHE4, EHE5, and EAE1 fractions) were analyzed by GC/MS, and nine chemical components were identified (1 to 9). The constituents denoted as (1), (3), (5), and (7) were identified in the solid obtained from the EHE1 fraction (besides the analysis on GC/MS, this material was also analyzed by 1D ^{1}H and ^{13}C-NMR and ^{13}C-NMR-DEPT 135). The constituents (2), (4), and (6) were identified in the material obtained from the EHE4 fraction. The constituents (1), (4), (6), (8), and (9) were identified from the EHE5 fraction. The solid obtained from the EAE1 fraction was a mixture containing (1), (4), and (6).

RESULT AND DISCUSSION

Qualitative analysis of the essential oil

The composition of the essential oil obtained from the leaves of *P. brasiliensis* is summarized in Table 1; the constituents are listed according to their elution order through the Agilent® DB-5MS capillary column.

The majority of the constituents of the essential oil were identified, with 14 monoterpenes and 11 sesquiterpenes.

Considering the areas of their peaks in the chromatogram, monoterpenes α-pinene (32.61%), α-thujene (17.21%), α-phellandrene (8.86%), β-pinene (7.55%), sabinene (4.44%), *E*-β-ocimene (4.15%), and sesquiterpene *E*-caryophyllene (6.87%) were the most representative constituents. These results differ from a previous study that reported the predominance of terpinenes and terpineols (Silva et al., 2015). In the present study, we observed a low yield of essential oil in comparison with previous research (Silva et al., 2015). These differences in chemical composition and essential oil yield between samples from different studies occur by several factors, such as the biotic and abiotic factors of the geographic regions where the specimens are found, genetic characteristics, season in which the plant was collected, and plant growth and development (Gobbo-Neto & Lopes, 2007).

As reported by Bohlmann et al. (1984) during their studies with the nonpolar extract of the above ground portions of *P. brasiliensis*, the terpenoids cadinene (0.85%), and spathulenol (0.46 %) were also identified in the essential oil. On the other hand, the sesquiterpenes described in that study (hydroxygermacrene, cadinol, and oplopanone), which also can be present in essential oil, were not detected in the analyzed sample. This could be explained by genetic, ontogenetic, and environmental differences between the studied specimens (Sangwan et al., 2001; Gobbo-Neto &

TABLE 1. Terpenes identified by GC / MS in the essential oil of fresh leaves of *P. brasiliensis*.

Constituents*	Relative area (%)	RRI cal	RRI lit
1. α-Thujene	17.21	924	931
2. α-Pinene	32.61	932	939
3. N.I.	0.18	939	-
4. N.I.	0.22	948	-
5. Sabinene	4.44	971	976
6. β-Pinene	7.55	977	980
7. β-Myrcene	3.22	987	991
8. α-Phellandrene	8.86	1007	1005
9. α-Terpinene	0.08	1016	1018
10. *p*-Cymene	0.52	1023	1026
11. Limonene	3.41	1028	1031
12. N.I.	0.05	1030	-
13. *Z*-β-Ocimene	0.10	1033	1040
14. *E*-β-Ocimene	4.15	1044	1050
15. γ-Terpinene	0.33	1056	1062
16. α-Terpinolene	0.16	1084	1088
17. N.I.	0.17	1112	-
18. α-Terpineol	0.31	1179	1189
19. δ-Elemene	0.13	1332	1339
20. α-Copaene	1.28	1372	1376
21. *E*-Caryophyllene	6.87	1415	1418
22. N.I.	0.23	1426	-
23. α-Humulene	0.15	1450	1454
24. Germacrene D	3.40	1476	1480
25. Bicyclogermacrene	1.54	1490	1494
26. α-Muurolene	0.19	1494	1499
27. δ-Cadinene	0.85	1514	1524
28. Germacrene B	1.12	1552	1556
29. Spathulenol	0.46	1571	1576
30. Caryophyllene oxide	0.21	1576	1581

Total identified constituents: 88.3%: 46.7% monoterpenes; 36.7% sesquiterpenes; 16,6% N.I.
RRI cal: Relative Retention Index calculated; RRI lit: Relative Retention Index from the literature; N.I.: not identified. * In order of elution

Lopes, 2007).

Chemical constituents in the hexane and ethyl acetate extracts

The chemical study of the hexane extract from leaves of *P. brasiliensis* resulted in the isolation and identification of the diterpene kaurenoic acid (1) and of the following triterpenes: α-amyrin (2), α-amyrin acetate (3), β-amyrin (4), β-amyrin acetate (5), lupeol (6), lupeol acetate (7), pseudotaraxasterol (8), and taraxasterol (9). In turn, from the EtOAc extract (chloroform phase), the secondary metabolites (1) (4), (6) were identified (Figure 1).

The identification of the structure in (1) was performed by MS and ^{1}H-NMR, ^{13}C-NMR ({^{13}C} and DEPT). Compounds (2)–(9) were identified by MS and showed RRI by GC compatible with those of terpene standards, which assisted in their identification. Spectral data for the terpenes (1)–(9) were compared to literature data and are shown in Table 2. The calculated RRI of terpenes (2)–(9) and the RRI for the standards are shown in Table 3.

This is the first time that the presence of kaurenoic acid in *P. brasiliensis* has been reported. There are studies that indicate some activities for kaurenoic acid and derivatives: anticonvulsant, anticancer, anti-inflammatory, and others (Okoye et al., 2013; Lima Silva et al., 2015; Simão et al., 2016). Chemotaxonomic studies have indicated the presence of terpenes in the Asteraceae family, and

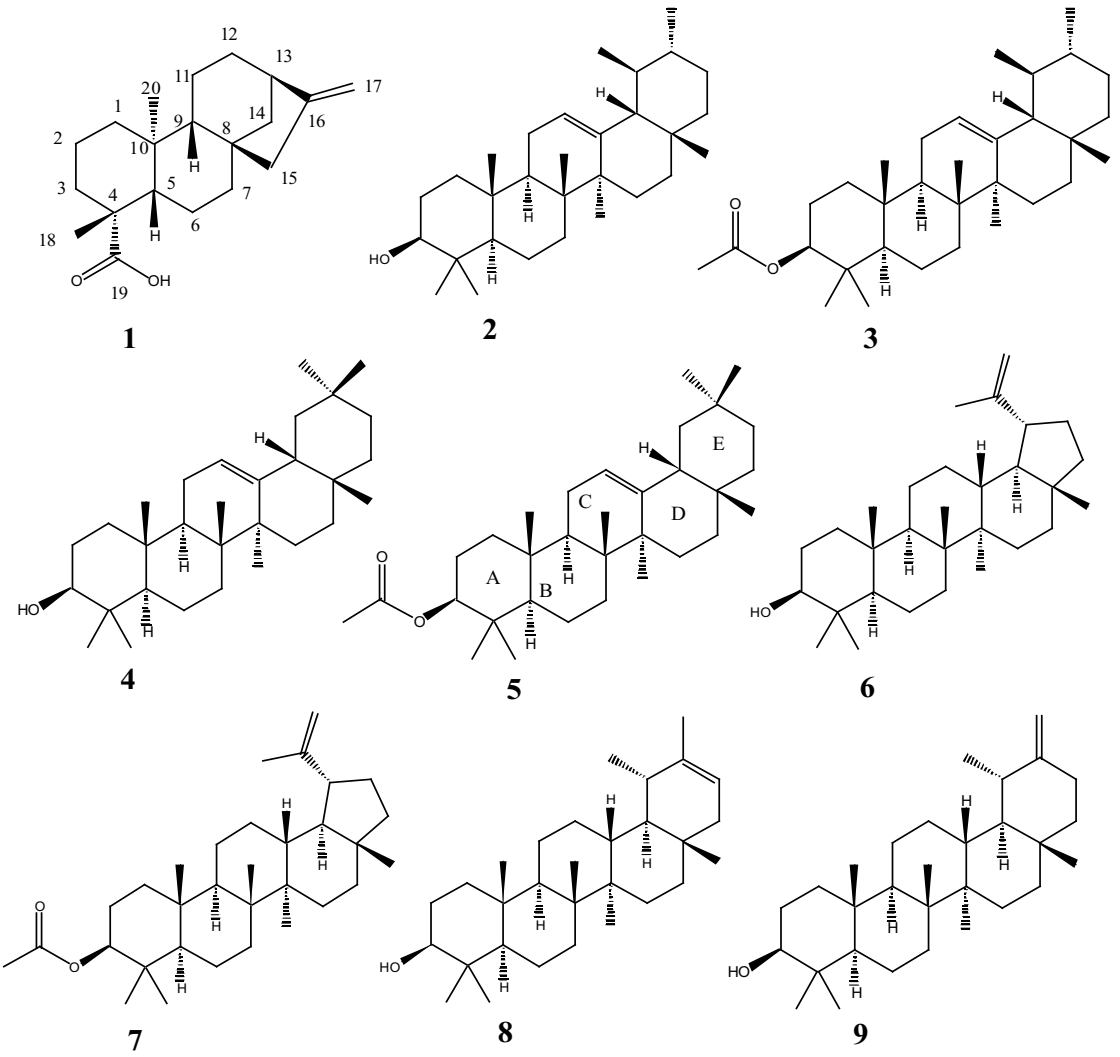

FIGURE 1. Terpenes identified in organic extracts (hexane and ethyl acetate) of the leaves of *P. brasiliensis.* 1: Kaurenoic acid; 2: α-Amyrin; 3: α-Amyrin acetate; 4: β-Amyrin; 5: β-Amyrin acetate; 6: Lupeol; 7: Lupeol acetate; 8: Pseudotaraxasterol; 9: Taraxasterol.

diterpenes with a kaurane skeleton was found in the Eupatorieae tribe (Alvarenga et al., 2005).

Triterpenes identified in this study with oleane, ursane, and lupeane skeletons are the characteristic of the family and are present in almost all of the tribes (Hegnauer, 1977; Zdero & Bohlmann, 1990). β-amyrin and lupeol have been previously described in *P. brasiliensis* (Bohlmann et al. 1984).

P. brasiliensis can be considered a substitute for Asteraceae *Arnica montana* L. This species is native to Europe and is used to treat bruises, inflammation, and muscular and rheumatic pains, whereby helenalin-type sesquiterpene lactones are mainly responsible for the anti-inflammatory activity (Blumenthal et al., 1998; Merfort, 2011). Some terpenoids of *P. brasiliensis* may be responsible for its anti-inflammatory activity, such as kaurenoic acid and the triterpenes lupeol, α-amyrin, β–amyrin, and taraxasterol, which are identified in this study. This is possible because the anti-inflammatory activity has been reported for these triterpenes (Almeida et al., 2015; Piao et al., 2015; Zhu et al., 2016) and for the diterpene acid (Lima Silva et al., 2015). Furthermore, α-pinene, β-pinene, myrcene, p-cymene, limonene and *E*-caryophyllene, among others present in the essential oil, are known for their anti-inflammatory activity, which may contribute to the use of the plant in popular medicine (Bonjardim et al., 2012; Woguem et al., 2014; Rufino et al., 2015).

P. brasiliensis is used in popular medicine. Since there are few studies about the plant, the data obtained in this study are a contribution to the knowledge of its chemical composition. Some compounds that may be related to the therapeutic use of the plant were identified; however, more phytochemical studies and research in pharmacological activity are needed to validate its use.

TABLE 2. Spectral data of terpenoid in extracts (hexane and ethyl acetate) from the leaves of *P. brasiliensis*, compared with literature descriptions.

Terpene	Spectrum	Relevant signals of the experimentally obtained spectra[a]	Literature
Kaurenoic acid (**1**)	^{1}H-NMR	2.64 (1H) allylic hydrogen attached to carbon C-13, characteristic of kaurene skeleton diterpenes. This structural type was confirmed by the characteristic signals related to hydrogens H-18 (1.24; s; 3H), H-20 (0.95; s; 3H), H-17 (4.80; s; 1H), and H-17 (4.74; s; 1H).	Vilegas et al., 1997; Neto et al., 2008.
	^{13}C-NMR	183.6 = carboxyl group (C-19); 155.3 (C-16) and 102.4 (C-17), related to the exocyclic double bond of the kaurene skeleton; and 56.4 (C-5) = *trans*-axial location between the carboxyl group and the H-5.	
	DEPT 135	Signals corresponding to 2 methyl carbons (C-18 and C-20), 10 methylene carbons, 3 methine carbons (C-5, C-9, C-13) and 5 non-hydrogenated carbons.	
	MS	302 (M^+), 287 (M^+ - CH_3), [Remark 3] 259, 241 (M^+ - CH_3 and - HCOO), 148, 121 ($C_9H_{13}^+$), 109, 105 ($C_8H_9^+$), 91 (tropylium ion) [100%]	
α-Amyrin (**2**) and β-Amyrin (**4**) [b]	MS	426 (M^+), 218 (fragment from Diels–Alder retro rearrangement: A and B + rings part of C or D and E rings + part of C) [100%], 203 (218 -CH_3 fragment).	Silva et al., 1998; Jeong & Lachance, 2001.
α- Amyrin acetate (**3**) and β-Amyrin acetate (**5**) [c]	MS	468 (M^+), 218 (fragment from Diels–Alder retro rearrangement) [100%], 203 (218 -CH_3 fragment)	
Lupeol (**6**),	MS	426 (M^+), 203 (D and E rings + part of C), 189(characteristic of lupane skeleton).	
Lupeol acetate (**7**)		468 (M^+), 189	
Pseudotaraxasterol (**8**) and Taraxasterol (**9**) [d]	MS	426 (M^+), 189 [100%]	

[a] Mass spectra fragments: *m/z*; NMR spectra: δ_H and δ_C in ppm and s = singlet . [b]Isomers : ursene (2) and oleanene (4) skeletons. [c]Isomers: ursene (3) and oleanene (5) acetylated. [d]Positional isomers: urs-20-ene (8) and urs-20 (30)-ene (9)

TABLE 3. Terpenes identified in fractions of the organic extracts (hexane and ethyl acetate) of the leaves of *P. brasiliensis.*

Fraction	Terpene	Area (%)	RRI cal	RRI stan
EHE1	Kaurenoic acid	77.09	0.7891	-
	β-Amyrin acetate	3.34	2.2977	2.305
	α-Amyrin acetate	2.19	2.4736	2.471
	Lupeol acetate	4.86	2.5022	2.505
EHE4	β-Amyrin	8.20	2.1818	2.184
	α-Amyrin	8.03	2.3706	2.370
	Lupeol	29.73	2.3889	2.390
EHE5	Kaurenoic acid	3.18	0.7914	-
	β-Amyrin	16.31	1.3368	1.334
	Lupeol	47.48	1.3854	1.383
	Pseudotaraxasterol	0.50	1.4835	1.480
	Taraxasterol	0.83	1.4977	1.494
AE1	Kaurenoic acid	25.01	0.7970	-
	β-Amyrin	0.25	1.3324	1.334
	Lupeol	0.96	1.3801	1.383

Area: relative peak area in the chromatogram; RRI cal: Relative Retention Index calculated; RRI stan: Relative Retention Index standards of terpenes.

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