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Original Article

Phytochemical study of *Harrisia adscendens*

George Luís Dias dos Santos[a], Emerson Leite Lemos[a], Anna Flávia Costa Fernandes[a], Wilma Raianny Vieira da Rocha[a], Raïssa Mayer Ramalho Catão[a], Raimundo Braz Filho[b], Josean Fechine Tavares[c], Ivana Maria Fechine[a], Harley da Silva Alves[a,*]

[a] Departamento de Farmácia, Programa de Pós-graduação em Ciências Farmacêuticas, Universidade Estadual da Paraíba, Campina Grande, PB, Brazil
[b] Departamento de Química, DEQUIM-ICE. Universidade Federal Rural do Rio de Janeiro, CEP 23894-374 Seropédica-RJ, Brazil
[c] Instituto de Pesquisa em Fármacos e Medicamentos, Universidade Federal da Paraíba, João Pessoa, PB, Brazil

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ABSTRACT

Harrisia adscendens (Gürke) Britton & Rose is a species of the family Cactaceae found in the northeastern semi-arid and popularly known as foxtail. In folk medicine, the roots of this species are used for the treatment of toothache and heartburn. The objective of this study was to perform the isolation and identification of the secondary metabolites obtained from the vegetal drug by chromatographic and spectroscopic techniques and to evaluate the antimicrobial activity of the extract. The qualitative phytochemical analysis of the extract showed suggestive results for the presence of alkaloids. Two compounds were isolated and identified: 2-methyl-9*H*-β-carboline-2-ion, a β-carboline alkaloid obtained for the first time as a natural product and 2′,6′-dihydroxy-4′-methoxyacetophenone-2′-*O*-β-glucoside. In the antimicrobial tests, it was possible to observe activity against *Pseudomonas aeruginosa*. The results obtained by spectroscopic techniques allowed to characterize the phytochemical properties of the vegetal drug and may be useful in future studies for production of herbal medicines.

Introduction

The World Health Organization (WHO, 2011) estimates that 70–90% of the population in developing countries need traditional medicine in primary health care. The culture of the use of plants with therapeutic properties has been valued by the society of the whole world.

Brazil has great potential for the development of phytotherapics/phytopharmaceuticals, since it presents the greatest plant diversity in the world. The use of these plants, linked to traditional knowledge and technology, can lead to the development of new drugs. About 82% of the Brazilian population uses herbal products as a therapeutic resource, from the consumption of the fresh plant and its derivatives to the use of herbal medicines (Ministério da Saúde, 2015).

Among the various families of plants found in Brazilian flora, the cacti stand out and call attention for their rusticity and beauty. They have great potential as a source of medicinal, cosmetic and food substances (Mariath et al., 2009), however phytochemical and pharmacological studies with these plants are scarce, although it is known that many species of the Cactaceae family have medicinal properties in the treatment of ulcers and bronchitis (Davet et al., 2009), as well as anti-inflammatory, diuretic and antiglycemic activity (Necchi et al., 2012; Dias et al., 2015).

The Cactaceae family is composed of approximately 1405 species divided into 127 genera (Barthlott and Hunt, 1993; Areces, 2004; Nyffeler and Eggli, 2010; Brito-Filho et al., 2017). They present the subfamily Cactoideae and are divided in three tribes – Pereskieae, Opuntieae and Cereae – being that *Harrisia adscendens* belongs to the Cereae tribe (Barroso et al., 1978). *Harrisia adscendens* (Gürke) Britton and Rose is a native caatinga (savana) species, popularly known as foxtail and is used in traditional medicine for the treatment of "burning", kidney problems and toothaches (Albuquerque et al., 2007).

Based on the above mentioned and in the perspective of collaborating for new therapeutic alternatives and confirming the popular information, the purpose of this work was to perform a phytochemical and microbiological screening of the ethanolic extracts and hydroalcoholics, as well as to isolate and identify possible substances originating from the secondary metabolism of the plant species through chromatographic and spectroscopic techniques.

* Corresponding author.
E-mail: harley.alves@ccbs.uepb.edu.br (H.S. Alves).

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Material and methods

Plant material

The roots were collected in March 2014, in the rural area of the city of Itaporanga, Paraíba backwoods (latitude 7,1845 S and longitude 38,0959 O). An exsicata was prepared and sent to the Herbarium Professor Lauro Pires Xavier of the Federal University of Paraíba, for proper identification and botanical name, registered under the number JPB 61259.

After harvesting, the roots were dehydrated in an air circulating oven, under a temperature of 40 °C for 96 h and then crushed in a mechanical knife mill, obtaining 1.430 g of the vegetal drug.

General experimental procedures

Chromatographic columns were packed with neutral aluminum oxide (70–270 mesh ASTM, Macherey-Nagel) and silica gel 60 (70–270 mesh ASTM, Macherey-Nagel) using glass columns and medium-pressure liquid chromatography (MPLC-model BÜCHI 688). Thin-layer chromatography (TLC) was performed on PF_{254} plates, and the spots were visualized under ultraviolet light (254 and 365 nm) and by Dragendorff's reagents. Isolated compounds were identified by infrared (IR; Perkin-Elmer, FT-IR-1750, and Shimadzu, IR prestige 21); the mass spectra was obtained using MS analysis performed on an Amazon X (Bruker) and high-resolution on a microTOF-II model (Bruker); and extensive one- and two-dimensional nuclear magnetic resonance (NMR) analysis acquired on the following spectrometers: 500 MHz Varian Mercury – IpeFarM/UFPB; 500 MHz Bruker-AC, CENAUREMN/UFC using deuterated solvents.

Extraction and isolation

The plant drug (1250 g) was treated with EtOH (6 × 2 l) with a 72 h interval to maximize the extraction process. The ethanolic extract was concentrated on a rotary evaporator to give 125 g of the crude ethanolic extract (CEE). Five samples (25 g each) of the plant drug were subjected to maceration with ethanol:water (v:v) solutions (125 ml) in the following proportions: 9:1, 7:3, 1:1, 3:7 and 1:9 to obtain the crude hydroalcoholic extracts (CHE). These macerates were also concentrated in a rotary evaporator and subjected to hot air flow for the evaporation of the solvents.

The CEE obtained underwent a march for the extraction of alkaloids and was treated with 2 l of a 3% HCl acid solution and subsequently filtered on filter paper. The residue was discarded and the filtrate was subjected to several extractions with chloroform. The acidic aqueous phase was basified with NH_4OH, under vigorous stirring, to pH 10 and extracted with chloroform. Subsequently, the chloroform fraction was evaporated under reduced pressure in a rotary evaporator at 40 °C yielding 1.95 g of the total alkaloid fraction (TAF).

The TAF (1.2 g) was chromatographed over an aluminum oxide (36 g) and eluted using a gradient of solvents with increasing polarity (dichloromethane, ethyl acetate and methanol). From this process, 66 fractions were obtained and combined by TLC. Compound **1** was the yellow crystal (12 mg) from fractions 46–47. Others 750 mg of the TAF were chromatographed on a silica gel column (22.5 g) under medium-pressure liquid chromatography, using hexane, ethyl acetate and methanol pure or in binary mixture and yielding 54 fractions. The pure fractions 14–15, eluted in ethyl acetate and methanol (9:1), yielded an amorphous white solid (10 mg) identified as the compound 2.

Antimicrobial activity assay

Microorganisms, microbial inoculum and preparation of CEE and CHE solutions

The microbial strains used in this study came from the American Type Culture Collection (ATCC): *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Candida albicans* ATCC 76645 and *Candida tropicalis* ATCC 1369. The selected strains were seeded in BHI broth for reactivation and incubated for 24 h/37 °C. After reactivation, the microorganisms were cultured in Mueller Hinton Agar for 18 h/37 °C, isolated colonies were transferred to sterile saline (0.85%) in turbidity equivalent to 0.5 McFarland scale (10^8 CFU ml^{-1}) (CLSI, 2016). CEE and CHE were solubilized in dimethylsulfoxide to 2% (aqueous DMSO) at an initial concentration of 8000 μg ml^{-1}.

Determination of minimum inhibitory concentration (MIC)

The MIC determination of CEE and CHE was performed by the microplate microdilution test (CLSI, 2016). Sterile 96-well microplates with lid were used in which 100 μl of Mueller Hinton broth were distributed aseptically. In the first well of each microplate, 100 μl of the test product (one for CEE and one for each CHE) at a concentration of 8000 μg ml^{-1} was added. Dilutions of 4000 to 300 μg ml^{-1} were performed. After the dilutions, 5 μl of the microbial inoculum was added to the horizontal lines (numbered 1–12). Each of the numbered lines corresponded to one strain. The positive control of the microbial growth was constituted by means of culture and 5 μl of the inoculum, the negative control only with the culture medium. It was used also gentamicin as control of antimicrobial activity against bacterial strains and fluconazole against *Candida* strains, besides the negative control of DMSO to 2%. The plates were closed, sealed and incubated for 24 h/37 °C. After the incubation period, 20 μl of 0.01% aqueous resazurin was added to each well. The plates were kept at room temperature for 2 h elutes after that time. The reading was performed visually characterized by the color change in the cavities. Results were read by viewing the color change from blue to pink for bacteria, and from colorless to pink for yeast, indicating growth of the microorganism. The lowest concentration of the product capable of inhibiting the growth of the microbial strain tested was considered as MIC (Mann and Markham, 1998; Salvat et al., 2001; Burt and Reinders, 2003; Alves, 2006). The tests were performed in triplicate and the result expressed by the mean.

Results and discussion

The structural assignments of compounds **1** and **2** were made based on spectral analysis and are in good agreement with those reported in the literature. Analysis of the mass spectrum of **1** gave a molecular formula $C_{12}H_{11}N_2^+$ determined by ESI/MS with *m*/*z* 183.09 confirmed by the high resolution mass spectrum obtained by micrOTOF-II, which showed a molecular ion peak in *m*/*z* 183.0933 (calculated for $C_{12}H_{11}N_2^+$, 183.2340) and a peak for the base ion in *m*/*z* 168.0703 suggestive of the outflow of a methyl group. In the ^1H NMR spectrum (δ, DMSO-d_6, 500 MHz) eight signals were visualized, seven of which were characteristic of hydrogens in aromatic systems at δ_H 9.27 (s, 1H), 8.70 (d, *J* = 6.2 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H) indicative of the presence of a 1,2-disubstituted phenyl ring which together with (δ_H 8.51 and δ_H 8.70) characterize α,β pyridine protons suggesting that the molecule is a β-carboline alkaloid (Gearhart et al., 2002), a coalescing multiplet of δ_H 7.76–7.81 (2H), which was split into two signals [7.78 (d, *J* = 8.3 Hz, 1H) and 7.74 (t, *J* = 7.4 Hz, 1H)] when the temperature of the experiment was increased from 26 to 60 °C, in addition to a singlet δ_H 4.47

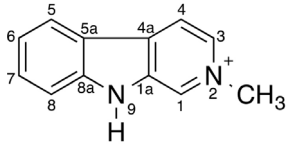
Table 1
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR for **1**, including results obtained by heteronuclear 2D shift-correlated HMQC ($^{1}J_{CH}$) and HMBC ($^{n}J_{CH}$, n = 2 and 3), and comparison with literature data. Chemical shifts (δ, ppm) and coupling constants (J, Hz) are shown in parentheses.

	1 (DMSO-d_6)					Gearhart et al. (2002) (DMSO-d_6)	
	δ_C	δ_H	HMBC	COSY	NOESY	δ_C	δ_H
1a	135.04	–	H-4, H-1	–	–	134.7	–
4a	131.85	–	H-1, H-3,H-4, H-5	–	–	131.7	–
5a	119.18	–	H-4, H-6, H-8	–	–	118.9	–
8a	144.19	–	H-5, H-7, H-8	–	–	143.8	–
1	130.44	9.27 (brs, 1H)	H-3, N^+CH_3	H-3,H-4, N^+CH_3	N^+CH_3	130.1	9.41 (s, 1H)
3	133.18	8.51 (d, J = 6.2 Hz, 1H)	H-1, H-4, N^+CH_3	H-4	H-4, N^+CH_3	133.1	8.64 (d, J = 6.0 Hz, 1H)
4	117.55	8.70 (d, J = 6.2 Hz, 1H)	H-3	H-1, H-3	H-3	117.4	8.76 (d, J = 6.0 Hz, 1H)
5	123.52	8.43 (d, J = 8.3 Hz, 1H)	H-7	H-6, H-8	H-6	123.4	8.46 (d, J = 8.0 Hz, 1H)
6	121.43	7.40 (t, J = 7.4 Hz, 1H)	H-7, H-8	H-5, H-7	H-5, H-7	121.3	7.43 (m, 1H)
7	131.77	7.74 (t, J = 7.4 Hz, 1H,)	H-5, H6	H-6, H-8	H-6, H-8	131.6	7.8 (m, 2H)
8	113.16	7.78 (d, J = 8.3 Hz, 1H)	H-6	H-5, H-7	H-7	112.9	7.8 (m, 2H)
N^+CH_3	47.61	4.47 (s, 3H)	H-1, H-3	H-1, H-3	H-1, H-3	47.5	4.53 (s, 3H)
NH	–	–	–	–	–	–	3.69 (brs, 1H)

Table 2
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR for 2 and comparison with literature data. The NMR data of the osydic unit were obtained in C_5D_5N. Chemical shifts (δ, ppm) and coupling constants (J, Hz) are shown in parentheses.

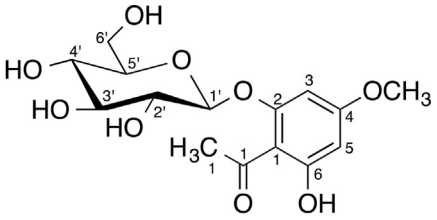
	2 (DMSO-d_6)		Delnavazi et al. (2015) (DMSO-d_6)	
	δ_C	δ_H	δ_C	δ_H
1	105.89	–	106.12	–
2	160.65	–	160.59	–
3	93.45	6.19 (d, J = 2.2 Hz, 1H)	93.43	6.28 (d, J = 2.0 Hz, 1H)
4	165.66		165.60	
5	94.99	6.04 (d, J = 2.2 Hz, 1H)	94.96	6.13 (d, J = 2.0 Hz, 1H)
6	165.59	–	165.53	–
7	203.55	–	203.47	–
8	33.17	2.64 (s, 3H)	33.09	2.66 (s, 3H)
1′	100.69	5.70 (d, J = 6.9 Hz, 1H)	100.64	5.00 (d, J = 7.4 Hz, 1H)
2′	73.17	4.29–4.38 (m, 4H)	73.09	3.10–3.75 (m, 6H)
3′	77.32	4.14 (s, 1H)	77.26	3.10–3.75 (m, 6H)
4′	69.72	4.29–4.38 (m, 4H)	69.64	3.10–3.75 (m, 6H)
5′	76.78	4.29–4.38 (m, 4H)	76.70	3.10–3.75 (m, 6H)
6a′ and **6b′**	60.71	4.58 (d, J = 11.6 Hz, 1H); 4.29–4.38 (m, 4H)	60.62	3.10–3.75 (m, 6H)
OH-6	–	13.65 (s, 1H)	–	13.72 (s, 1H)
OCH_3	55.64	3.78 (s, 3H)	55.59	3.80 (s, 3H)

(3H) which in HSQC ($^{1}H \times {}^{13}C$) showed direct correlation with the peak at δ_C 47.61, it is suggested to be a methyl group bound to tetravalent nitrogen (Kitajima et al., 2014). Compound **1** (Table 1), known by the trivial name of 2-methyl-norharmanium, has already been found in the literature as an intermediate derivative in processes of synthesis of organic molecules (Blom et al., 2006; Rook et al., 2010), however it was isolated as a natural product for the first time.



1

The spectroscopic data of compound **2** were found to be similar to those reported for pleoside or domesticoside isolated from the roots from *Rhodiola algida* var. *tangutica* and roots from *Dorema glabrum* Fisch. and C.A Mey (Bukreeva and Pimenov, 1991; Zhang et al., 2010; Delnavazi et al., 2015), however was first obtained in the Cactaceae family.



2

2-Methyl-9H-β-carbolin-2-ion (**1**). Yellowish powder with $C_{12}H_{11}N_2^+$ molecular formula; mp 242–245 °C; ESI/MS m/z 183.09; HRESIMS m/z 183.0933 (calcd. for para $C_{12}H_{11}N_2^+$, 183.2340 ($[M^+]$); IR (KBr) ν_{max} (cm^{-1}) 3446 (N—H), 1647 (N—H Ar), 1629 (C=C Ar), 1091 (C—N), 798 (N—H); ^{1}H NMR (δ, DMSO, 500 MHz): 9.27 (brs, H-1), 8.52 (d, J = 6.2 Hz, H-3), 8.70 (d, J = 6.2 Hz, H-4), 8.43 (d, J = 8.3 Hz, H-5), 7.40 (t, J = 7.4 Hz, H-6), 7.74 (t, J = 7.4 Hz, H-7), 7.80 (d, J = 8.3 Hz, H-8), 4.47 (N^+CH_3). ^{13}C NMR (δ, DMSO, 125 MHz): 135.04 (C-1a), 131.85 (C-4a), 119.18 (C-5a), 144.19 (C-8a), 130.44 (C-1), 133.18 (C-3), 117.55 (C-4), 123.52 (C-5), 121.43 (C-6), 131.77 (C-7), 113.16 (C-8), 47.61 (N^+CH_3). ^{1}H and ^{13}C NMR spectroscopic data are shown in Table 1.

2′,6′-Dihydroxy-4′-methoxyacetophenone-2′O-β-glucopyranoside (**2**). Amorphous powder with $C_{15}H_{20}O_9$ molecular

Table 3
Minimal Inhibitory Concentration (MIC) of the CHE and CEE of the roots from *Harrisia adscendens*.

	Inhibitory Minimal Concentration – MIC ($\mu g\,ml^{-1}$)					
	CHE					CEE
	9:1	7:3	1:1	3:7	1:9	
S. aureus ATCC 25923	–	–	–	–	–	–
E. coli ATCC 25922	–	–	–	–	–	–
P. aeruginosa ATCC 27853	–	–	–	4.000	–	–
C. tropicalis ATCC 1369	–	–	–	–	–	–
C. albicans ATCC 76645	–	–	–	–	–	–

formula; IR (KBr) ν_{max} (cm^{-1}) 3500, 3435 (OH), 2916 (C—H sp^3), 1631 (C=O), 1589 (C=C Ar), 1277, 1082 (C—O—C); ^1H NMR (δ, DMSO, 500 MHz): 6.19 (d, J = 2.2 Hz, H-3), 6.04 (d, J = 2.2 Hz, H-5), 3.78 (s, OCH_3), 2.64 (s, CH_3), 13.65 (s, OH). ^1H NMR (δ, C_5D_5N, 500 MHz): 5.70 (d, J = 6.9 Hz, H-1′), 4.14 (s, H-3′), 4.58 (d, J = 11.6 Hz, H-6a′) and 4.29–4.38 (m, H-2′, H-4′, H-5′ e H-6b′). ^{13}C NMR (δ, DMSO, 125 MHz): 105.89 (C-1), 160.65 (C-2), 93.45 (C-3), 165.66 (C-4), 94.99 (C-5), 165.59 (C-6), 203.55 (C-7), 100.69 (C-1′), 73.17 (C-2′), 77.32 (C-3′), 69.72 (C-4′), 76.78 (C-5′), 60.71 (C-6′), 55.64 (OCH_3), 33.17 (CH_3). The ^1H and ^{13}C NMR data are consistent with literature (Zhang et al., 2010; Delnavazi et al., 2015) and are shown in Table 2.

Antimicrobial activities

According to the results obtained in the preliminary evaluation of the antimicrobial activity of CEE and CHE of *Harrisia adscendens* (Table 3), it was possible to demonstrate biological activity against the strain of *Pseudomonas aeruginosa* ATCC 27853 in the MIC of 4 mg ml^{-1}. Davet et al. (2009) evaluated the antimicrobial potential of *Cereus jamacaru* against cultures of some bacteria, which showed antimicrobial activity against strains of *Staphylococcus epidermidis*, *S. aureus* and *Pseudomonas aeruginosa*, presenting MIC values above 6 mg ml^{-1}.

Although the activity of the other strains tested in this study is not good, the result of the antimicrobial activity of CEE and CHE from *Harrisia adscendens* against the *P. aeruginosa* strain is quite promising since this pathogen is considered an opportunist capable of causing the most infections, especially in hospitalized patients and in severe conditions (Gellatly and Hancock, 2013). In addition, these strains present intrinsic resistance to antimicrobial agents and may also present important resistance profiles with enzymes such as beta-lactamases and metallo-beta-lactamases (Koneman et al., 1993), making it difficult to treat patients with these infections.

It is recommended the study of antibacterial activity against strains of *P. aeruginosa*, highlighting the possibility of interaction studies with antimicrobials of conventional use of the clinic, looking for a possible synergism and a reduction in the MIC of these antimicrobials.

Conclusions

The phytochemical study resulted in the isolation of an unprecedented alkaloid as a natural product and an acetophenone. One of the uses of *Harrisia adscendens* in folk medicine is against the fight of pain and the presence of the β-carboline alkaloid may justify this use, since this class of nitrogen compounds are known to act in the central nervous system. However, previous research has shown that beta carbolin compounds have a structure similar to *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a structure known to be a dopaminergic toxin and one of the endogenous agents responsible Parkinson's disease. The analytical techniques used in this research were useful for the characterization chemistry and microbiological of the vegetal drug obtained from the foxtail, but other biological tests with the isolated compounds are necessary in order to validate the popular knowledge.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Authors' contributions

ELL and AFCF performed the extraction and isolation. GLDS, JFT, RBF and HSA were involved extraction and identification of constituents. WRVR and RMRC performed in the microbiological activities. HAS and IMF designed the study and supervised the laboratory work. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

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