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Phytochemistry 63 (2003) 221–225

PHYTOCHEMISTRY

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Volatile constituents of *Aristolochia argentina*

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Received 26 August 2002; received in revised form 12 December 2002

Abstract

The essential oils from leaves, aerial stems and underground organs of *Aristolochia argentina* Gris., a medicinal plant popularly known as "charrúa", were obtained by hydrodistillation and analyzed by GC and GC/MS. Forty-three components were identified in the oils. All parts of the plant afforded volatile oils characterized by high levels of argentilactone (57–89%) and the presence of undecatriene isomers (0.3–4.0%), these latter compounds providing the essential oils and extracts with an intense particular odor. Terpenes account for the remaining portion of the essential oils (5–29%). Bicyclogermacrene predominates in the aerial parts of the plant, whereas ishwarane is the main terpene of the subterranean organs. Argentilactone, a suspected carcinogenic compound, was also identified in a medicinal commercial tincture of *A. argentina*.

Keywords: *Aristolochia argentina*; Aristolochiaceae; "Charrúa"; Essential oil; Argentilactone; Undecatrienes; Olfactive properties; Carcinogenic α,β-unsaturated lactones

1. Introduction

Aristolochia argentina Gris. (family *Aristolochiaceae*), popularly known as "charrúa", is a vine which occurs in the semiarid (500 mm rainfall) western Chaco region (dry Chaco) of Argentina and Bolivia. This species develops a strong underground system of subterranean stems and roots, usually referred to as tuberous and rhizomatous roots. For the sake of simplicity the underground system of *A. argentina* in the following is named as roots, whereas by stems we always mean aerial stems. The roots of this plant are used in folk medicine and are commercially available. Their infusions and tinctures are reputed to have antidiarrheic, astringent, antihemorrhoidal and emmenagogue properties and externally can be used for dermatological treatments (Hieronymus, 1882; Domínguez, 1928). Extracts of *A. argentina* also showed antibacterial and antifungal activities (Gutkind et al., 1981). Previous investigations *of A. argentina* revealed the presence of aristolochic acids, alkaloids and an 5-hydroxyacid lactone (Priestap et al., 1977; Priestap, 1987, 1989). The whole plant is odorous and its essential oils or hexane extracts possess a powerful earthy pleasant smell. The aim of the present study was to identify the volatile compounds of *A. argentina*.

2. Results and discussion

The results of the qualitative and quantitative analyses of the essential oils from the roots, stems and leaves of *A. argentina* from two sites are presented in Table 1. In addition, the composition of the volatile fraction of two hexane extracts from the roots of the plant (R3 and R4) are also shown. The roots of *A. argentina* afforded ca. 4 ml/kg (fr. wt) essential oil (7 h of hydrodistillation), whereas, under the same conditions, the leaves and stems yielded ca. 1 ml/kg (fr. wt).

A total of 43 compounds were identified, constituting 84–98% of total essential oils. The essential oils of *A. argentina* are characterized by the unusual presence of argentilactone (**1**) and isomers of undecatriene. The remaining portions of the oils consist of known terpenes.

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0031-9422/03/$ - see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0031-9422(02)00751-3

Table 1
Chemical composition of the essential oils and extracts of *Aristolochia argentina*

Compound	Kovats Index		Level (%)							
	KI[1]	KI[2]	L-1	S-1	R-1	L-2	S-2	R-2	R-3	R-4
α-Pinene	940	1037	t	0.1	0.6	0.1	0.1	0.4	t	t
Camphene	954	1073	0.1	t	1.0	0.1	t	0.6	t	t
β-Pinene	979	1108	t	t	0.3	t	–	0.2	–	t
Myrcene	991	1153	t	0.1	t	–	–	–	–	t
α-Phellandrene	1003	1168	t	0.6	0.1	–	–	–	–	t
o-Methylanisole	1009	1409	t	t	t	–	–	t	–	t
p-Cymene	1025	1273	t	0.1	t	t	0.1	t	t	t
Limonene	1030	1206	t	t	0.1	t	0.1	t	–	t
β-Phellandrene	1030	1219	t	t	t	t	t	t	–	t
1,8-Cineol	1033	1223	–	–	0.2	–	–	0.1	–	–
cis-β-Ocimene	1040	1234	1.7	0.6	t	0.3	0.1	t	t	t
trans-β-Ocimene	1051	1252	0.2	0.2	t	0.1	t	t	t	–
Linalool	1104	1557	0.8	0.4	0.2	–	–	0.2	t	t
Borneol	1170	1733	–	–	0.4	–	–	0.1	t	0.5
(3*E*,5*Z*)1,3,5-Undecatriene(**2**)	1174	1392	3.6	2.8	3.2	0.9	0.6	0.3	0.3	0.4
(*E*,*E*)1,3,5-Undecatriene(**3**)	1181	1405	0.4	0.6	0.3	0.3	0.2	0.1	t	0.1
(3*Z*,5*E*)1,3,5-Undecatriene (**4**)	1182	1408	–	–	t	t	–	–	–	t
Ethyl octanoate	–	1438	–	–	t	–	–	–	–	t
β-Cyclocitral	1218	1623	t	–	0.3	–	–	0.2	t	t
Isobornyl formate	1227	1574	t	–	0.6	–	t	1.0	0.2	0.3
(*Z*,*Z*,*E*)2,4,6-Undecatriene (**6**)	1233	1470	–	–	t	t	–	t	–	t
Bornyl acetate	1291	1580	–	–	0.1	0.1	0.1	0.3	t	0.1
δ-Elemene	1340	1468	0.3	0.3	t	0.6	0.2	t	–	t
α-Terpenyl acetate	1352	–	–	–	–	t	–	t	–	–
α-Copaene	1370	1486	t	0.1	t	0.1	0.1	t	–	–
β-Bourbonene	1380	1512	0.1	0.2	–	0.2	0.2	–	–	–
β-Elemene	1389	1585	t	0.1	0.2	0.1	t	0.2	0.3	0.3
Cyperene	1391	–	–	–	–	–	–	t	–	t
isocaryophyllene	1399	–	–	–	–	–	t	0.2	–	–
β-Caryophyllene	1417	1589	2.7	4.1	0.1	5.5	7.3	0.3	1.9	0.5
β-Gurjunene	1423	1596	–	–	t	t	t	–	–	0.4
α-*trans*-Bergamotene	1434	–	0.6	0.6	t	1.1	1.3	t	t	–
α-Humulene	1447	1677	0.2	0.2	t	0.3	0.4	t	t	0.2
Ishwarane	1455	1644	–	t	1.0	–	t	2.8	2.5	2.7
(E)-β-Farnesene	1460	1684	1.8	1.3	t	1.9	1.6	t	t	t
Germacrene D	1474	1727	2.3	2.0	t	2.7	0.3	t	t	0.2
Bicyclogermacrene	1490	1757	16.0	11.8	t	8.4	4.2	0.4	0.8	1.7
Selina-3,7(11)-diene	1532	1800	–	–	t	–	t	0.2	0.5	t
Spathulenol	1578	2126	4.4	3.5	–	3.5	1.4	t	t	0.1
Argentilactone (**1**)	1666	2515	59.5	64.4	89.1	57.5	66.1	86.4	88.7	80.6
Palmitic acid	1984	–	0.8	0.8	0.1	0.1	0.1	t	t	0.4
Kaurene	2025	–	–	–	–	–	t	t	–	–
Oleic acid	2161	–	t	0.4	t	–	t	–	–	t
Total identified			95.5	95.3	97.9	84.2	84.5	94.6	95.2	88.5
Monoterpene hydrocarbons			2.0	1.7	2.1	0.6	0.4	1.2	0.0	0.0
Oxygenated monoterpenes			0.8	0.4	1.8	0.4	0.1	1.9	0.2	0.9
Sesquiterpene hydrocarbons			24.0	20.7	1.3	20.9	15.6	4.7	6.0	6.0
Oxygenated sesquiterpenes			4.4	3.5	0.0	3.5	1.4	0.0	0.0	0.1
Others			64.3	69.0	92.7	58.8	67.0	86.8	89.0	81.5

Levels as % by area of total GC–FID peaks. L-1, S-1 and R-1: essential oils from leaves, aerial stems and underground organs, respectively, of *A. argentina* (Cruz Alta, Tucumán); volume of the oils: 1, 1 and 4 ml/kg fr. wt, respectively (7 h of hydrodistillation). L-2, S-2 and R-2: essential oils from leaves, aerial stems and underground organs, respectively, of *A. argentina* (Facultad de Agronomía, Buenos Aires) (3 h of hydrodistillation). R-3: hexane extract from underground organs of *A. argentina* (Facultad de Agronomía). R-4: hexane extract from underground organs of *A. argentina* (Villa Allende, Córdoba). KI[1], KI[2]: Kovats index with reference to homologous series of alkanes on DB-5 and Carbowax 20M, respectively. t = Traces ($<0.05\%$).

2.1. *Argentilactone (1)*

All essential oils analyzed show a high level of argentilactone (**1**) (57–89%), a volatile compound which accumulates in all parts of the plant and was previously identified as the lactone of the (−)-(5*R*)-5-hydroxydodeca-*Z*,*Z*-2,6-dienoic acid, or [*R*-(*Z*)]-6-(1-heptenyl)-5,6-dihydro-*2H*-pyran-2-one (1) (Priestap et al., 1977). The content of argentilactone (**1**) in leaves and stems is estimated to be 0.7–0.8 g/kg (fr. wt) but the amount of this compound in the roots may reach 5 g/kg (fr. wt). Argentilactone (**1**) is so far documented only from *A. argentina*, *Annona haematantha* Miq. (Waechter et al., 1997), *Chorisia crispiflora* HBK (Matsuda et al., 1994) and flowers of *Coryanthes* spp. (Kaiser, 2000). Its presence and quantitative prevalence over any other component in the volatile oils is the most relevant chemical characteristic of *A. argentina*.

The MS of argentilactone (**1**) as recorded under GC/MS conditions in the present study showed significant differences with that earlier measured in a Varian Mat CH-5 instrument (Priestap et al., 1977). Some peaks are now significantly reduced (*m/z* 119, 91, 79) or even no longer observed (*m/z* 150, 117). A plausible explanation is that during the previous MS measurement argentilactone (**1**) has suffered thermal decomposition prior to ionization by electron impact. MS of pure argentilactone (**1**) samples were now recorded again in a Shimadzu QP-5000 mass spectrometer. No indication of decomposition was observed.

Argentilactone (**1**) has irritative effects on the skin and mucosa and also may cause allergic reactions on the skin (personal observations). The biological properties of argentilactone (**1**) has been barely studied, knowing only the antileishmanial (Waechter et al., 1997) and antimitotic (Matsuda et al., 1994) activities.

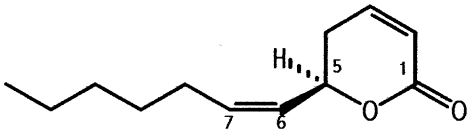
Tinctures of “charrúa” are used in traditional medicine as previously stated. A medicinal “charrúa” tincture, i.e. a hydroalcoholic extract of *A. argentina*, purchased from a herbal shop in Buenos Aires was extracted with Cl_2CH_2 and the volatile components analyzed by GC and GC/MS. Argentilactone (**1**) was found as the main volatile compound extracted from the tincture and its content determined to be 0.05 mg/ml. Argentilactone (**1**) bears a close structural relation with parasorbic acid (**7**). Parasorbic acid (**7**) and a series of α,β-unsaturated lactones have been reported to induce cancer in rats (Dickens and Jones, 1961, 1963a,b). While the carcinogenicity of argentilactone (**1**) has not been established, we must warn about the health risk of ingesting this tincture due to the possible carcinogenic activity of argentilactone (**1**).

Aristolochia spp. cultivated in Buenos Aires are severely affected by two major pests, namely *Battus polydamas* (an specialist *Aristolochia*-feeding lepidopteran) and the red spider (*Tetranychus* sp.). The fact that both organisms grow and multiply as successfully on *A. argentina* as on other *Aristolochia* spp., the tissues of which do not contain argentilactone (**1**), would indicate that this lactone is not effective in protecting *A. argentina* against these particular pests.

2.2. The undecatrienes (**2**–**6**)

Four isomers of undecatriene (**2**, **3**, **4** and **6**) were identified in the essential oils of *A. argentina* which together usually range between 0.3 and 4%. They are found as 3:1 to 10:1 mixtures of the *E*,*Z* (2) and *E*,*E* (3) isomers of 1,3,5-undecatriene whilst the other two isomers are always found in trace amount. Their content in the tissues of the roots may be ca. 0.1 g/kg (fr. wt), while the leaves and stems contain a lower amount.

1,3,5-Undecatrienes have been isolated from the essential oils of galbanum (Näf et al., 1975), lavender (Kaiser



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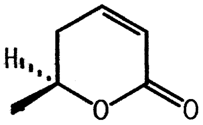

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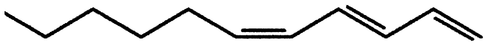

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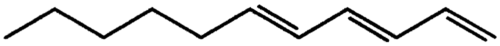

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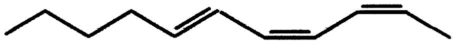

6

and Lamparsky, 1984) and also occur in seaweeds of the genus *Dictyopteris* (Moore, 1977; Kajiwara et al., 1989). These compounds are reported to have very interesting olfactive properties: the mixture of the *E*,*Z* and *E*,*E* isomers is an important perfumery raw material, of which the *E*,*Z*-isomer is the responsible of the highly priced earthy-green scent of galbanum oil (Näf et al., 1975; Fehr et al., 1992). The strong earthy odor that the essential oils of *A. argentina* display can be also largely assigned to the presence of these two undecatriene isomers.

There are four possible isomers for 1,3,5-undecatriene (**2**, **3**, **4** and **5**). All of them have been synthesized (Näf et al., 1975). The isomers **2**, **3** and **4** are stable but the *Z*,*Z*-isomer (**5**) always rearranges to yield **6** under all conditions tried due to its tendency to undergo a thermal (1,7)-hydrogen shift slightly above room temperature (Näf et al., 1975). It is also known that undecatriene isomers can be photo or thermally isomerized to give equilibration mixtures in which the *E*,*Z*- and *E*,*E*-isomers predominate (Moore et al., 1974; Moore, 1977).

The tentative assignment of isomers as given in Table 1 is based on (i) similarity indexes between unknown and reference mass spectra (NIST Database, 1992) and (ii) reported retention times (**2**, 17.2; **3**, 17.9; **4**, 18.2; **6**, 21.5 min, Apiezon glass capillary column, 120 °C, Näf et al., 1975; **3**, KI 1177, on apolar column, Kajiwara et al. 1989).

The structures of argentilactone (**1**) and the undecatrienes (**2**–**6**) suggest that these latter compounds are decomposition products of argentilactone (**1**). Argentilactone (**1**) could decompose under the acidic conditions of hydrodistillation (Linskens and Jackson, 1997) or could be pyrolysed at the injection port during GC analyses (Fehr et al., 1992). Experiments were conducted to check the stability of argentilactone and the eventual generation of undecatrienes as artifacts: fresh plant material was hydrodistilled in a HCl acidifed aq. phase and the pure lactone and essential oils were separately analyzed by GC-FID at different injection port temperatures. Results indicated that argentilactone is stable under usual laboratory conditions and the undecatrienes are not formed from argentilactone or other precursor by the critical hydrodistillation conditions nor by influx of high temperature during GC and GC/MS runs. The hexane extract obtained at room temperature (Table 1, R-3) compares with the hydrodistilled oils and also supports that the undecatrienes are genuine natural constituents of the plant.

2.3. The terpenes

Leaving argentilactone (**1**) and the undecatrienes (**2**–**6**) out of consideration, the oils essentially consist of terpenes. Their percentages in the oils are given in Table 1. Taking into account that the roots produce by hydrodistillation about four times the amount of essential oil than leaves and stems, it follows that the total amount of terpenes is more or less constant through all parts of the plant (ca. 0.2–0.3 g/kg fr. wt). However, the total terpene fraction drops from about 20–30% in leaf and stem oils to ca. 5–8% in the root oils due to a greater accumulation of argentilactone (**1**) in such plant parts.

The content of sesquiterpenes in leaves and stems is far higher than that of monoterpenes (17–28% sesquiterpenes vs. 0.5–3% monoterpenes), but their respective amounts are rather equilibrated in the roots.

The principal sesquiterpenes are bicyclogermacrene, β-caryophyllene, germacrene D and spathulenol, which are mostly found in leaves and stems. In contrast, the sesquiterpene ishwarane predominates in the subterranean organs of the plant. Results with *n*-hexane extracts (Table 1, R-3, R-4) were comparable with those obtained with the hydrodistilled oils.

3. Experimental

3.1. Plant material and isolation method

3.1.1. Hydrodistillation in a Clevenger-type apparatus

Essential oils L-1, S-1 and R-1: leaves, aerial stems and underground parts, respectively, of *A. argentina* gathered in Cruz Alta, Tucumán, Argentina (August 1997). After fresh weights were obtained, the samples were stored at room temperature until 3–4 days after the harvest, when extractions were conducted. The essential oils were obtained by 7 h hydrodistillation. A voucher specimen was deposited in the Herbarium of the Centro de Estudios Farmacológicos y Botánicos (CEFYBO-CONICET), Argentina, under the number BACP 4602.

Essential oils L-2, S-2 and R-2: leaves, aerial stems and underground organs, respectively, of *A. argentina* collected in Facultad de Agronomía, Buenos Aires, Argentina (April 2001)(cultivated plants of unknown origin; voucher specimen No. BAA 24819 of Jardín Botánico de la Facultad de Agronomía, Universidad de Buenos Aires). The plant material was immediately hydrodistilled for 3 h to give the essential oils L-2, S-2 and R-3, respectively.

3.1.2. Cold extraction with n-hexane

Hexane extract R-3: a small portion of the underground parts of the above plant (Facultad de Agronomía), was cut into small pieces, left to dry several days at room temperature and extracted with *n*-hexane at room temperature. The hexane extract was dried with anhydrous Na_2SO_4, and evaporated to dryness in vacuo to give an oil (sample R-3) which was directly analyzed.

3.1.3. Extraction with boiling n-hexane

Hexane extract R-4: air-dried subterranean organs (100 g dry wt.) from plants of *A. argentina* collected in

Villa Allende, Córdoba, Argentina, were exhaustively extracted with boiling n-hexane (bp 69 °C). The volatile fraction (3 g, sample R-4) was obtained from the crude hexane extract (5 g) by distillation (bp 60–165 °C) in vacuo (0.3 mm).

3.1.4. Extraction of a commercial tincture of the Argentinean drug "charrúa"

A commercial tincture of "charrúa" (30 ml), was concentrated under reduced pressure at room temperature to about half its initial volume, extracted with Cl_2CH_2 (3×15 ml) and dried with anh. Na_2SO_4. Evaporation of the Cl_2CH_2 extract yielded an oil which was subjected to analysis.

3.1.5. GC and GC/MS analyses

The essential oils and hexane extracts were subjected to GC/FID and GC/MS analyses as previously reported (Priestap et al., 2002).

Tentative identification of the components was made on the basis of their Kovats indices (KI) in SE-30, DB-5 and Carbowax 20M stationary phases and mass spectra by matching them against standards reported in the literature (Jennings and Shibamoto, 1980; Davies, 1990; NIST Standard Reference Database, 1992; Adams, 1995). Mass spectra of pure argentilactone (**1**) were also recorded under different conditions in a Shimadzu QP-5000 Mass Spectrometer.

3.2. Compound characterization

*3.2.1. Argentilactone (**1**)*

GC–MS, 70 ev, *m/z* (rel. int.): 194 $[M]^+$ (1), 152 (1), 137 (1), 133 (1), 123 (3), 119 (2), 110 (4), 109(4), 97 (14), 95 (6), 93 (5), 91 (5), 84 (5), 79 (9), 69(14), 68 (100), 55 (22), 43 (12), 42 (13), 41 (53), 40 (25).

*3.2.2. (E,Z)-1,3,5-Undecatriene (**2**)*

GC–MS, 70 eV, *m/z* (rel. int.): 150 (28), 93 (28), 91 (51), 81 (9), 80 (66), 79 (100), 78 (17), 77 (47), 66 (8), 65 (9), 53 (7), 43 (6).

Acknowledgements

The authors are indebted to Ana D'Ambrogio, Facultad de Agronomía, Universidad de Buenos Aires, Argentina, for providing specimens of *A. argentina*. Part of this work was supported by Grant BO-34 (UBACYT).

References

Adams, R.P., 1995. Identification of Essential Oil Components by Gas Chromatography/Mass Spectrometry. Allured Publishing Corporation, Carol Stream, IL.

Davies, N.W., 1990. Gas chromatographic retention indices of monoterpenes and sesquiterpenes on methyl silicone and Carbowax 20M phases. Journal of Chromatography 503, 1–24.

Dickens, F., Jones, H.E.H., 1961. Carcinogenic activity of a series of reactive lactones and related substances. Br. J. Cancer 15, 85–100.

Dickens, F., Jones, H.E.H., 1963a. Further studies on the carcinogenic and growth-inhibitory activity of lactones and related substances. Br. J. Cancer 17, 100–108.

Dickens, F., Jones, H.E.H., 1963b. The carcinogenic action of aflatoxin after its subcutaneous injection in the rat. Br. J. Cancer 17, 691–697.

Domínguez, J.A., 1928. Contribuciones a la Materia Medica Argentina Peuser, Buenos Aires.

Fehr, Ch., Galindo, J., Chappuis, S., 1992. New triene synthesis from sorbic acid: two-step synthesis of *cis*- and *trans*-galbanolenes. Tetrahedron Lett. 2465-2468.

Gutkind, G.O., Martino, V., Graña, N., Coussio, J.D., de Torres, R.A., 1981. Screening of South American plants for biological activities. I. Antibacterial and antifungal activity. Fitoterapia 52, 213–218.

Hieronymus, J., 1882. Plantae diaphoricae florae argentinae. Bol. Acad. Nac. Ciencias (Córdoba) 4, 199–598.

Jennings, W., Shibamoto, T., 1980. Qualitative Analysis of Flavor and Fragrance Volatiles by Glass Capillary Gas Chromatography, Academic Press.

Kaiser, R., Lamparsky, D., 1984. New carbonyl compounds in the high- boiling fraction of lavender oil. Helv. Chim. Acta 67, 1184–1197.

Kaiser, R., 2000. Scents from rain forests. Chimia 54, 346–363.

Kajiwara, K., Hatanaka, A., Tanaka, Y., Kawai, T., Ishihara, M., Tsuneya, T., Fujimura, T., 1989. Volatile constituents from marine brown algae of Japanese *Dictyopteris*. Phytochemistry 28, 636–639.

Linskens, H.F., Jackson, J.F., 1997. Plant volatile analysis. Springer-Verlag, Berlin, Heidelberg, pp. 152–154.

Matsuda, M., Endo, Y, Fushiya, S.Endo, T. Nozoe, S., 1994. Cytotoxic 6-substituted 5,6-dihydro-2H-pyran-2-ones from a Brazilian medicinal plant, *Chorisia crispiflora*. Heterocycles 38, 1229–1232.

Moore, R.E., Pettus, J.A., Mistysyn, J., 1974. Odoriferous C11 hydrocarbons from Hawaiian *Dictyopteris*. J. Org. Chem. 39, 2201–2207.

Moore, R.E., 1977. Volatile compounds from marine algae. Accounts of Chemical Research 10, 40–47.

Näf, F., Decorzant, R., Thommen, W., Willhalm, B., Ohloff, G., 1975. The four isomeric 1,3,5-undecatrienes. Synthesis and configurational assignment. Helv. Chim. Acta 58, 1016–1037.

NIST Standard Reference Database Series 1a, 1992. The NIST/EPA/NIH Mass Spectral Database, Version 4.1.

Priestap, H.A., Bonafede, J.D., Rúveda, E.A., 1977. Argentilactone, a novel 5-hydroxyacid lactone from *Aristolochia argentina*. Phytochemistry 16, 1579–1582.

Priestap, H.A., 1987. Minor aristolochic acids from *Aristolochia argentina* and mass spectral analysis of aristolochic acids. Phytochemistry 26, 519–529.

Priestap, H.A., 1989. ^{13}C NMR spectroscopy of aristolochic acids and aristololactams. Magn. Reson. Chem. 27, 460–469.

Priestap, H.A., van Baren, C.M., Di Leo Lira, P., Prado, H.J., Neugebauer, M., Mayer, R., Bandoni, A.L., 2002. Essential oils from aerial parts of *Aristolochia gibertii* Hook. Flavour Fragr. J. 17, 69–71.

Waechter, A.L., Ferreira, M.E., Fournet, A., Rojas de Arias, A., Nakayama, H., Torres, S., Hocquemiller, R., Cave, A., 1997. Experimental treatment of cutaneous leishmaniasis with argentilactone isolated from *Annona haematantha*. Planta Med. 63, 433–435.