Artigo

CHEMICAL CONSTITUENTS OF *Salacia elliptica* (CELASTRACEAE)

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The chemical investigation of *Salacia elliptica* allowed to the isolation of 20 constituents: two polyols, one xanthone, a mixture of long chain hydrocarbons, one carboxylic acid, one polymer, two steroidal compounds, one aromatic ester and eleven pentacyclic triterpenes. These triterpenes include 3β-stearyloxy-oleanane, 3β-stearyloxy-ursane, one *seco*-friedelane, and eight compounds of the friedelane serie. The chemical structure and the relative configuration of a new triterpene 1,3-dioxo-16α-hydroxyfriedelane (**15**) were established through ^{1}H and ^{13}C NMR including 2D experiments (HMBC, HMQC, COSY and NOESY) and herein reported for the first time.

Keywords: *Salacia elliptica*; Celastraceae; 1,3-dioxo-16α-hydroxyfriedelane.

INTRODUCTION

The family Celastraceae includes 98 genera with approximately 1210 species.[1] These are widespread in tropical and subtropical regions including North Africa, South America and East Asia, particularly in China.[2] Some species of this family have been used in traditional medicine, and their different pharmacological activities have been described in the literature.[3]

During the last 10 years our research group has been systematically studied chemical constituents of Brazilian species of the Celastraceae family, and until this moment different constituents, mainly pentacyclic triterpenes (PCTT) have been identified.[4-7] In according to reported data, some of them present potential pharmacologic activity.[4-6] Among of these PCTT highlight esters of PCTT and quinonemethides.[7-9] Compounds of the friedelane, oleanane, lupane and ursane serie are frequently the main constituents isolated from species of the Celastraceae family.[10]

The *Salacia* genus is found in Brazil and others countries of South America, and twenty one Brazilian species of the *Salacia* genera, including *S. elliptica*, were botanically identified by Gonçalves-Esteves.[11] In according to this author, *S. elliptica* Reissek is a tree naturally located in the Cerrado regions of Brazil.[11]

Species of the genus *Salacia* are known by the production of catechins,[11] phenolic acids, friedooleananes,[11] quinonemethides,[11-16] gutta-percha,[16] dulcitol,[16] mangiferin[17] and canophyllol.[18] Phytochemical studies of *S. reticulata* have brought results from isolation of long chain hydrocarbons, gutta-percha,[14] 3β-sitosterol[14] and mangiferin,[19,20] what is commonly considered as the main constituent of *Salacia* species.[12] From the root bark of *S. reticulata*[14] have been isolated pristimerin, *epi*-kokoondiol, salacenonal and salaciquinone. The compounds iguesterin, pristimerin and *epi*-kokoondiol have been obtained from the stem bark of *S. reticulata*,[14,21] and, from its branches have been isolated the salasonone A, B and C, and salaquinone A.[12] In Sri Lanka, India, and Thailand, extracts of the roots, stems, and leaves of *Salacia reticulata*, *S. oblonga*, and *S. chinensis* have been traditionally used in treatments of diabetes and also as a functional food recommended for the people with slight degree of diabetes.[22]

The present work deals with the isolation and identification of 20 constituents from leaves and branches of a specimen of *S. elliptica* collected in Mata Samuel de Paula, Nova Lima, in the State of Minas Gerais, Brazil (Figure 1).

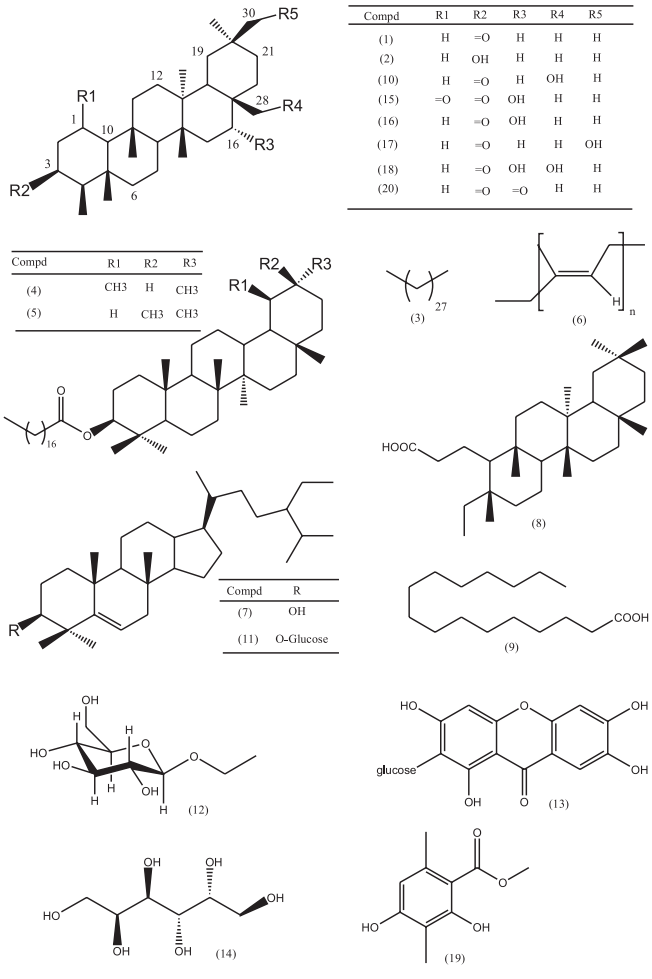

Figure 1. *Chemical structures of constituents isolated from Salacia elliptica*

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RESULTS AND DISCUSSION

As previously reported, the genus *Salacia* is a rich source of pentacyclic triterpenes, mainly those of the friedelane, oleanane and ursane serie.[12,18] In agreement with published data, the following pentacyclic triterpenes (PCTT), 3-oxofriedelane (**1**), 3β-hydroxyfriedelane (**2**), 3β-stearyloxyurs-12-en (**4**), 3β-stearyloxyolean-12-en (**5**), 3,4-*seco*-friedelan-3-oic acid (**8**), 28-hydroxy-3-oxofriedelane (canophyllol) (**10**), 1,3-dioxo-16α-hydroxyfriedelane (**15**), 16α-hydroxy-3-oxofriedelane (**16**), 30-hydroxy-3-oxofriedelane (**17**), 16α,28-dihydroxy-3-oxofriedelane (celasdin-B) (**18**) and 3,16-dioxofriedelane (**20**) (Figure 1) were isolated from the hexane extract of *Salacia elliptica*. Some of these compounds were identified by TLC, using compounds previously isolated from other species of the Celastraceae family, and NMR (1D/2D) spectroscopical data. The compounds **1**, **2**, **4**, **5**, **8**, **10**, **18** and **20** were also isolated from other species of the Celastraceae family.[4-9,23]

To the best of our knowledge, until this moment the triterpene 16α-hydroxy-3-oxofriedelane (16) has not been isolated from some species of the genera *Salacia*. However, this compound was previously described as a constituent of the *Antidesma menasu* Miq.ex.Tul[24] and the 2D NMR (HSQC, HMBC, COSY and NOESY) data of this PCTT were recently published.[25]

The xanthone glucoside mangiferin (**13**) has been commonly found in species of the genus *Salacia*.[17,26,27] This compound correspond to one constituent which was associated to the antidiabetic effect of *Salacia reticulata*.[22] Salacinol and kotalanol are the two others constituents which were also associated to this pharmacological activity.[20,28] In this work, mangiferin (**13**) was found in ethanol extract of leaves. The two other active antidiabetic compounds salacinol and kotalanol, isolated from extracts of *Salacia reticulata*, *S. oblonga*, and *S. chinensis*[22] have not been still founded in *S. elliptica*. The presence of mangiferin (**13**) in *S. elliptica* represents perspectives for the use of its extracts and polar constituents in experimental antidiabetic tests.

The compounds 3-oxofriedelane (**1**), 3β-hydroxyfriedelane (**2**), β-sitosterol (**7**), 28-hydroxy-3-oxofriedelane (**10**) and dulcitol (**14**) were isolated from extracts of leaves as well as branches of *S. elliptica*. The triterpenes **1**, **2** and **1**0 were previously cited in the literature as been constituents of *S. chinensis*, *S. reticulata* and *S. campestris*.[18,22] 3β-Stearyloxyurs-12-en (**4**), 3β-stearyloxy-olean-12-en (**5**), gutta-percha (**6**), 3,4-*seco*-friedelan-3-oic acid (**8**), palmitic acid (**9**), β-sistosterol glucoside (**11**), ethyl glucopyranoside (**12**) and mangiferin (**13**) were isolated only from extracts of *S. elliptica* leaves. Like in *S. reticulata*[19,20] the biopolymer gutta-percha (**6**) was also isolated from hexane extract of *S. elliptica* leaves. The compounds 1,3-dioxo-16α-hydroxyfriedelane (**15**), 16α-hydroxy-3-oxofriedelane (**16**), 30-hydroxy-3-oxofriedelane (**17**), celasdin B (**18**), methyl 2,4-dihydroxy-3,6-dimethylbenzoate (**19**) and 3,16-dioxofriedelane (**20**) were isolated only from extracts of branches.

The ^{13}C NMR spectrum of 1,3-dioxo-16α-hydroxyfriedelane (**15**) showed signals at δ 202.44, δ 203.76 and δ 75.49, which were respectively associated with two carbonyls and a carbon bonded to hydroxyl group. In the HMBC contour map, the carbon signal at δ 203.76 was correlated with the methyl hydrogen signal at δ 1.04 which has carbon signal at δ 6.99 (HMQC), this is commonly attributed to methyl C-23 of the friedelane serie compounds due to the presence of carbonyl at C-3.[29] This fact indicated the presence of carbonyl group at C-3.[29] It was also observed the correlation of the carbonyl signal (δ_C 203.76) with a methylenic signal at δ 3.38 attributed to H-2. The hydrogen signal of H-2 correlated with another carbonylic signal at δ 202.44 becoming possible to deduce its position at carbon 1. The signal of carbinolic hydrogen (δ 3.99) showed correlation with four carbons signals: one methylic, two methylenic and with one non-hydrogenated carbon. This sequence of correlations is only possible with the hydroxyl position at C-16. On the NOESY contour map, the signal of hydrogen H-16 (δ 3.99) has showed correlations with the signals of hydrogen H-26 (δ 0.92) and H-28 (δ 1.20) indicating that the hydroxyl is on α side of the molecule. By detailed analysis of the contour maps HMQC, HMBC and NOESY was possible to attribute all chemical shift assignments of the compound **15** (Table 1).

Table 1. NMR data of 1,3-dioxo-16α-hydroxyfriedelane (**15**)

C_n	δ_C	Type	δ_H	HMBC	COSY	NOESY
1	202.44	C		2,10		
2	60.43	CH_2	3.38*ax* (*J*=15.6), 3.23*eq* (*J*=15.2)	1,3,23,9,4,10		23
3	203.76	C		23,4,2		
4	58.64	CH	2.6 (*J*=6.0)	23,24,5,6	23	
5	37.46	C				
6	40.24	CH_2	1.88*eq*, 1.39*ax*	10,8		
7	17.88	CH_2	1.61*ax*, 1.39*eq*			
8	48.84	CH	1.39	25,27		
9	36.57	C				
10	71.55	CH	2.47	25,24,5,8,4		11*ax*,8
11	33.68	CH_2	2.19*eq*, 1.55*ax*	8,12,25		25
12	29.14	CH_2	1.33			
13	39.33	C				
14	38.80	C				
15	38.69	CH_2	1.86*eq*, 1.32*ax*	16,13,14		
16	75.49	CH	3.99 (*J*=6.4, 11.2)	28,22,15,14	15	28,26,16*eq*,8
17	36.97	C				
18	45.60	CH	1.59	26,28		26,28
19	33.77	CH_2	1.53			
20	27.70	C				
21	33.20	CH_2	1.57			
22	26.25	CH_2	1.74*ax*, 1.55*eq*			
23	6.99	CH_3	1.04	3,10,5,4	4	4, 6*eq*
24	15.73	CH_3	0.67	4,5,10,6		25, 6*eq*, 7*ax*
25	18.85	CH_3	1.23	10,8,11,9		
26	16.77	CH_3	0.92	8,13,14,15		16*ax*, 6*ax*, 25, 28,15*eq*
27	19.11	CH_3	1.18	13,14,18,12		29,7*ax*,15*ax*
28	29.92	CH_3	1.20	18,22,16,17		22*eq*, 21*ax*, 18
29	31.79	CH_3	0.99	20,21,19,30		27
30	36.18	CH_3	0.97	20,29,21,19		19*ax*,21

$CDCl_3$, with two drops of pyridine-d_5, 100 and 400 MHz, *J* = Hz.

The isolation of the compounds **3** to **9**, **11** to **15**, **19** and **20** from *Salacia elliptica* is here reported for the first time. The results of this work suggest *S. elliptica* as a new source of these compounds, and the presence of these constituents may be used as a base for further chemotaxonomic studies of other species of the genus *Salacia* and of the Celastraceae family. This is the first report of the compound 1,3-dioxo-16α-hydroxyfriedelane (**15**).

EXPERIMENTAL

Plant material

The leaves and branches of *S. elliptica* were collected from specimen that is situated in the Mata Samuel de Paula, Nova Lima,

in Minas Gerais, Brazil, in August 2005. The specimen studied was identified by Prof. A. Salino of Departamento de Botânica, UFMG, and the exsiccate was deposited (N^0 BHCB 9703) at Herbário do Departamento de Botânica, UFMG, Brazil.

Extraction and isolation of the constituents

The dried leaves and branches of *S. elliptica* were powdered on a mill furnishing grounded leaves (394 g) and branches (1158 g). Then, each material of *S. elliptica* was exhaustively macerated with hexane, ethyl acetate and finally with ethanol at room temperature (r.t.).

Extracts from leaves

During the hexane evaporation in a rotavapor, a white solid was formed and after natural cooling at r.t., it was separated by filtration. The dried white solid material (386.0 mg) was submitted to CC by elution with CH_2Cl_2, AcOEt and EtOH, pure or in mixtures of enhanced polarity, giving 17 fractions (Fr.) of 20 mL each. Fraction 3 (63.0 mg) was identified as 3-oxofriedelane (**1**)[30-32] and Fr. 4 (153.0 mg) as 3β-hydroxyfriedelane (**2**).[29] The remaining hexane was removed through drying, giving a crude hexanic extract (7.98 g). This material was fractionated by CC eluted with hexane, $CHCl_3$, AcOEt, and MeOH, pure or in mixtures of enhanced polarity, furnishing 143 fractions of 100 mL. The Fr. 2-5 was characterized as hydrocarbon mixture (208.0 mg)[33] and, through HR-GC, the n-nonacosane $C_{29}H_{60}$ (**3**) was identified as been the main constituent (78.0%). From Fr. 39-42 was isolated a mixture (120.0 mg) constituted by 3β-stearyloxyurs-12-en (**4**)[5] and 3β-stearyloxyolean-12-en (**5**)[6] which were identified by NMR spectrometry. The polymer gutta-percha (**6**) (101.0 mg)[8] was obtained from Fr. 51-59, after eluent evaporation. The solid obtained from Fr. 90-98 was identified as β-sistosterol (**7**) (15.0 mg).[34] The dry residue resulted from Fr. 99-106 was submitted to CC furnishing two main groups of fractions (Fr.45-52 and Fr. 77-128). The first group, Fr. 45-52 (900.0 mg) was submitted to CC and the subfraction 102-105 (205.6 mg) was purified by preparative TLC (eluted with $CHCl_3$), furnishing the triterpene 3,4-*seco*-friedelan-3-oic acid (**8**) (18.1 mg).[9,34] And the second group, Fr. 77-128, furnished palmitic acid (**9**) (28.6 mg).

After drying, the ethyl acetate extract (8.8 g) was fractionated by CC, eluted with CH_2Cl_2, AcOEt, and EtOH pure or in mixtures of enhanced polarity furnishing 33 fractions of 200 mL. The solid material of the Fr. 2 was identified as gutta-percha (**6**) (160.0 mg). After the eluent evaporation, Fr. 3-4 gave a white solid that was characterized as 3β-hydroxyfriedelane (**2**) (25.0 mg). Canophyllol (**10**) (51.0 mg)[31,35] was isolated from the Fr. 6-7. And, Fr. 30 was identified as been β-sistosterol glucoside (**11**) (12.0 mg).[31]

The ethanol extract (25.6 g) of leaves was submitted to CC eluted with gradient of AcOEt, EtOH and H_2O, furnishing 172 fractions of 300 mL each. The solid obtained from Fr. 27-31 was identified as ethyl glucopyranoside (**12**)[36] (20.0 mg). Fraction 40-44 furnished a mixture of glycosilated flavonoids (92.6 mg).[37] The constituent mangiferin (**13**) (32.4 mg)[12,26] was isolated in high pureness degree from Fr. 145-150, and the polyol galactitol or dulcitol (**14**) (313.2 mg),[7,34,38] from Fr. 169-170.

Extracts from branches

A white solid material (0.98 g) was also formed during the partial solvent removal of the hexane extract of branches, and separated by filtration. After drying, this material was submitted to CC eluted with gradient of $CHCl_3$, AcOEt and EtOH, giving 69 fractions of 50 mL. The triterpene 3-oxofriedelane (**1**) (10.0 mg) pure was isolated from Fr. 4-5. The Fr. 6-7 gave a white solid which was characterized by NMR as been a mixture (33.7 mg) of 3-oxofriedelane (**1**) and 3β-hydroxyfriedelane (**2**). By HR-GC was possible to determine the proportion of **1** (~95%) and **2** (5%) in this mixture. By recrystallization ($CHCl_3$-EtOH) the constituent 1,3-dioxo-16α-hydroxyfriedelane (**15**) (21.0 mg) was purified from Fr. 09-12 and after dried Fr. 13-15 furnished canophyllol (**10**) (96.0 mg). Fraction 18 submitted to CC using gradient of $CHCl_3$, AcOEt and EtOH (66 Fr. of 20 mL each), furnished 16α-hydroxy-3-oxofriedelane (**16**)[25] (Fr. 49-53, 18.0 mg) and 30-hydroxy-3-oxofriedelane (**17**)[39] (Fr. 59-60, 103.0 mg). The solid material from Fr. 46-47 was identified as celasdin-B (**18**)[23] (39.0 mg).

The remaining hexane was removed through drying at r.t., furnishing the hexane extract (6.0 g), which was submitted to CC eluted with $CHCl_3$, AcOEt and MeOH pure or in mixtures of enhanced polarities, giving 170 fractions of 150 mL. After concentration in a rotatory evaporator, the similar fractions, observed by TLC were grouped. Fraction 2-6 (430.0 mg) was characterized by HR-GC as been a mixture of long chain hydrocarbons in which the n-nonacosane $C_{29}H_{60}$ (**3**) represented the main constituent (86.0%). Fraction 73-75 (43.2 mg) was identified by NMR as been a mixture of 3-oxofriedelane (**1**) and 3β-hydroxyfriedelane (**2**). Through column chromatography of Fr. 80-91 were isolated β-sistosterol (**7**) (268.0 mg) and methyl 2,4-dihydroxy-3,6-dimethyl-benzoate (**19**)[40] (5.5 mg). And, also by CC, Fr. 123-126 afforded 3,16-dioxofriedelane (maytensifolin-B) (12.5 mg) (**20**).[29]

The ethyl acetate extract (8.2 g) was dissolved in MeOH/H_2O and submitted to successive partition with hexane, $CHCl_3$ and finally with AcOEt. The ethyl acetate fraction was fractioned by CC eluted with a gradient of hexane, $CHCl_3$, AcOEt and MeOH, giving 110 fractions (125 mL). Through this process the following constituents were obtained: 3-oxofriedelane (**1**) (12.0 mg) (Fr. 5-6), 3β-hydroxyfriedelane (**2**) (23.0 mg) (Fr. 7-8) and canophyllol (**10**) (Fr. 14-17) (9.1 mg). Through the purification of Fr. 19-28 by CC, canophyllol (**10**) (15.0 mg), 30-hydroxy-3-oxofriedelane (**17**) (20.0 mg) and celasdin B (**18**) (11.0 mg) were obtained.

The ethanol extract (7.03 g) was dissolved in MeOH and, under stirring; diethyl ether was slowly added, furnishing a solid material which was filtered. By recrystallization with ethanol/water, galactitol (**14**) (2.79 g) was obtained as a white solid.

General procedures

^{1}H and ^{13}C NMR spectra (1D and 2D) were run on Bruker AVANCE DRX 400 or on Bruker DPX 200 spectrometers. The sample was dissolved in $CDCl_3$, Py-D_5 or D_2O, and TMS was used as referential ($\delta_H = \delta_C = 0$). IR spectra were obtained with a KBr disc, using a Perkin Elmer Spectrum One SN 74759 spectrophotometer. High resolution Gas chromatography (HR-GC) analysis was carried out on Varian CP-3380 Chromatograph, with HP1 column 30 m length, 0.32 mm i.d., column temperature at 200 °C isotherm condition for 1 min followed by linear temperature program of 10 °C/min up to 300 °C; injector temp. 300 °C, split: 1/50; flame ionization detector (FID) at 300 °C, and with 2 mL/min hydrogen flow rate. Optical rotations $[\alpha]_D$ were measured on a Perkin-Elmer 341 polarimeter using a 100 mm, capacity: 1.0 mL cell tube. Melting points (m.p.) were measured on Mettler FP 80 HT apparatus and are uncorrected. Mass spectrometry was carried out on an electrospray ionisation (ESI) Mass Spectrometer Thermo Scientific model LCQ Fleet, positive mode, using N_2 gas flow rate (15 μL/min), 4.8 kV spray voltage, 290 °C capillary temp., and 2.0 V capillary voltage. Plates of silica gel G-60 (0.25 mm, Merck) previously activated in an oven at 100 °C were used in thin layer chromatography (TLC). The chromatoplates were revealed by UV

light, I_2 vapor or vanillin/perchloric acid. Silica gel (Merck, 230-400 Mesh, ASTM) was used in column chromatography (CC) processes.

Identification of the chemical constituents

The compounds **1** to **20** (Figure 1) isolated from *S. elliptica* were characterized by melting point and its IR and NMR spectral data. The identification of compounds **1**, **2**, and **10** was initially performed by TLC, together standards of pentacyclic triterpenes that are frequently isolated from species of the Celastraceae family, and also by comparison of the respective NMR spectral features with literature data.[29] The structural elucidation, including the relative configuration of the compounds was based on the chemical shifts assignments obtained from 1D (^{1}H, ^{13}C and DEPT-135) and 2D (HSQC, HMBC, COSY and NOESY) NMR spectral data.

Chemical data of 1,3-dioxo-16-hydroxyfriedelane (**15**)

White solid, m.p. 180.0-185.0 ºC, $[\alpha]_D$ ($CHCl_3$, 11.66 x 10^{-4} g/mL): -8.0. MS ((+)-ESI): *m/z* = 457.39 (65%), ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR: see Table 1.

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