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Ethnobotany, Pharmacology and Phytochemical Investigations of the Seeds of *Pentaclethra macrophylla* Benth (Mimosaceae)

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Abstract

Phytochemical investigation of the seeds of *Pentaclethra macrophylla* led to the isolation of a mixture of two new aromatic monoterpene glycosides, pentamacrophylloside A (**1a**) and pentamacrophylloside B (**1b**), together with six known secondary metabolites: Comososide (**2**), secopentaclethroside (**3**), caffeoylputrescine (**4**), *β*-sitosterol-3-*O*-*β*-D-glucopyranoside (**5**), 2-hydroxymethyl-5-(2-hydroxypropan-2-yl)phenol (**6**), and sucrose (**7**). Their structures were elucidated mainly by extensive spectroscopic analysis (1D and 2D NMR), high-resolution mass spectrometry and by comparison of their spectral data with those of related compounds. The extracts and compounds **3** and **4** were screened for their antimicrobial activity. The *n*-BuOH fraction showed a weak effect against three microbial strains: *Candida albicans* (MIC: 256 µg/mL), *Enterococcus faecalis* (MIC: 512 µg/mL), and *Proteus mirabilis* (MIC: 512 µg/mL) while no significant inhibition was observed for pure compounds when compared to ketoconazole and ciprofloxacin used as references. Furthermore, the ethnobotany and pharmacology of this plant are reviewed, and the chemophenetic significance of the isolation of the above secondary metabolites is discussed. This is the first report on the isolation of aromatic monoterpenoids from a plant of the genus *Pentaclethra.*

Keywords

Pentaclethra macrophylla, Ethnobotany, Pharmacology, Aromatic Monoterpenoids, Chemophenetic Significance, Antimicrobial Activity

1. Introduction

Plants have been used in traditional medicine worldwide for the treatment of diseases and many drugs have been developed from their chemical constituents. This is also the case for species of the genus *Pentaclethra* belonging to the Mimosaceae family comprising plants widely distributed in Africa and South America [1]. This genus contains only three species including *Pentaclethra eetveldeana*, *Pentaclethra macroloba* and *Pentaclethra macrophylla* [2]. *Pentaclethra macrophylla* can have 21 m in high and approximatively 60 cm in diameter and is known as the African oil bean tree. It is mostly found in the forests of the Eastern and Western regions of Nigeria and in some regions of Senegal, Angola, Cameroon and Gabon [3]. Plants of the genus *Pentaclethra* have an ethnopharmacological background in the African traditional medicine where they are used for the treatment of several diseases such as itch, gonorrhoea, diarrhoea, small pox and infertility [4] [5]. Previous phytochemical studies revealed that plants of the genus *Pentaclethra* are a rich source of secondary metabolites such as saponins, tannins, alkaloids, flavonoids and monoglycerides [6]. Previous chemical investigation of the seeds of *P. macrophylla* led to the isolation of two diterpernoids, secopentaclethrolide and secopentaclethroside; one alkaloid, caffeoylputrescine and one glycerol derivative, glyceryl monotetracosanoate [7]. Recent pharmacological studies on stem bark, and leaves of this plant revealed its antinociceptive [4], antidiarrheal [8], antimicrobial [9] [10], and hepatoprotective [11] activities. In the course of our continuing search for bioactive secondary metabolites from medicinal plants growing in Cameroon [12] [13] [14], we undertook the phytochemical investigation of the *n*-butanol soluble fraction from the ethanol extract of the seeds of *P. macrophylla* leading to the isolation and structure elucidation of an inseparable mixture of two new aromatic monoterpene glycosides together with six known compounds (**Figure 1**).

2. Ethnobotanical and Traditional Uses of *Pentaclethra macrophylla*

Pentaclethra macrophylla popularly known as African oil bean is a member of the Leguminosae family. A decoction of fermented extract of seeds of this plant has been known to be effective in the management of malnutrition, gastrointestinal disorders and dental caries [15]. The bark, fruits, seeds and the leaves are used as anthelmintics, for gonorrhea, convulsion, and as analgesic [16] [17] [18]. The extracted oil from the seeds is used as remedy against pruritus, worms, and dysentery [19] [20] [21]. Moreover, the seeds are used for the treatment of diabetes in Nigerian folk medicine [22]. In addition, it is used for the treatment of itching and pain in animals and in man [23].

3. Pharmacological Properties of *Pentaclethra macrophylla* Seeds

3.1. Antiulcerogenic Activity

The antiulcerogenic potentials of aqueous extract of fermented *P. macrophylla*

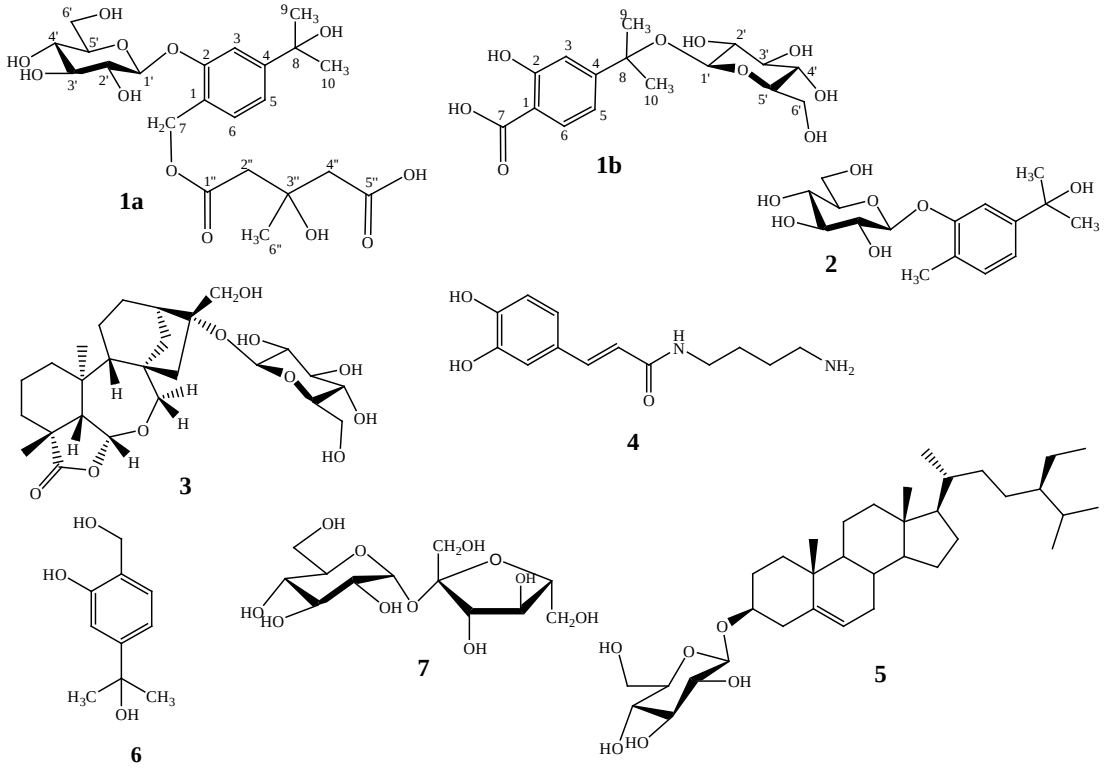


Figure 1. Structures of compounds (**1-7**).

seeds were studied using acetic acid, aspirin, ethanol, indomethacin and pyloric ligation of ethanol induced ulcer models at the doses of 400 and 800 mg/kg body weight. Omeprazole at 5 mg/kg was used as a standard reference drug. The different doses of the extract and the reference drug decreased significantly ($p < 0.05$) the ulcer parameters in a dose-dependent manner in all the ulcer models. Moreover the result of the acute toxicity test showed that the extract did not cause any mortality of the animals possessing 5000 mg/kg body weight. Therefore, the enhanced cessation of gastric erosions could be attributed to the synergistic role of biochemicals and microbiomes residents in fermented aqueous extract of *P. macrophylla* seeds; suggesting that a decoction of fermented aqueous extract of seeds of this plant could be employed in ethnomedicine for the treatment of peptic ulcer [15].

3.2. Antiinflammatory and Analgesic Activities

The leaves and seeds of *P. macrophylla* extracts were tested for analgesic and anti-inflammatory activities using mice with *in-vivo* and *in-vitro* experimental models. The extracts at 30 and 60 mg/kg exhibited analgesic activity and anti-inflammatory property using the flick and hot plate tests, acetic acid induced writhing test; and leucocyte counts, pulmonary oedema and oedema paw of mice in a dose-dependent manner. This result therefore explains and justifies the ethnomedical uses of seeds of *P. macrophylla* in the treatment of itching (inflammatory response) and pain in animals and in man [23].

3.3. Antimicrobial Activity

The antimicrobial efficacy of the ethanol, methanol and water extracts of *P. macrophylla* seeds was evaluated against seven selected pathogens including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella species*, *Salmonella typhi*, *Aspergillus niger* and *Candida albicans* using paper disc and hole diffusion methods. The results showed that the growths of test organisms were inhibited by extracts used and the minimum inhibitory concentration of the extracts ranges between 62.5 - 250 mg/ml on the tested isolates. However, the antimicrobial potency of *P. macrophylla* seeds was more prominent against bacterial isolates than fungal isolates [24].

3.4. Antioxidant Activity

The antioxidant capacity of the extracts from three samples (raw, dried and autoclaved) of *P. macrophylla* seeds oil was evaluated using 2,2-diphenyl-1-picryphydrazyl (DPPH). For each sample three different solvents were used for extraction (70% ethanol, 80% acetone and acidic 70% acetone). Globally the 70% ethanol extracted samples showed the greatest antioxidant activity in the DPPH free radical assay [25].

3.5. Anti-Hyperlipidemic Activity

The antihyperlipidemic effects of the *P. macrophylla* seeds in high fat diet and streptozotocin-induced diabetic wistar rats were evaluated. Blood glucose and Lipid prolife of animals were analyzed 6 days after STZ injection and feeding to confirm hyperlipidemia and hyperglycemia. 50% rat feed was substituted with 50% of the various processed *P. macrophylla* seeds (raw, 1st cooking, 2nd cooking, fermented and fermented and salted) and used to feed the animals [22]. Metformin was administered daily by intra-gastric gavages for 2, 4, 6 and 8 weeks. Treatment of high fat diet and streptozotocin-induced diabetic rats with various processed *P. macrophylla* seeds over a period of 8 weeks significantly ($p < 0.05$) reduced the levels of plasma, total cholesterol, triglycerides and LDL-cholesterol and increased HDL-cholesterol compared to rats not feed with various processed *P. macrophylla* seeds. The various processed *P. macrophylla* seeds also exhibited hypolipidemic activities in high fat diet and streptozotocin-induced diabetic wistar rats for the 8-weeks of treatment. They could be used as source of functional foods providing essential micronutrient preventing progression to cardiovascular diseases [22].

4. Materials and Methods

4.1. General Experimental Procedures

Melting points were recorded on SMP20 apparatus. ^{1}H and ^{13}C NMR, COSY, HSQC and HMBC spectra were performed in deuterated solvents (CD_3OD; DMSO-d_6) on a Bruker AVANCE 500 and 600 spectrometers (Bruker, Germany) at 500 MHz/125 MHz and 600 MHz/150 MHz. All chemical shifts (δ) are

given in ppm units with reference to tetramethylsilane (TMS) as internal standard, while the coupling constants (J values) are given in Hertz (Hz). Positive ion mode ESI mass spectra were carried out on an Agilent 6210 ESI-TOF mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) and on an Agilent Technologies LC/MSD Trap SL (G2445D SL). Purification of fractions and sub-fractions were carried out by column chromatography, Medium-Pressure Liquid Chromatography (MPLC) system [Büchi pump manager C-615, Büchi pump module C-605, Büchi column (460 × 15 mm and 230 × 15 mm)] using silica gel 60 (0.006 - 0.035 mm, 0.063 - 0.200 mm and 0.04 - 0.063 mm) and sephadex LH-20. The following solvent systems were used: MeOH for Sephadex column chromatography, mixtures of Hexane-EtOAc, EtOAc-MeOH and EtOAc-MeOH-H_2O for silica gel column chromatography, EtOAc-MeOH and EtOAc-MeOH-H_2O for MPLC. TLC was carried out on precoated silica gel 60 F254 (Merck) plates developed with Hexane-EtOAc, EtOAc-MeOH and EtOAc-MeOH-H_2O. The spots were visualized under UV light (254 and 365 nm) of lamp multiband (Model UVGL-58 Upland CA 91786, U.S.A) and by spraying with 10% H_2SO_4 followed by heating for 10 min.

4.2. Plant Material

The seeds of *Pentaclethra macrophylla* were collected in Lo'Obiyeng village (with the location 2˚57'35"N, 11˚7'23"E), Mvilla division, South Region of Cameroon, in June 2016. The plant material was identified by Mr NANA Victor, botanist at the Cameroon National Herbarium, Yaoundé (Cameroon) in comparison with a voucher specimen deposited on number 30002/HNC.

4.3. Extraction and Isolation

The seeds of *P. macrophylla* were air-dried, ground to give 5 Kg of powder. This powder was extracted by maceration with 8 L of ethanol (95%) at room temperature three times (each time for 24 h). After filtration, the solvent was removed by evaporation under reduced pressure to yield a crude ethanol extract (420 g). Part of this extract (400 g) was suspended in distilled water (500 mL) and successively extracted with ethyl acetate (800 mL) and *n*-butanol (750 mL). The resulting soluble fractions were concentrated to dryness under reduced pressure to give the ethyl acetate (55 g) and *n*-butanol (49 g) fractions respectively. Part of the *n*-butanol fraction (45 g) was submitted to silica gel column chromatography, using EtOAc and a gradient of MeOH in EtOAc ranging from (1:0) to (1:1) to afford three main sub-fractions (A-C). Recrystallization and filtration of sub-fraction A (1 g) yielded compound **5** (100 mg) and the resulting filtrate was chromatographed on silica gel column using isocratic elution with EtOAc to give two sub-fractions A1 and A2. Sub-fraction A1 (0.3 g) was chromatographed over silica gel column eluted by EtOAc to afford compound **6** (15 mg). The sub-fraction A2 (0.2 g) was also subjected to silica gel column chromatography using EtOAc as eluent, yielding compound **2** (20 mg). Sub-fraction B (2 g)

was chromatographed on silica gel column eluted with a mixture of EtOAc-MeOH (19:1) to yield a mixture of white powder which was further purified by Medium Pressure Liquid Chromatography (MPLC) on normal phase (silica gel: 6.3 - 35 µm) eluted with EtOAc-MeOH (98:2) to give compound **3** (20 mg). Sub-fraction C (8 g) was submitted to silica gel column chromatography eluted with EtOAc-MeOH-H_2O (8:2:1) to afford three sub-fractions C1-C3. Sub-fraction C3 (500 mg) was purified by MPLC on normal phase, eluted with mixture of EtOAc-MeOH-H_2O (8:1.8:0.2) to yield compound **7** (15 mg) and compound **1** (20 mg) which was finally revealed as a mixture of two inseparable compounds (**1a** and **1b**) after using several purification techniques. Sub-fraction C2 (2.5 g) was recrystallized several times with EtOAc-MeOH (80-20) to give 600 mg of compound **4**.

4.4. Methodology of Antimicrobial Assay

The antimicrobial assay of extracts and some compounds was performed using a microdilution method [26] to determine their minimum inhibitory concentrations (MIC) against five bacterial strains (*Staphylococcus aureus* (ATCC 1026), *Enterococcus faecalis* (ATCC 29212), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC74117), and one isolate: *Proteus mirabilis*) and three yeasts (One strain of *Candida albicans* ATCC 9028, and two isolates: *Candida glabrata* and *Candida dubiniensis*). Ciprofloxacin and ketoconazole were used as references. Briefly, the test sample and the selected antibiotic were dissolved in dimethylsulfoxide-Mueller Hinton broth (DMSO-MHB) and dimethylsulfoxide-Sabouraud Dextrose broth (DMSO-SDB). The solution obtained was then added to MHB and SDB and serially diluted twofold in 96-well microplates to give a final concentration range of 2 to 1024 µg/mL for extracts and from 0.5 - 128 µg/mL for pure compounds and references. One hundred microliters of inoculums prepared in MHB at a concentration of 1.5×10^6 CFU/mL were then added, even for SDB. The plates were covered with a sterile plate sealer and then agitated with a shaker to mix the contents of the wells and incubated at 37˚C. The final concentration of DMSO was less than 2.5%, and DMSO did not affect the microbial growth. Wells containing only MHB or SDB, 100 µL of any inoculum and DMSO at a final concentration of 2.5% served as the negative control. The MICs of samples were detected after 18 h, following addition of 40 µL of INT 0.2 mg/mL and incubation at 37˚C for 30 min. Viable bacteria reduced the yellow dye to pink. The MIC was defined as the lowest sample concentration that prevented the colour change and that resulted in the complete inhibition of microbial growth. Each assay was repeated three times independently. For the determination of the minimum bactericidal concentration (MBC), a portion of the liquid (5 µL) from each well that showed no change in colour was plated on MHB and incubated at 37˚C for 24 h. The lowest concentration that yielded no growth after this sub-culturing was taken as the MBC. Even, the low concentrations which induced an absence of turbidity at the bottom of the well after incu-

bation were noted as the MFC.

5. Results and Discussion

The structures of compounds **2** - **7** were determined on the basis of their spectroscopic and mass spectrometric data in comparison with those reported in the literature as comososide (**2**) [27], secopentaclethroside (**3**) [7], caffeoylputrescine (**4**) [28] [29], *β*-sitosterol-3-*O*-*β*-D-glucopyranoside (**5**) [30], 2-hydroxymethyl-5-(2-hydroxypropan-2-yl)phenol (**6**) [31], and sucrose (**7**) [32].

Compound **1** was obtained as colorless oil. Despite the apparent homogeneity of its spot on TLC, it was deduced to be a mixture of two compounds from its spectroscopic analysis. After repeated column chromatography and MPLC separation using different adsorbents (silica gel, Sephadex LH-20, RP-18) no separation was attempted. The negative mode HRESI-MS showed two quasi-molecular ions peaks at *m*/*z* 487.1841 $[M-H]^-$ (calcd. for $C_{22}H_{31}O_{12}$: 487.1821) and at *m*/*z* 357.1202 $[M-H]^-$ (calcd. for $C_{16}H_{21}O_9$: 357.1191) corresponding to the molecular formulas of $C_{22}H_{32}O_{12}$ and $C_{16}H_{22}O_9$ for compounds **1a** and **1b**, respectively. This was also confirmed by the positive mode HRESI-MS which showed two ion clusters at *m*/*z* 511.1759 $[M+Na]^+$ (calcd. for $C_{22}H_{32}NaO_{12}$: 511.1786 corresponding to $C_{22}H_{32}O_{12}$) and at *m*/*z* 381.1157 $[M+Na]^+$ (calcd. for $C_{16}H_{22}NaO_9$: 381.1156 corresponding to $C_{16}H_{22}O_9$). The ^{1}H-NMR spectrum showed signals of two ABX-spin systems of aromatic protons at δ_H 7.32 (*d*, *J* = 8.0 Hz, H_{1a}-6), 7.16 (*dd*, *J* = 1.5; 8.0 Hz, H_{1a}-5), 7.37 (*d*, *J* = 1.5 Hz, H_{1a}-3) and at δ_H 7.77 (*d*, *J* = 8.0 Hz, H_{1b}-6), 7.07 (*dd*, *J* = 1.6; 8.0 Hz, H_{1b}-5) and 7.09 (*d*, *J* = 1.6 Hz, H_{1b}-3), characteristic of two 1,2,4-trisubstituted phenyl rings [31]. Signals of two pairs of singlets at δ_H 1.58 (H_{1b}-9), 1.68 (H_{1b}-10), and 1.54 (*s*, H_{1b}-9/H_{1b}-10) assignable to four methyl groups are also found, suggesting the presence of two isopropanolic hydroxyl groups [33]. The presence of two oxygenated methylene protons was evidenced by signals at δ_H 5.28 (*d*, *J* = 12.4 Hz, H_{1a}-7a) and 5.23 (*d*, *J* = 12.4 Hz, H_{1a}-7b). This spectrum also showed two anomeric protons at δ_H 4.93 (*o*) and 4.35 (*d*; *J* = 7.6 Hz; H_{1b}-1') suggesting the presence of two *β*-glucopyranosyl moieties [34] (**Table 1**). The above data suggested that, the aglycone parts of the two aromatic compounds are derivatives of 2-hydroxymethyl-5-(2-hydroxypropan-2-yl)-phenol [27] [31]. The ^{13}C NMR spectrum exhibited signals for two pairs of methyl groups at δ_C 30.4 (C_{1a}-9), 30.3 (C_{1a}-10) and 29.4 (C_{1b}-9), 26.8 (C_{1b}-10); two oxygenated aromatic carbons at δ_C 155.3 (C_{1a}-2) and at δ_C 161.0 (C_{1b}-2); four substituted aromatic carbons [δ_C 113.5 (C_{1b}-1), 123.5 (C_{1a}-1), 151.6 (C_{1a}-4), 151.9 (C_{1b}-4)]; six methine aromatic carbons [δ_C 129.0 (C_{1a}-6), 118.3 (C_{1a}-5), 111.9 (C_{1a}-3) and 129.7 (C_{1b}-6), 116.7 (C_{1b}-5), 114.0 (C_{1b}-3)]; two oxygenated sp^3 quaternary carbons at δ_C 71.6 (C_{1a}-8) and at δ_C 78.6 (C_{1b}-9) and two anomeric carbons at δ_C 101.5 (C_{1a}-1') and at δ_C 98.3 (C_{1b}-1'). From the ^{1}H and ^{13}C NMR data (**Table 1**), it was evident that **1** was a mixture of two glycosylated aromatic monoterpenoids. The difference between the two aglycone parts was the presence of only one oxymethylene group at δ_C 61.3 (C_{1a}-7) in compound **1a** and a carboxyl group at δ_C 174.5 (C_{1b}-7) in compound

Table 1. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) data of compounds **1a** and **1b**, CD_3OD, δ in ppm multiplicity and J (Hz) in brackets.

Position	1a		1b	
	δ_H	δ_C	δ_H	δ_C
1		123.5		113.5
2		155.3		161.0
3	7.37 (d, J = 1.5 Hz)	111.9	7.09 (d, J = 1.6 Hz)	114.0
4		151.6		151.9
5	7.16 (dd, J = 8.0, 1.5 Hz)	118.3	7.07 (dd, J = 8.0, 1.6 Hz)	116.7
6	7.32 (d, J = 8.0 Hz)	129.0	7.77 (d, J = 8.0 Hz)	129.7
7	5.23 (d, J = 12.4 Hz) 5.28 (d, J = 12.4 Hz)	61.3		174.5
8		71.6		78.6
9	1.54 (s)	30.4	1.58 (s)	29.4
10	1.54 (s)	30.3	1.68 (s)	26.8
1’	4.93 (o)	101.5	4.35 (d, J = 7.6 Hz)	98.3
2’	3.51	73.5	3.24	74.0
3’	3.29	76.9	3.46	76.7
4’	3.42	70.0	3.30	70.3
5’	3.46	76.6	3.12	76.2
6’	3.78 (dd, 11.9, 2.4) 3.62 (dd, 11.9, 5.7)	61.2	3.92 (dd, 12.1, 2.2) 3.71 (dd, 12.1, 5.6)	61.1
1”		171.3		
2”	2.70 (s)	45.3		
3”		69.5		
4”	2.58 (d, J = 12.6) 2.63 (d, J = 15.6)	45.3		
5”		175.2		
6”	1.38 (s)	26.4		

O: Overlapped signal.

1b. The position of this carboxyl group was evidenced by the HMBC correlation depicted between the signal at δ_H 7.77 (d, J = 8.0 Hz, H_{1b}-6) and C_{1b}-7 (δ_C 174.5). The different linkage sites of the sugar moieties to the aglycones were determined by the HMBC cross-peak correlations depicted between the anomeric protons at δ_H 4.93 (H_{1a}-1’), 4.35 (H_{1b}-1’) and carbons at δ_C 155.3 (C_{1a}-2) and 78.6 (C_{1b}-8), respectively (**Figure 2**). Additionally, the ^{13}C NMR spectrum exhibited six signals including a methyl at δ_C 26.4 (C_{1a}-6”), two methylene groups at δ_C 45.3 (C_{1a}-4”, C_{1a}-2”), an hydroxymethine group at δ_C 69.5 (C_{1a}-3”), an ester carbonyl at δ_C 171.5 (C_{1a}-1”) as well as a carboxyl group at δ_C 175.2 (C_{1a}-5”) characteristic of a 3-hydroxy-3-methylglutaric acid moiety [35]. The location of

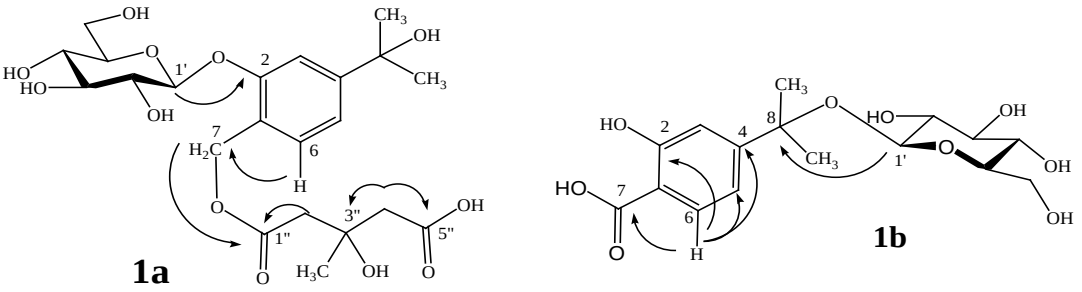
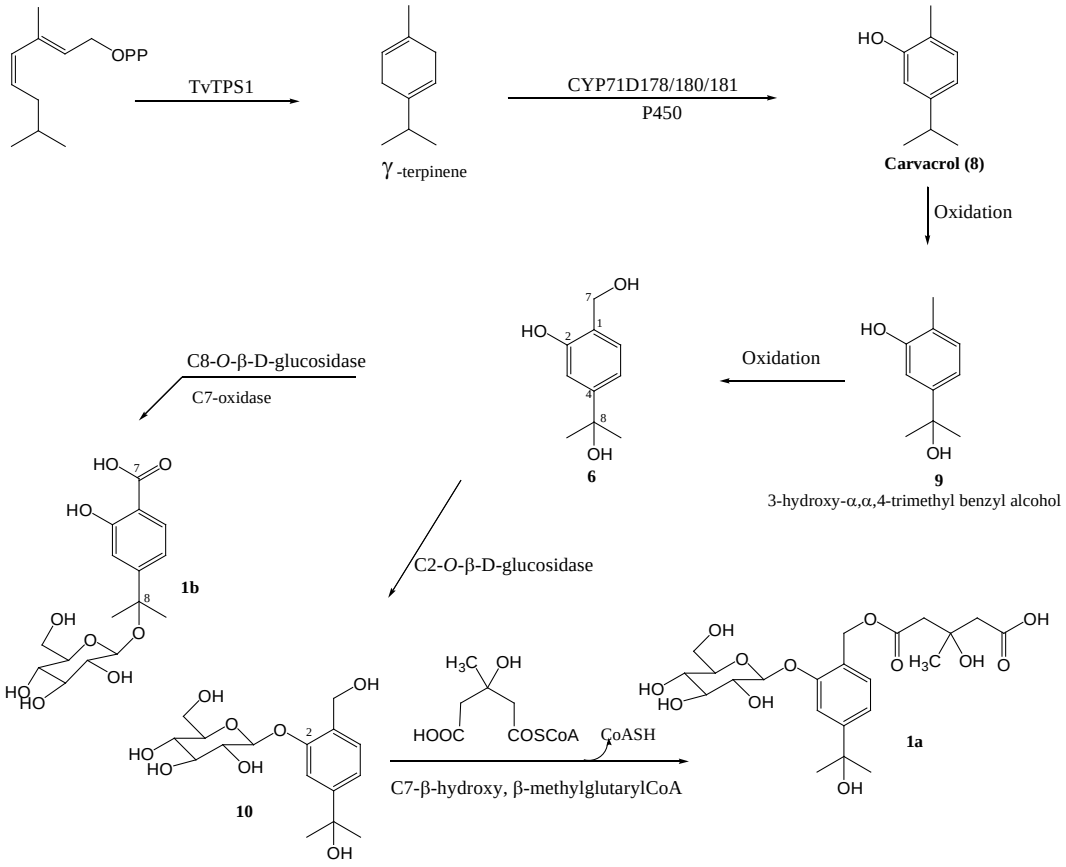


Figure 2. Some important HMBC correlations of compounds **1a** and **1b**.

the 3-hydroxy-3-methylglutaric acid moiety on C_{1a}-7 was evidenced from the HMBC correlation depicted between the proton at δ_H 5.23 (d, J = 12.4 Hz, H_{1a}-7) and the carbon at δ_C 171.3 (C_{1a}-1"). On the basis of the above data, the structures of compounds **1a** and **1b** were elucidated as two new naturally occurring aromatic monoterpenoids to which the trivial names pentamacrophyllosides A (**1a**) and B (**1b**) were given.

Compounds **1a** and **1b** are aromatic monoterpenoids and could biosynthetically derive from geranyl diphosphate. γ-terpinene synthase (TvTPS1) which is a member of the monoterpene synthase family could produce γ-terpinene through cyclization of geranyl diphosphate (Scheme 1). Enzymes such as CYP71D178, CYP71D180 and CYP71D181 belonging to the cytochrome P450 monooxygenases are also involved in further modifications of γ-terpinene backbone to yield carvacrol (**8**) [36]. Oxidation of carvacrol could lead to 3-hydroxy-α,α,4-trimethyl benzyl alcohol (**9**) previously isolated from *Lavandula gibsonii* [33] and compound **6** [31], respectively. The action of C8-*O*-β-D-glucosidase on **6** could yield pentamacrophylloside B (**1b**). The enzyme C2-*O*-β-D-glucosidase could then convert 2-hydroxymethyl-5-(2-hydroxypropan-2-yl)phenol (**6**) to mariaterpenoside A (**10**) previously isolated from *Silybum marianum* [31] while the esterification of compound **10** by β-hydroxy, β-methylglutaryl-CoA could afford pentamacrophylloside A (**1a**) (Scheme 1).

Phytochemical studies have previously been carried out only on stem bark and roots of other species of the genus *Pentaclethra*. Therefore, previous studies on stem bark of *P. macroloba*, and *P. eetveldeana* led to the isolation of saponins [2] [37] [38], phenolic compounds [39] [40] [41], and fatty acid derivatives [37] [39]. Furthermore, tannins were isolated from stem bark of *P. macroloba and P. macrophylla* [39] [40] [41]. Previous pharmacological studies on other species of the genus *Pentaclethra* particularly on *P. macroloba* seeds showed its antioxidant, and antimicrobial activities [42] [43]. Compounds **3** and **4** were previously isolated from *P. macrophylla* seeds [7]. Concerning caffeoylputrescine (**4**), it was the first secondary metabolite isolated from a plant of the genus *Pentaclethra* [44]. Its isolation from the fruits of *P. macrophylla* during our investigation is not surprising since it was reported that putrescine, spermidine, spermine and their derivatives are the main polyamines present in plants, involved in the regulation of diverse physiological processes such as flower development, embryogenesis,



Scheme 1. Proposed biogenetic pathways to the formation of compounds **1a** and **1b** from geranylpyrophosphate.

organogenesis, senescence, and fruit maturation and development [45]. Aromatic monoterpenoids comososide (**2**) and 2-hydroxymethyl-5-(2-hydroxypropan-2-yl)phenol (**6**) were previously obtained from *Curcuma comosa* (Zingiberaceae) [27] and *Silibum marinum* (Asteraceae) [31], respectively. To the best of our knowledge this is the first report on the isolation of this class of compounds from a plant of the genus *Pentaclethra.*

Although the *n*-BuOH extract showed a moderate activity against *Candida albicans* ATCC 9028, *Enterococcus faecalis* (ATCC 29212) and *Proteus mirabilis* with MIC values of 256, 512 and 512 μg/mL, respectively (Table 2), the isolated compounds were not active against the five tested bacterial and three yeasts strains compared to ciprofloxacin and ketoconazole used as references, respectively.

6. Spectroscopic Data of Compounds 1 - 7

Pentamacrophylloside A (1a): Colorless oil; ^{1}H NMR data (600 MHz, CD_3OD) and ^{13}C NMR data (150 MHz, CD_3OD) see Table 1; HR-ESI-MS (negative ion mode) *m*/*z* 487.1841 $[M-H]^-$ (Calcd. for molecular formula $C_{22}H_{31}O_{12}$: 487.1821) and HR-ESI-MS (positive ion mode) *m*/*z* 511.1759 $[M+Na]^+$ (Calcd for $C_{22}H_{32}NaO_{12}$: 511.1786).

Table 2. The minimum inhibitory concentration (μg/mL) of extracts and some isolated compounds against the tested microorganisms.

Samples	Microorganisms															
	Ca		Cg		Cd		Ec		Sa		Pa		Ef		Pm	
	MIC	MFC	MIC	MFC	MIC	MFC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Ethanol extract	-	-	-	-	-	-	1024	-	-	-	512	-	512	-	-	-
EtOAc fraction	-	-	-	-	-	-	1024	-	-	-	256	-	512	-	-	-
n-BuOH fraction	256	-	1024	-	1024	-	1024	-	1024	-	1024	-	512	-	512	-
3	-	-	-	-	-	-	-	-	-	-		-	-	-	-	-
4	-	-	-	-	-	-	1024	-	-	-	512	-	512	-	-	-
Ketoconazole	0.5	64	0.25	8	8	8	-	-	-	-	-	-	-	-	-	-
Ciprofloxacin	-	-	-	-	-	-	2	512	1	512	2	8	4	4	2	8

-: ≥1024 μg/mL; Ca: *Candida albicans*, Cg: *Candida glabrata*, Cd: *Candida dubiniensis*, Ec: *Escherichia coli*, Sa: *Staphylococcus aureus*, Pa: *Pseudomonas aeruginosa*, Ef: *Enterococcus faecalis*, Pm: *Proteus mirabilis*.

Pentamacrophylloside B (1b): Colorless oil; ^{1}H NMR data (600 MHz, CD_3OD) and ^{13}C NMR data (150 MHz, CD_3OD) see Table 1; HR-ES-IMS (negative ion mode) *m*/*z* 357.1202 $[M-H]^-$ (Calcd for $C_{16}H_{21}O_9$: 357.1191) and HR-ESI-MS (positive ion mode) *m*/*z* 381.1157 $[M+Na]^+$ (Calcd for $C_{16}H_{22}NaO_9$: 381.1156).

Comososide (2): Yellow oil; ^{1}H NMR (CD_3OD, 600 MHz): δ_H = 7.27 (*d*, *J* = 1.0 Hz, H-3), 7.09 (*d*, *J* = 7.8 Hz, H-6), 7.04 (*dd*, *J* = 1.0, 7.8 Hz, H-5), 4.91 (*d*, 7.3, H-1'), 3.84 (*dd*, *J* = 1.9; 12.0 Hz, 1H, H-6'), 3.70 (*dd*, *J* = 12.0 Hz, 4.9 Hz, H-6'), 3.49 - 3.50 (*m*, H-2'), 3.39 - 3.40 (*m*, H-4'), 3.46 - 3.47 (*m*, H-2', H-5'), 2.26 (*s*, H-7), 1.53 (*s*, H-9, H-10); ^{13}C NMR (CD_3OD, 150 MHz): δ_C = 155.5 (C-2), 148.6 (C-4), 129.7 (C-6), 125.4 (C-1), 118.0 (C-5), 111.5 (C-3), 101.3 (C-1'), 76.8 (C-5'), 76.7 (C-3'), 73.6 (C-2'), 71.6 (C-8), 70.0 (C-4'), 61,4 (C-6'), 30.5 (C-10), 30.4 (C-9), 14.7 (C-7).

Secopenthaclethroside (3): White amorphous powder; ^{1}H NMR (DMSO-d_6, 600 MHz): δ_H = 5.93 (*d*, *J* = 4.3 Hz, H-6), 4.28 (*d*, *J* = 7.9, H-1'), 3.97 (*t*, *J* = 7.0 Hz, H-17β), 3.67 (*d*, *J* = 12.4 Hz, H-7β), 3.60 - 3.64 (*m*, H-6'), 3.57 (*t*, *J* = 7.4 Hz, H-17α), 3.41 (*d*, *J* = 4.0 Hz, H-7α), 3.39 - 3.40 (*m*, H-6'), 3.15 (*t*, *J* = 8.9 Hz, H-3'), 3.09 - 3.13 (*m*, H-5'), 3.05 (*t*, *J* = 8.8 Hz, H-4'), 2.95 (*td*, *J* = 8.6, 4.3, H-2'), 2.51 - 2.53 (*m*, H-10), 2.16 (*d*, *J* = 4.2 Hz, H-5), 2.11 (*brs*, H-13), 1.92 - 1.93 (*m*, H-14), 1.90 (*d*, *J* = 3.7, H-3), 1.78 - 1.82 (*m*, H-11), 1.65 - 1.67 (*m*, H-1), 1.49 (*o*, H-12), 1.47 (*o*, H-15), 1.39 - 1.42 (*m*, H-2), 1.23 - 1.25 (*m*, H-9), 1.22 (*s*, H-18), 1.12 (*s*, H-20); ^{13}C NMR (DMSO-d_6, 150 MHz): δ_C = 178.2 (C-19), 103.0 (C-6), 97.3 (C-1'), 89.8 (C-16), 77.3 (C-3'), 77.1 (C-5'), 73.8 (C-2'), 73.7 (C-7), 70.4 (C-4'), 61.9 (C-17), 61.4 (C-6'), 56.8 (C-9), 56.1 (C-5), 49.8 (C-8), 45.6 (C-15), 44.1 (C-4), 42.0 (C-13), 39.2 (C-10), 37.9 (C-14), 36.6 (C-1), 30.4 (C-3), 26.9 (C-18), 26.0 (C-12), 19.6 (C-20), 18.6 (C-11), 18.0 (C-2).

Caffeoylputrescine (4): Yellow amorphous powder; ^{1}H NMR (CD_3OD, 500 MHz): δ_H = 7.41 (*d*, 15.7 Hz, H-7'), 7.02 (*d*, *J* = 2.0, H-2'), 6.90 (*dd*, *J* = 8.3, 2.0

Hz, H-6'), 6.78 (*d*, *J* = 8.3 Hz, H-5'), 6.40 (*d*, 15.7 Hz, H-8'), 3.30 - 3.35 (*m*, H-2), 2.95 - 2.99 (*m*, 2H, H-5), 1.67 - 1.74 (*m*, H-4), 1.62 - 1.67 (*m*, H-3); ^{13}C NMR (CD_3OD, 125 MHz): δ_C = 169.6 (C-9'), 149.8 (C-4'), 146.9 (C-3'), 142.5 (C-7'), 128.3 (C-1'), 122.8 (C-6'), 118.4 (C-8'), 116.6 (C-5'), 115.1 (C-2'), 40.6 (C-5), 39.6 (C-2), 27.6 (C-3), 26.0 (C-4).

β-sitosterol 3-*O*-β-D-glucopyranoside (5): White crystals from methanol, mp: 290˚C - 292˚C [(lit. 290˚C - 291˚C] [30].

2-hydroxymethyl-5-(2-hydroxypropan-2-yl)phenol (6): Yellow oil; ^{1}H NMR (CD_3OD, 500 MHz): δ_H = 7.19 (*d*, 7.8, 1H, H-3), 6.94 (*d*, *J* = 1.8, H-6), 6.91 (*dd*, *J* = 7.8, 1.8, H-4), 4.52 (*s*, H-7a/7b), 1.50 (*s*, H-9/10); ^{13}C NMR (CD_3OD, 125 MHz): δ_C = 156.1 (C-1), 151.7 (C-5), 129.1 (C-3), 126.6 (C-2), 116.7 (C-4), 112.7 (C-6), 72.9 (C-8), 61.1 (C-7), 32.0 (C-9/10).

Sucrose 7: White amorphous powder; ^{1}H NMR (CD_3OD, 600 MHz): δ_H = 5.40 (*d*, *J* = 4.0 Hz, H-1), 4.11 (*d*, *J* = 8.3 Hz, H-3'), 4.04 (*t*, *J* = 5.02 Hz, H-4'), 3.80 - 3.84 (m, H-4), 3.79 - 381 (m, H-6), 3.76 - 3.79 (m, H-5'), 3.77 - 3.78 (m, H-6'), 3.73 - 3.75 (m, H-6), 3.69 - 3.74 (m, H-3), 3.60 - 3.65 (m, H-1'), 3.42 - 3.45 (m, H-2), 3.37 (*dd*, *J* = 5.0; 1.8 Hz, H-5); ^{13}C NMR (CD_3OD, 150 MHz): δ_C = 103.9 (C-2'), 92.2 (C-1), 82.3 (C-5'), 77.8 (C-3'), 74.2 (C-4'), 73.2 (C-3), 72.8 (C-4), 71.8 (C-2), 69.8 (C-5), 62.5 (C-1'), 61.9 (C-6'), 60.7 (C-6).

7. Conclusion

In the present study, the seeds of the medicinal plant *P. macrophylla* were investigated, leading to the isolation of a mixture of two new aromatic monoterpene glycosides, pentamacrophylloside A (**1a**) and pentamacrophylloside B (**1b**), together with six known compounds. Their structures were elucidated mainly by extensive spectroscopic analysis, high-resolution mass spectrometry and by comparison of their spectral data with those of related compounds. The chemophenetic significance of their isolation was discussed. To the best of our knowledge, this is the first report on the isolation of aromatic monoterpenoids from a plant of the genus *Pentaclethra*.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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