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Dodoneine, its Bicyclic Lactone and a Dihydroxyl-lupeol Palmitate from *Tapinanthus globiferus*

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ABSTRACT

Tapinanthus globiferus is a mistletoe plant that is used in traditional medicines throughout equatorial Africa. A chloroform extract of aerial parts of the mistletoe plant epiphytic to a *Parkia biglobosa* tree was fractionated using silica gel column chromatography, resulting in the isolation of three compounds identified as 7β, 15α-dihydroxy-lup-20-(29)-ene-2β-*O*-palmitate, (R)-6-[(S)-2-hydroxy-4-(4-hydroxyphenyl) butyl]-5, 6-dihydropyran-2-one (Dodoneine) and (1R,5S,7S)-7-[2-(4-hydroxyphenyl)ethyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one (Dodoneine bicyclic lactone). Their structures were determined using NMR and mass spectroscopic methods, as well as comparisons to the literature. This is the first report on the isolation of these compounds from *Tapinanthus globiferus.*

Keywords: *Tapinanthus globiferus*, Dodoneine, Dodoneine bicyclolactone, Lupeol palmitate, Mistletoe.

Introduction

Mistletoes are hemiparasitic plants that grow on the branches of shrubs and trees. They carry out their photosynthesis independently but obtain water and minerals from the host plant.[1] While *Tapinanthus globiferus*, along with other members of the parasitic mistletoe family, poses a serious threat to mature parkland trees across the African savannah, the mistletoe plants are used extensively by African traditional medicine practitioners for the treatment of various human and animals ailments.[2] Extracts of mistletoe have been used to manage or treat high blood pressure, respiratory distress, diabetes, dysentery, diarrhea and cancer.[2-6] Previous studies on the phytochemical constituents of mistletoes have identified saponins, triterpenoids, flavonoids and their glycosides.[7- 9] *Tapinanthus globiferus* (Loranthaceae) is used in traditional medicine to treat diabetes mellitus, stroke, ulcers and headache.[10-13] Its extracts have also demonstrated good anti-inflammatory, antibacterial and antioxidant activities. Previous studies have reported the isolation of lupeol acetate from the plant.[7] However, not much has been reported on its biological activities, ethnobotanical uses and its secondary metabolites. This report is on the isolation and characterization of some of the plant's secondary metabolites.

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Materials and Methods

General Experimental procedure
Silica gel 60 (0.063-0.200 mm, Merck, Germany) was used for the column chromatography and silica gel 60F254 on aluminum sheets (0.2 mm thickness, Merck, Germany) for TLC plates. The solvents (hexane, ethyl acetate and methanol) were commercially obtained and were redistilled. NMR spectra were acquired on a Bruker AVIII 400 MHz spectrophotometer using $CDCl_3$ and chemical shifts are reported in ppm relative to TMS.

Plant source and collection of plant materials
The aerial parts (stem and leaves) of *T. globiferus* were collected from species growing on *Parkia biglobosa* trees in Quanpan Local government area of Plateau State. The Plant was identified at the Department of Plant Technology, School of Forestry, Jos, Nigeria. A voucher specimen with herbarium number FS-345 was deposited at the School Herbarium.

Extraction/ isolation
The air-dried powder (500 g) of the aerial parts of the plant was successively extracted with hexane and methanol for 48 hours each. The solvents were recovered using a simple distillation apparatus. The methanol extract (10 g) was weighed and dissolved in 50 mL of methanol and partitioned between chloroform and water. This was repeated five times and the chloroform or organic layers were pooled together and concentrated to yield 3.0 g of extract. This was dissolved in chloroform and adsorbed with 20 g of silica gel. The slurry was allowed to dry into a free-flowing powder and later introduced into a glass column packed with silica gel in hexane. The column was eluted using hexane: ethyl acetate (100:0, 90:10, 80:20, 70:30. 60:40, 50:50, 40:60, 30:70,20:80, 10:90) and ethyl acetate: methanol (100:0, 90:10 and 80:20). Fractions were collected in flasks (100 mL) and monitored by TLC resulting in 12 major fractions. Fraction 10 (500 mg) eluted with 100 mL of 90:10 mixture of ethyl acetate: methanol was further purified by column chromatography eluted with hexane: ethyl acetate 7:3, 6:4, 1:1, 1:2, 1:3 and 1:4 to yield compounds **1**, **2** and **3**. These compounds were analyzed using ^{1}H and ^{13}C and 2D NMR. Their structures were elucidated using the spectral data and comparison with literature reports.

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Results and Discussion

*Characterization of compound **1***

Compound **1** gave a purple spot on TLC, typical (on spraying with vanillin-sulfuric acid reagent and heating) or characteristic of terpenoids. The ^{1}H-NMR spectrum for compound **1** displayed proton signals for seven tertiary methyl groups at δ_H (ppm) 0.86, 0.87, 0.89, 0.89, 1.01, 1.01, 1.10 and 1.72; two nonequivalent methylene protons at 4.71 (1H, d, *J* = 2.3 Hz, H-29a) and 4.62 (1H, d, *J* = 1.9 Hz, H-29b) and three oxygen-bearing methine protons at 4.99 (1H, dd, *J* = 11.6, 4.7 Hz, H-3), 4.18 (1H, dd, *J* = 5.2, 12.2 Hz, H-7) and 3.83 (1H, dd, *J* = 11.1, 4.9 Hz, H-15) typical of a substituted lupane skeleton[14, 15]. Also, a triplet of doublets at δ_H 2.36 (1H, td, *J* = 11.0, 5.6 Hz) further suggested a lupane triterpenoid skeleton (Table 1). Furthermore, comparison with literature revealed the signals to be identical to those for lupeol, excepting the oxymethine signal at δ_H 3.19.[18] There is a strong methyl signal at 0.86 and other overlapping protons indicating a long chain hydrocarbon.[9] The ^{13}C-NMR of compound **1**, indicated seven methyl groups, nine methylenes, (one of which was an olefinic carbon), eight methines including three oxygen bearing carbons and six quaternary carbons. The remaining signal at δ_C 173.7 ppm (ester carbonyl) and other several overlapping aliphatic carbons were for the palmitic acid side chain[9]. The HSQC spectrum identified the protons and the corresponding carbon atoms bearing them. In the HMBC spectrum, the proton at δ_H 4.49 at position C-3 of the lupeol skeleton indicated a long-range correlation with the ester carbonyl (δ_C = 173.7) of the palmitic acid showing that the fatty acid is esterified to the hydroxyl group at position C-3 of the lupeol. The NMR, H-H COSY, HSQC, HMBC data; and comparisons with published data[9] identified the compound **1** as 7*β*, 15*α*-dihydroxy-lup-20-(29)-ene-3*β*-*O*-palmitate (Figure 1).

*Characterization of compound **2***

The ^{1}H-NMR spectrum for compound **2** revealed signals for two symmetrical protons at δ_H 6.69 (2H, dd, *J* = 8.5, 2.5 Hz) and 7.07 (H, d, *J* = 8.5 Hz) suggesting a para-substituted benzene ring[16]. Two vinylic proton signals were observed at δ 6.03 (H, dt, *J* = 10.4, 1.5 Hz) and 6.88 (H, dt, *J* = 9.7, 4.3 Hz) (Table 2) indicating the presence of a cis-double bond attached to a ring carbonyl or a lactone type ring[17]. Signals between δ_H 1.70 to δ 4.65 ppm indicated the presence of aliphatic chains. Also, two signals at δ_H 1.70 and 2.17 were for hydroxyl groups. The ^{13}C-NMR spectrum also showed a carbonyl lactone signal at δ_C 163.8ppm (C-2), two olefinic carbons at δ_C 121.5 and 145.3, two aromatic CH signals at δ_C 129.7 (C-2 and C-6), 115.5 (C-3 and C-5) and two quaternary aromatic carbons at δ_C 133.5 and 154.0 for C-1 and C-4 respectively. Six aliphatic carbons signals at δ_C 29.7 to 77.9 ppm were also observed in the ^{13}C-NMR spectrum. The compound was identified as (R)-6-[(S)-2-hydroxy-4-(4-hydroxyphenyl) butyl]-5, 6-dihydropyran-2-one (Figure 2) and its NMR spectral data were in agreement with literature reports.[16]

*Characterization of compound **3***

The compound **3** has great similarities with compound **2** in its proton and carbon spectra. The ^{1}H-NMR (Table 3) had similar identical protons at δ_H 6.75 (H, d, *J* = 8.4 Hz) and 7.02 (H, d, *J* = 8.3 Hz) also for a para-substituted benzene ring[17]. The two vinylic proton signals at δ 6.03 and 6.88 ppm observed in compound **2** were absent in compound **3** and were replaced by two aliphatic proton signals. This suggests a reduction of the double bond of the lactone ring in **2** and formation of a tetrahydropyran ring fused to the lactone ring**.** This was confirmed by the eight aliphatic proton signals observed between δ_H 1.58 to δ 4.89 and only one hydroxyl signal at δ_H 2.17. The ^{13}C-NMR spectrum displayed signals at δ_C 170.2 for the carbonyl of a lactone ring[17] and at 65.0, 66.1, and 73.3 for three oxygenated aliphatic carbon atoms including the extra oxygenated carbon from the tetrahydropyran ring. Using the information and correlations in its ^{1}H, ^{13}C, HMBC, HSQC and COSY spectra and compared to literature reports, the compound was identified as (1R,5S,7S)-7-[2-(4-hydroxyphenyl)ethyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one (Figure 3). *Tapinanthus globiferus* can now be considered chemotaxonomically as a true member of the mistletoe family, based on the foregoing, because compounds **1**, **2**, and **3** have previously been isolated from other Loranthaceae species.[16,19-20] The bioactivity of these compounds has been well documented, which lends credence to some of the plant's ethnomedicinal uses.

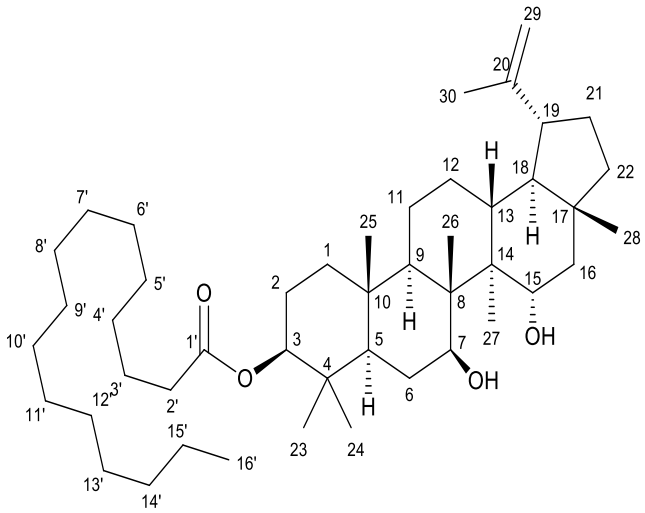

Figure 1: Chemical Structure of Compound **1:** 7*β*, 15*α*-dihydroxy-lup-20-(29)-ene-3*β*-*O*-palmitate

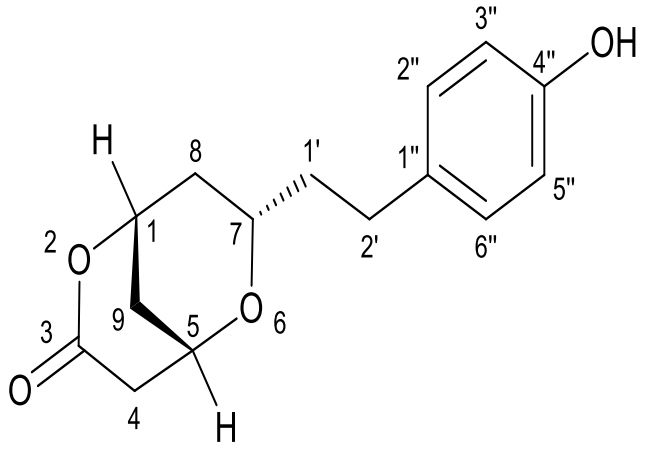

Figure 2: Chemical Structure of Compound **2**: (R)-6-[(S)-2-hydroxy-4-(4-hydroxyphenyl) butyl]-5, 6-dihydropyran-2-one

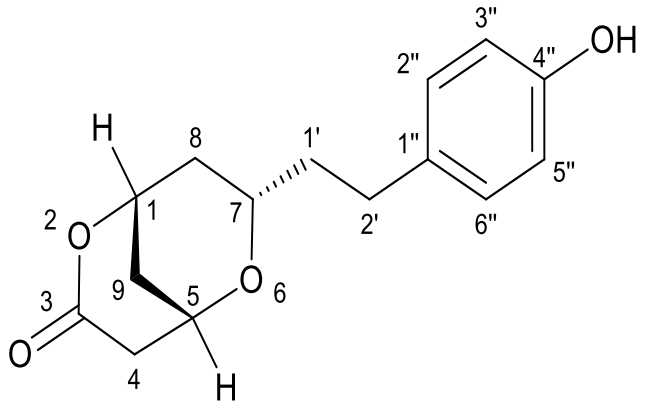

Figure 3: Chemical Structure of Compound **3:** (1R,5S,7S)-7-[2-(4-hydroxyphenyl)ethyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one

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Table 1: ^{1}H- and ^{13}C-NMR chemical shifts for compound 1 in $CDCl_3$

Position	Experimental		Literature[19]	
	Chemical shift (δ ppm) (mult. *J* (Hz))			
	Proton	Carbon	Proton	Carbon
1	1.65, 0.89	38.4	-	38.6
2	1.58	23.7	-	24.0
3	4.49 (t, 1.89)	80.3	4.45	80.4
4	-	37.6	-	37.8
5	0.68	53.1	-	52.3
6	1.52, 1.37	27.9	-	28.3
7	4.18 (dd, 11.6, 4.7)	72.6	4.14	72.7
8	-	48.1	-	48.1
9	1.27	50.3	-	50.4
10	-	37.2	-	37.4
11	1.44, 1.18	20.6	-	20.8
12	1.63, 1.04	25.2	-	25.0
13	1.65	37.5	-	37.6
14	-	48.9		49.2
15	3.83 (dd, 11.1, 4.9)	68.0	3.79	68.3
16	1.95, 1.21	45.5	-	45.9
17	-	42.5	-	42.8
18	1.55	47.9	-	48.3
19	2.38	47.6	-	47.8
20	-	150.3	-	10.5
21	1.96, 1.46	30.1		30.3
22	1.90, 1.06	39.7	-	39.9
23	0.95 (s)	16.5	-	16.7
24	0.77 (s)	27.9	-	28.1
25	0.83 (s)	15.6	-	15.8
26	1.04 (s)	10.9	--	11.2
27	0.98 (s)	8.3	-	8.6
28	0.80 (s)	42.6	-	42.8
29	4.71 (d, 2.3), 4.62 (d, 1.9)	109.7	4.66, 4.57	109.9
30	1.69 (s)	19.5		19.6
Palmitic acid ester side chain	2.31 (t, 7.5, H-2') 1.63 (m, H-3') 1.28 (m, H-4) 1.28 (m, H5'-H-15') 0.90 (t, H-16')	173.7 (C-1') 34.8 (C-2'), 25.2 (C-3'), 29.4 (C-4'), 22.7-29.9 (C-5'- C-15') 14.1 (C-16')		173.91 (C-1'), 35.'5 (C-2'), 25.38 (C-3'), 29.82 (C-4'), 29.69 (C-5'), 29.59 (C-6'), 29.49 (C-7'), 29.39 (C-8'), 29.92 (C-9'), 29.9' (C-10'), 29.89 (C-11'), 29.87 (C-12'), (C-13'), 32.15 (C-14'), 22.92 (C-15') 14.36 (C-16')

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Table 2: ^{1}H- and ^{13}C-NMR chemical shifts for Compound **2**

Position	Experimental			Literature[16]	
	Chemical shift (δ ppm) (mult. *J* (Hz))				
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C
1	-		-	-	-
2	-	163.8	-	-	164.7
3	6.03 (dt, 10.4, 1.5)	121.5	C-5	6.02 (dt, 10.4, 1.5)	121.6
4	6.88 (dt, 9.7, 4.3)	145.3		6.88 (dt, 9.7, 4.3)	145.9
5	2.38 (2H, m)	29.7		2.38 (2H, m)	29.9
6	4.65 (m)	77.9		4.64 (dddd, 7.7, 7.7, 7.7, 5.4)	77.5
7	2.01 (m), 1.80 (m)	42.2		2.00 (dt, *J*) 14.7, 8.2 Hz, 1H ; 1.78 (m, 1H, H-1′),	42.4
2’	3.89 (m)	68.8		3.80 (br multiplet, 1H)	69.0
3’	1.70 (2H, m)	39.6		1.72 (m, 2H),	39.7
4’	2.65 (2H, m)	31.0	C-1',C-6"	2.60 (m, 2H)	31.2
1”	-	133.5	C-4, C-6	-	133.9
2”	7.07 (d, 8.5)	129.7	C-4', C-4", C-6"	6.98 (d, *J*) 8.5 Hz, 2H,	129.8
3”	6.69 (dt, 8.5, 2.5)	115.5	C-5	6.69 (dt, *J*) 8.5, 2.5 Hz, 2H)	115.7
4”	-	154.3	-	-	154.6
5”	6.69 (dt, 8.5, 2.5)	115.5		6.69 (dt, 8.5)	115.7
6”	7.07 (d, 8.5)	129.7	C-4', C-2", C-4"	6.98 (d, 8.5)	129.8
4"-OH	2.17 (br s)			2.15 (br s,)	-
2'-OH	1.70 (br s)			1.5 (br s)	-

Table 3: ^{1}H- and ^{13}C-NMR Chemical Shifts for Compound **3**

Position	Experimental			Literature[16]		Literature[20]	
	Chemical shift (δ ppm) (mult. *J* (Hz))						
	^{1}H	^{13}C	HMBC	^{1}H	^{13}C	^{1}H	^{13}C
1	4.89	73.3	C-3	4.87 (m)	73.3	4.87 (m, 1H, >CH-O)	74.7
2	-	-			-		
3	-	170.2			170.3		172.4
4	2.72, 2.84	36.6			36.5	2.6 (cm, 4H)	36.8
5	4.38	66.1	C-3, C-6, C-7	4.34 (br s)	66	4.34 (br s, 1H, >CH-O)	66.8
7	3.73	65		3.65 (m)	65	3.65 (m, 1H, >CH-O)	65.5
8	1.58, 1.99	37.1		1.98 (m)	37.1	1.98 (m, 3H)	37.6
9	1.92, 2.02	30		1.92 (m)	29.9	1.92 (m, 1H)	30.1
1'	1.73, 1.83	38		1.7 (m)	38	1.7 (cm, 3H)	38.6
2'	2.57, 2.71	30.6		2.6 (m)	30.7	2.6 (cm, 4H)	31.1
1”	-	133.8		-	133.6		133.3
2”	7.03	129.6		7.02 (d, 8.3)	129.5	6.99 (dt, *J*) 8.5, 2.4 Hz, 2H, meta-phenol)	130
3”	6.75	115.5	C-1", C-5"	6.75 (d, 8.4)	115.5	6.71 (dt, *J*) 8.5, 2.5 Hz,2H, ortho-phenol)	115.9
4”	-	154	, C-4",	-	154.1		155.9
5”	6.75	115.5		6.75 (d)	115.5	6.71 (dt, *J*) 8.5, 2.5 Hz,2H, ortho-phenol)	115.9
6”	7.03	129.6		7.02 (d)	129.5	6.99 (dt, *J*) 8.5, 2.4 Hz, 2H, meta-phenol)	130
4"-OH	2.17 (s)	-		-	-		

Conclusion

7β, 15α-dihydroxy-lup-20-(29)-ene-2β-O-palmitate, (R)-6-[(S)-2-hydroxy-4-(4-hydroxyphenyl) butyl]-5, 6-dihydropyran-2-one and (1R,5S,7S)-7-[2-(4-hydroxyphenyl)ethyl]-2,6-dioxabicyclo[3.3.1]nonan-3-one were isolated and characterized from *Tapinanthus globiferus*. This is an initial report of these compounds from this plant material.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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