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Potential Antitumor Agents from *Lantana camara* : Structures of Flavonoid - , and Phenylpropanoid Glycosides

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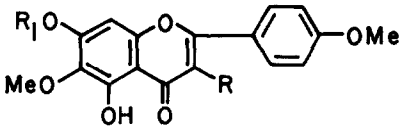
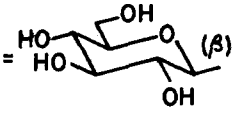
Abstract: Besides the known glycosides, verbascoside and a flavone glycoside, a novel flanonol glycoside named camaraside and a new phenylpropanoid glycoside, lantanaside have been isolated from the leaves of ***Lantana camara*** and defined as 3,5-dihydroxy-4',6-dimethoxyflavonol-7-*O*-glucopyranoside and 3,4-dihydroxy-β-phenylethyl-*O*-α-L-rhamnopyranosyl (1→3)-4-*O*-***cis***-caffeoyl-β-D-glucopyranoside respectively by spectroscopic methods and chemical transformations.

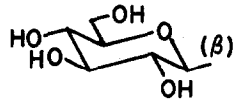
Lantana camara Linn var ***aculeata*** (verbenaceae) is a woody straggling plant with a number of flower colours ***viz.*** red, pink, white, yellow and violet.[1] The plant has encroached upon a vast expanse of pastures, orchards and forest areas in many tropical and subtropical parts of the world.[1,2] *L. camara* var. ***aculeata*** (red) is the most prevalent in submountaneous regions of India in the North-Western states. The plant has the notoriety of causing hepatotoxicity and photosensitization in grazing animals.[1-3] The plant has also the reputation of being used in traditional medicine.[4] Considerable phytochemical work on this plant led to the isolation of a number of triterpenoids, umuhengerin, a partially methylated flavonoid and essential oils which have been covered in a recent review.[5] These products are essentially nonpolar. The allelochemicals, from the plant associated with insecticidal, pesticidal and weedicidal activities have been suggested to be polar.[6] Herbert ***et al.***[7] recently isolated from the plant, verbascoside, a polar constituent possessing antimicrobial, immunosuppressive and antitumor activities.[8-10] Besides isolation of verbascoside no other polar compound appears to have been isolated from *L. camara*. Thus it seemed pertinent to take up phytochemical investigation in detail of the polar constituents from the plant to explore the possibility of beneficial utilization of the huge plant biomass available. This paper reports the isolation and characterization of flavonoid-, and phenylpropanoid glycosides from the leaves of the plant.

RESULTS AND DISCUSSION

The *n*-BuOH soluble fraction of the MeOH extract of the leaves of the plant was partially purified by adsorption in silica gel followed by successive extraction with $CHCl_3$, EtOAc and 20% MeOH in $CHCl_3$. The ethyl acetate extract on chromatographic purification yielded compounds A and B. The MeOH-$CHCl_3$ extract on separation using a combination of sephadex LH-20 chromatography, Si-gel CC and preparative TLC on silica gel G afforded compounds C and D. The UV and IR spectral data of compound A (**1**) suggested it to be a flavone glycoside. On hydrolysis with aq. MeOH-HCl, **1** yielded pectolinarigenin[11,12] as the aglycone and D-glucose as the sugar constituent. The various spectroscopic data disclosed the identity of compound A (**1**) with pectolinarigenin-7-*O*-glucoside which has previously been isolated from *Eria ravanica*.[13] Except UV no other physical or spectral data of the compound are available.



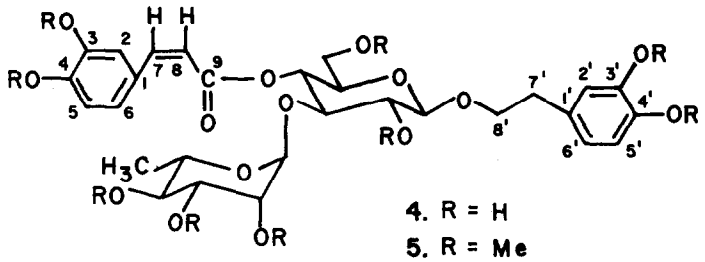
1. Pectolinarigenin-7-O-glucoside; R = H; R_1 = 

2. Camaraside; R = OH; R_1 = 

3. 3,5,7-trihydroxy-4',6-dimethoxyflavonol; R = OH; R_1 = H

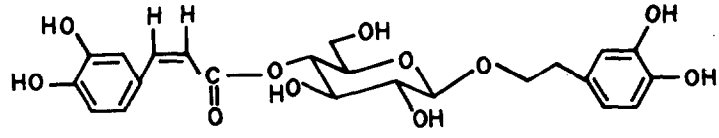
Compound B (**2**) named camaraside displayed UV and IR spectral characteristics of a flavonol glycoside. The positive ion FAB mass spectrum showed the ion peaks at *m/z* 515 and 492 ascribed to $[M+Na]^+$ and $[M]^+$ respectively. Hydrolysis with aq. MeOH-HCl furnished a new flavonol, characterized as 3,5,7-trihydroxy-4',6-dimethoxy flavonol (**3**) from its MS, ^1H and ^{13}C NMR spectra. The aqueous portion of the hydrolysate on usual workup and PC and GC studies revealed the presence of D-glucose. The linkage of the glucose unit with C-7 of the aglycone was inferred from the UV and ^{13}C NMR data. Thus camaraside was characterized as 3,5-dihydroxy-4',6-dimethoxy flavonol-7-*O*-glucopyranoside (**2**).

Compound C designated Lantanaside (**4**) gave positive Molisch test for sugars and $FeCl_3$ test for phenols. Its IR and UV spectra displayed bands indicating the presence of hydroxyl and conjugated enone system. The positive ion FAB-MS displayed peaks at *m/z* 647, 625, 624 and 460 assignable to $[M+Na]^+$, $[M+H]^+$, $[M]^+$ and $[M-rha]^+$ respectively. The positive ion FAB-MS with NaCl added displayed the $[M+Na]^+$ ion peak at *m/z* 647 as the base peak. The negative ion FAB-MS showed an ion peak at *m/z* 623 as the base peak assigned to $[M-H]^-$. The data disclosed the M_r of lantanaside to be 624.



4. R = H
5. R = Me

Alkaline treatment followed by acid hydrolysis yielded products identified as (E)-3(3,4-dihydroxyphenyl) propenoic acid; 3,4-dihydroxyphenylethyl alcohol; D-glucose and L-rhamnose by spectroscopic and GC studies. The formation of these products of hydrolysis of lantanaside (4) apparently indicated its identity with verbascoside[14,15] also known as acteoside. However, significant differences were observed particularly in the UV and NMR data of the compound and those reported for verbascoside.[14,15] The ^{1}H NMR spectrum of compound 4 exhibited two doublets at δ 6.20 (J 13Hz) and 7.48 (J13Hz) assignable to the olefinic protons of *cis*-caffeoyl moiety. The J values 12.4 end 13 Hz reported for (Z)-3-(4-hydroxyphenyl) propenoic acid[16] and for *cis*-cinnamic acid derivatives[17] respectively are comparable. Reported J value for the olefinic protons of *trans* caffeoyl esters e.g. verbascoside[15] and *trans* cinnamic acid derivatives[17] is 16 Hz. Moreover, ^{13}C NMR spectrum of lantanaside showed a two-carbon peak at δ 128.2 assigned to C-7 and C-8 of compound 4 was absent in the ^{13}C NMR spectrum of verbascoside. The UV spectrum of 4 displayed an absorption band at λ_{max} 256 nm (ε13,600) suggesting the presence of a *cis*-caffeoyl moiety [lit.[18] *cis*-cinnamoyl λ_{max} 254 nm (ε10,600) *trans* cinnamoyl 277 nm (ε2300)]. The results led to the conclusion that in lantanaside (4) *cis*-caffeoyl moiety is present which is converted to *trans* isomer, caffeic acid during hydrolysis. Permethylation of 4 by Hakomori's method[19] yielded the permethylate (5) which on hydrolysis furnished 2,6-di-*O*-methyl-D-glucose and 2,3,4-tri-*O*-methyl-L-rhamnose identified by GC of their alditol acetates. No other permethylate except 5 could be detected which indicated that acyl migration did not occur during the methylation process. Mild hydrolysis of 4 with aqueous 0.1M HCl/MeOH (1:1) at water-bath temperature afforded L-rhamnose as the only detectable sugar, a major partial hydrolysate 6



6

and a minor one. The product 6 was characterized from its spectroscopic data by comparison with those of a similar product obtained by partial hydrolysis of verbascoside.[15] The minor hydrolysate, apparently an acyl migrated product displayed very

similar FAB-MS to those of **6** but could not be fully characterized due to paucity of material. Consequently, the structure of lantanaside was defined as 3,4-dihydroxy-β-phenylethyl-*O*-α-L-rhamnopyranosyl (1→3)-4-*O*-*cis*-caffeoyl-β-D-glucopyranoside **(4)**. The ^{13}C NMR spectral data were found to be compatible with the structure and were assigned taking into consideration the chemical shift values, INEPT studies and comparison of its shift data with verbascoside[15] and celallocinine,[20,21] a spermidine alkaloid containing the rare *cis*-cinnamoyl moiety.

Compound D **(7)** was characterized as verbascoside by comparison of its spectral data with those reported in literature.[15]

Verbascoside isolated form *L. camara* has been reported[7] to be an inhibitor of protein kinase C (PKC) which plays a key role in cellular growth and differentiation.[22] The compound also showed a potent antiproliferative effect *in vitro* against L-1210 cells

Table : ^{13}C chemical shifts (δppm) of flavone glycoside **(1)**, camaraside **(2)**, flavonol **(3)** and lantanaside **(4)**.

Carbon No.	(1)	(2)	(3)	Carbon No.	(4)	Carbon	(4)
2	163.5[a]	156.5	146.2	1	125.8	g-5	74.6
3	103.1	136.1	135.9	2	114.8	g-6	61.0
4	182.0	176.3	177.0	3	114.5	r-1	101.1
5	152.2	151.4[a]	150.1[a]	4	148.4	r-2	70.6[a]
6	132.6	132.0	132.3	5	113.9	r-3	70.2[a]
7	156.2	159.4	158.1	6	121.5	r-4	72.0
8	94.4	93.5	94.0	7	128.2	r-5	68.8
9	151.8	152.0[a]	151.0[a]	8	128.2	r-6	18.1
10	105.6	103.7	102.9	9	165.8		
1'	122.5	123.0	122.8	1'	129.6		
2'	128.0	128.0	127.7	2'	116.4		
3'	114.3	115.5	114.9	3'	145.0		
4'	162.1[a]	163.5	163.1	4'	143.5		
5'	114.3	115.5	114.9	5'	115.6		
6'	128.0	128.0	127.7	6'	119.7		
g-1	100.3	100.4		7'	35.1		
g-2	73.1	73.8		8'	70.4		
g-3	76.6	76.2		g-1	102.4		
g-4	69.7	70.1		g-2	74.6		
g-5	77.1	78.0		g-3	79.5		
g-6	60.7	60.8		g-4	69.5		

g = glucose, r = rhamnose, [a]Assignments within a column of each compound may be interchanged.

and the authors[7] suggested for exploring the possibility of using verbascoside for therapeutic intervention in a wide range of diseases including cancer, inflammation and immune disorders. It is noteworthy that flavonol glycosides have also been reported to have inhibitory effects on 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced tumor promotion and the effects have been attributed at least partly to activation of immune responses against tumors.[23] Yasukawa *et al.* also reported inhibitory effect of flavonol glycosides on TPA-induced inflammation in mice.[24] These reports strongly suggest that the flavone and flavonol glycosides reported in this paper may also be responsible for the antitumor and possibly other medicinal properties of *L. camara*[4]. We believe that lantanaside (**4**) is the first reported phenylpropanoid glycoside possessing *cis*-caffeoyl moiety and studies are underway to evaluate antitumor activities of the four potential compounds isolated.

EXPERIMENTAL

The leaves of the plant were collected from the vicinity of Indian Veterinary Research Institute, Palampur, India. All melting points were measured on a capillary melting point apparatus and are uncorrected. Preparative TLC was carried out on silica gel G (BDH) plates with solvent $CHCl_3$-MeOH-H_2O (12:6:1) and spots were visualized in an iodine chamber. IR spectra were taken on a JASCO-700 instrument in KBr discs. UV spectra were recorded on a Shimadzu model, UV-260 spectrophotometer. GC was performed on a Hewlett-Packard model 5730A instrument using the columns (i) ECNSS-M, 3% on Gas Chrome Q at 190°C for alditol acetates and (ii) OV-225 on Gas Chrome Q at 195°C for partially methylated alditol acetates. ^1H and ^{13}C NMR spectra were recorded on a JEOL-FX-100 spectrometer operating at 99.6 MHz or 25.05 MHz with TMS as internal standard. Fast atom bombardment mass spectra were obtained on a VG ZAB-SE mass spectrometer using glycerol-thioglycerol as matrix. Electron impact mass spectra were recorded on a JEOL-AX-500 mass spectrometer by direct inlet mode at 70 eV.

The air dried powdered leaves (1.5 kg) of *L. camara* were successively extracted in a soxhlet with petroleum ether (60-80°C), $CHCl_3$ and MeOH. The MeOH extract was concentrated and partitioned between water and *n*-BuOH. The *n*-BuOH layer was washed with water, and distilled off under reduced pressure. The residue (35g) thus obtained was dissolved in minimum amount of methanol, adsorbed in Si-gel, dried and extracted successively with $CHCl_3$, EtOAc and $CHCl_3$-MeOH (4:1).

Isolation of pectolinarigenin-7-*O*-glucoside (1) and camaraside (2). The EtOAc extract (5.2g) was chromatographed on silica gel (70g) with $CHCl_3$, $CHCl_3$-EtOAc (1:1), EtOAc and various ratios of EtOAc and MeOH. The fractions were monitored by TLC and similar fractions were combined. Earlier fractions eluted with EtOAc-MeOH (19:1) on further purification by rechromatography followed by crystallization from MeOH furnished **1** as light yellow fine needles (1.5g), mp 266-268°C : λ_{max} (MeOH) 253, 278, 340 (NaOAc) 252, 277, 340 (NaOMe) 290,305 nm; ^1H NMR (DMSO-d_6) δ 3.76 (3H,s,-OCH_3, 3.84 (3H,s,-OCH_3), 5.4 (1H,d, *J* 7Hz, H-1 of glucose), 6.94 (1H, s,H-3). 7.04 (1H,s,H-8), 7.16 (2H,d, *J* 9Hz,

H-3' and H-5'), 8.08 (2H,d,*J* 9Hz, H-2' and H-6') and 12.92 (1H,s,O*H*-5); FAB-MS (positive) *m/z* (rel. int.) 521 $[M+2Na+H]^+$ (40), 499 $[M+Na]^+$ (55), 315 $[M+H-glu]^+$ (55).

Compound A **(1)** (100 mg) on hydrolysis with 5% aq. MeOH-HCl under reflux for 3h followed by usual work up furnished pectolinarigenin and D-glucose.

Fractions eluated with EtOAc-MeOH (23:2) were combined, further purified by rechromatography and crystallized from MeOH to yield yellowish micro needles (120 mg) of camaraside **(2)**, mp 202-204°C; λ_{max} (MeOH) 331, 277 (NaOAc) 330, 276 (NaOMe) 370, 275 and ($AlCl_3$) 301, 350 nm; ^1H NMR (DMSO-d_6) δ 3.74, 3.82 (each 3H,s,2X-OCH_3), 5.06 (1H,d,*J*7.5 Hz, H-1 of glucose unit), 6.88 (1H,s,H-8), 7.09 (2H,d, *J* 10Hz, H-3' and H-5'), 8.03 (2H,d, *J* 10Hz, H-2' and H-6'). ^{13}C NMR (Table); FAB-MS (Positive) *m/z* (rel. int.) 515 $[M+Na]^+$ (12), 492$[M]^+$ (18), 330$[M-glc]^+$ (47) and 315$[M-glc-Me]^+$ (35).

Compound B **(2)** (100 mg) was dissolved in 5% MeOH-HCl (aq.) (30 ml) and refluxed for 3h. Usual work up and chromatographic purification followed by crystallization from MeOH furnished 3,5,7-trihydroxy-6,4'-dimethoxy flavanol, mp 186-188°C ; ^1H NMR (DMSO-d_6) δ 3.7, 3.78 (each 3H,s,2X-OCH_3), 6.8 (1H,s,H-8), 7.0 (2H,d *J*9.5Hz , H-3' and H-5') and 8.04 (2H,d *J* 9.5Hz, H-2' and H-6'); ^{13}C NMR (Table) ; EIMS *m/z* (rel.int.) 330 (M^+) (50), 315 (M^+-Me) (80), 312 (M^+-H_2O) (22), 301 (M^+-CHO) (18) and 287 (M^+-COMe) (70). The aqueous hydrolyzate was worked up in the usual way and only D-glucose was identified as its alditol acetate by GLC.

Isolation of lantanaside (4) and verbascoside (6). The $CHCl_3$-MeOH (4:1) extract (6.5g) was dissolved in minimum amount of MeOH and eluated with $CHCl_3$-MeOH (4:1) over a column of sephadex LH-20 (60 g) and the residue thus obtained (2.2g) was further purified by repeated Si-gel CC and preparative TLC to furnish lantanaside **(4)** (90 mg) and verbascoside (130 mg) as amorphous powders. Lantanaside **(4)**, IR ν_{max} cm^{-1} 3450 (br,OH), 1710, 1650, 1600; λ_{max} (MeOH) 256 (ε 13,600), 267 (sh) (ε 10,200); ^1H NMR (DMSO-d_6) δ 1.03 (3H,d, *J*7Hz, CH_3 of rhamnose), 4.36 (1H,d, *J*8Hz,H-1 of glucose), 5.04 (1H,brs,H-1 of rhamnose), 6.20 (1H,d, *J*13Hz, Ar-CH=C*H*-), 6.44-7.04 (6H,m,aromatic-H) and 7.48 (1H,d, *J*13Hz, Ar-C*H*=CH-), ^{13}C NMR (Table); FAB-MS (Positive) *m/z* (rel.int.) 647 $[M+Na]^+$ (8), 625 $[M+H]^+$ (22), 624 $[M]^+$ (25), 478 (24), 460 [M-rhamnose]$^+$ (100) and 443 [M-caffeoyl moiety]$^+$ (15); FAB-MS (negative) *m/z* (rel.int.) 623 $[M-H]^-$ (100), 477 [M-H-rhamnose]$^-$ (10) and 443 [M-H-caffeoyl moiety]$^-$ (8). (Found : C, 55.80; H, 5.73; $C_{29}H_{36}O_{15}$ requires C, 55.76; H, 5.8%).

Hydrolysis of lantanaside (4). The compound 4 (100 mg) was hydrolysed with 5% MeOH-KOH (aq.) at boiling water bath temperature for 3h. cooled, acidified with 2M HCl and extracted with EtOAc. The EtOAc layer was washed free from acid, solvent distilled off, the residue was purified by CC and crystallized from MeOH to furnish needles (15 mg), mp 220-222°C (lit.[25] mp 223-225°C). The aqueous layer was extracted with

n-BuOH washed with water and evaporated under reduced pressure. The residue was hydrolysed with 5% MeOH-HCl (aq.) at water bath temperature to furnish 3,4-dihydroxyphenylethyl alcohol, identified from its ^{1}H NMR spectra.[15] The aqueous hydrolyzate was worked up as described[26] and subjected to GC analysis using column (i). Two peaks corresponding to glucitol acetate and rhamnitol acetate were detected using authentic specimens.

Permethylation of lantanaside (4) and acid hydrolysis of the permethylate (5). Lantanaside (4) (50 mg) was completely methylated with NaH/Me_2SO/CH_3I according to Hakomori's method[19] and the product was purified by CC to furnish the permethylate (5) as powder (25 mg). ^{1}H NMR ($CDCl_3$) δ 4.32 (1H,d, *J* 7Hz,H-1 of glucose unit) 5.02 (1H,brs,H-1 of rhamnose unit). The permethylate (5) was hydrolysed with 5% MeOH-HCl (aq.) under reflux for 3h. Usual work-up afforded a mixture of alditol acetates which was subjected to GC analysis using column (ii). The peaks corresponding to 2,6-di-*O*-methyl-D-glucitol diacetate (R_t 3.32) and 2,3,4-tri-*O*-methyl-L-rhamnitol diacetate (R_t 0.40) were identified by comparison with authentic samples.[27,28]

Partial hydrolysis of lantanaside (4). Compound 4 (40 mg) was refluxed at water-bath temperature for 25 min with 0.1M HCl-MeOH (aq.) (5 ml). Worked up as usual and the residue was chromatographed over Si-gel (5g). Elution with $CHCl_3$-MeOH (24:1) furnished a colourless amorphous powder 6 (10 mg). FAB-MS (positive) *m/z*479 $[M+H]^+$, 478 $[M]^+$ and 298 [M-caffeoyl moiety]$^+$; IR ν_{max} cm^{-1} 3595, 3500, 1705, 1625; ^{1}H NMR (DMSO-d_6) δ 4.34 (1H,d, *J*7Hz, H-1 of glucose), 6.22 (1H,d, *J* 13Hz, Ar-CH=C*H*-), 6.42-7.05 (6H,m,aromatic-H) and 7.46 (1H,d, *J* 13Hz, Ar-C*H*=CH-). (Found:C,57.72; H,5,50; $C_{23}H_{26}O_{11}$ requires C,57.74; H, 5.48%). Further elution with $CHCl_3$-MeOH (9:1) gave a minor product, FAB-MS (positive) *m/z* 479$[M+H]^+$, 478 $[M]^+$ and 298 [M-caffeoyl moiety]$^+$.

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