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FLAVONOID METHYL ETHERS ON THE EXTERNAL LEAF SURFACE OF *LARREA TRIDENTATA* AND *L. DIVARICATA*

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Key Word Index—*Larrea tridentata*; *L. divaricata*; Zygophyllaceae; external resin; flavonol methyl ethers; flavone methyl ethers; nordihydroguaiaretic acid; plant polyploidy; chemistry and plant speciation.

Abstract—The external phenolic resin on the leaves of *Larrea tridentata* contains eighteen flavone and flavonol aglycones (mostly as methyl ethers), one dihydroflavonol and two lignans (including nordihydroguaiaretic acid). Except for a few isolated 2*n* populations which exhibited minor differences, a single chemical type was observed for all three ploidy levels (2*n*, 4*n* and 6*n*) in the North American *L. tridentata* suggesting an autoploid origin for the tetraploid and hexaploid races. The resin chemistry of the North American taxon was most similar to that of the Argentinian diploid *L. divaricata*, although the resin of the latter taxon did not contain the three 8-hydroxyflavonols; however, 8-hydroxyflavonol aglycones were detected in Peruvian populations of *L. divaricata*.

INTRODUCTION

Larrea Cav. (Zygophyllaceae) is composed of five species distributed in the arid and semi-arid areas of North and South America. Three species, *L. cuneifolia* Cav. ($n = 26$), *L. nitida* Cav. ($n = 13$) and *L. ameghinoi* Speg. ($n = 13$), are restricted to Argentina. This paper concerns the two remaining species, *L. divaricata* (DC.) Coville ($n = 13$) which occurs primarily in Argentina and with a few small, isolated populations in Peru, Chile and Bolivia, and *L. tridentata* Cav. which occurs in North America as three ploidy levels—the diploid ($n = 13$) in the Chihuahuan Desert, the tetraploid ($n = 26$) in the Sonoran Desert, and the hexaploid ($n = 39$) in the Mojave Desert [1–3].

The external resin chemistry of *Larrea* has long been of interest because it represents 10–15% of the dry weight of the leaves; the resin is composed of approximately 50% nordihydroguaiaretic acid (NDGA) (**20**), one of the most powerful antioxidants known to man (see Oliveto [4] for a review of the uses of NDGA), and 50% as flavonoids.

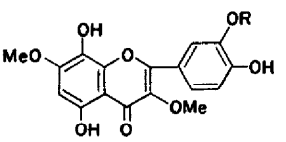
The flavonoid chemistry of *Larrea* has only recently attracted attention. Despite reports of flavonoids from *Larrea* as early as 1945 [5,6], the first account of the total structures of flavonoids in *Larrea* was the 1972 description of eleven flavonoid aglycones from *L. cuneifolia* from our laboratory [7].

More recently, Chirikdjian isolated and identified eight flavonoids from *L. tridentata*: the aglycones kaempferol, kaempferol 3-methyl ether (isokaempferide), quercetin, isorhamnetin and quercetin 3-methyl ether, and the glycosides kaempferol 3-*O*-rhamnoglucoside (nicotiflorin), quercetin 3-*O*-rhamnoglucoside (rutin), and quercetin 3-*O*-glucoside (isoquercitrin) [8,9].

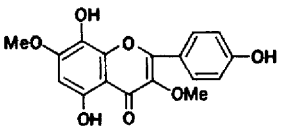
Here we report the detection of twenty-four flavonoids, mainly methyl ethers of flavonols, in the external leaf resin of South American *Larrea divaricata* and North American *L. tridentata*.

RESULTS

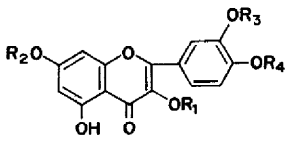
Nineteen flavonoids were isolated and fully characterized from the hexaploid race of *Larrea tridentata*; three of the constituents, gossypetin 3,7,3′-trimethyl ether (**1**) [10], gossypetin 3,7-dimethyl ether (**2**) [11] and herbacetin 3,7-dimethyl ether (**3**) [10], were recently described as new natural products from this taxon. Two other flavonols, quercetin 3,7,3′-trimethyl ether (**5**) and quercetin 7,3′,4′-trimethyl ether (**6**), were reported as new natural products from *Larrea cuneifolia* [7]. The remaining previously known flavonoids were quercetin 3,7,3′,4′-tetramethyl ether (**4**) [7,10,12,13] (retusine), quercetin 3,7-dimethyl ether (**7**) [7,14], quercetin 3,3′-dimethyl ether (**8**) [7,15], quercetin 7,3′-dimethyl ether (**9**) [7,14] (rham-



(**1**) R = Me
(**2**) R = H



(**3**)



(**4**) R_1, R_2, R_3, R_4 = Me
(**5**) R_1, R_2, R_3 = Me; R_4 = H
(**6**) R_2, R_3, R_4 = Me; R_1 = H
(**7**) R_1, R_2 = Me; R_3, R_4 = H
(**8**) R_1, R_3 = Me; R_2, R_4 = H
(**9**) R_2, R_3 = Me; R_1, R_4 = H
(**10**) R_3 = Me; R_1, R_2, R_4 = H

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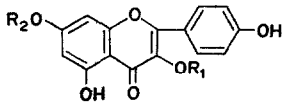
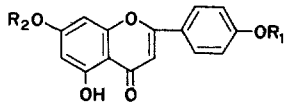
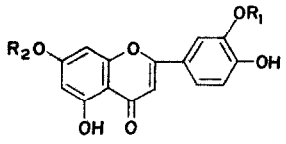
nazin), quercetin 3'-methyl ether (**10**) [7,15,16,17] (isorhamnetin), kaempferol 3,7-dimethyl ether (**11**) [7,15, 18] (kumatakenin), kaempferol 3-methyl ether (**12**) [7,8,15,19] (isokaempferide), kaempferol 7-methyl ether (**13**) [19,20,21] (rhamnocitrin), kaempferol (**14**) [8,17], luteolin 7,3'-dimethyl ether (**15**) [22] (velutin), luteolin 3'-methyl ether (**16**) [17] (chrysoeriol), apigenin 7-methyl ether (**17**) [19] (genkwanin), apigenin (**18**) [17] and dihydromyricetin 3',5'-dimethyl ether (**19**) [23] (dihydrosyringetin). All compounds were identified by UV, MS, NMR and/or co-chromatography (see Tables 1–4). Compounds **21**, **22**, **23** and **24** are under further investigation.



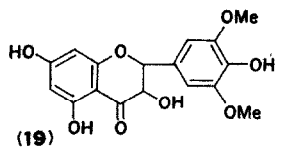
(**11**) R_1, R_2 = Me
(**12**) R_1 = Me; R_2 = H
(**13**) R_2 = Me; R_1 = H
(**14**) R_1, R_2 = H



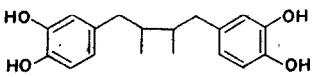
(**17**) R_2 = Me; R_1 = H
(**18**) R_1, R_2 = H



(**15**) R_1, R_2 = Me
(**16**) R_1 = Me; R_2 = H



(**19**)



(**20**)

No qualitative differences were observed for the flavonoid aglycones in the resin among the three ploidy races of *Larrea tridentata* which occur over a North-South range of more than a thousand miles in the United States and Mexico; moreover, the internal flavonoid glycoside patterns, as determined by two-dimensional paper chromatography, were also identical except for a few small populations in Querétaro, Mexico, (150 miles northwest of Mexico City), which contained all the aglycones and all but two of the glycosides. Two of the three new flavonols, **2** and **3**, which are distinguished by having hydroxyl groups at the 8-position, along with compound **21**, were observed in *L. tridentata* and in *L. divaricata* from Peru, but not Argentina, while compound **24** was only detected in *L. divaricata*. Compounds **22** and **23** require additional investigation to establish whether or not they are the same compound. The remaining sixteen flavonoids discussed here occur in the resin produced by both species.

DISCUSSION

Prior to 1970, *Larrea divaricata* and *L. tridentata* were generally recognized by most taxonomists as distinct species. However, Felger and Lowe [24] recently treated them as subspecies because they interpreted the morphological differences to be minor. That is, such differences as the fact that *L. tridentata* has acute stipules while *L. divaricata* has obtuse ones were considered to be insufficient for species recognition. More recently, on the basis of unpublished data, Hunziker and co-workers suggested that these two taxa represent allopatric semispecies [25] the treatment also employed here.

Earlier data have shown that the genus contains two major sections: section *Bifolium*, consisting of *L. divaricata*, *L. tridentata* and *L. cuneifolia* with bifoliolate leaves and large, hairy mericarps; and section *Larrea*, consisting of two species, *L. ameghinoi* and *L. nitida*, with multifoliolate leaves and smaller, puberulous mericarps. Within the first section *L. divaricata* and *L. tridentata* are more closely related to each other than to *L. cuneifolia*; for example, *L. cuneifolia* is distinguished from *L. divaricata* and *L. tridentata* by having its two leaflets almost entirely attached at the midrib, whereas the latter two species have leaflets attached at the base only [1]. Previous chemical evidence supports a close relationship of *L. divaricata* to *L. tridentata*; both were reported to exhibit similar phenolic patterns and essentially no differences in seed albumin proteins [1].

Comparison of the flavonoid data for *L. cuneifolia* with the more complex pattern detected in *L. divaricata* shows a difference of seven compounds, primarily resulting from the absence of flavones in *L. cuneifolia*. Our data also show a close relationship between *L. divaricata* and *L. tridentata* since there is a difference of only two (**1** and **19**) of the nineteen major flavonoid components. Thus, at this time, our chemical data indicate that within section *Bifolium*, *L. divaricata* (n = 13) is closer to *L. tridentata* (n = 13,26,39) than to *L. cuneifolia* (n = 26), even though *L. cuneifolia* is an amphidiploid containing one genome of *L. divaricata* [1,2,25] (Our preliminary chemical results for *L. nitida* and *L. ameghinoi* clearly distinguish them from section *Bifolium*).

As to the origin of *Larrea tridentata* in North America, three opposing views are generally considered. Hunziker [1] favours a South-to-North American pattern of migration because: (1) the genus exhibits species diversity in northern Patagonia, Argentina (four species and five interspecific hybrids) and (2) the role played by *Larrea divaricata* in the origin of the relatively old species *L. cuneifolia* (the latter species contains one genome of the former). On the other hand, Porter [26] suggested that "the South American species of *Larrea* have been derived from Mexico via long-distance dispersal," species diversity being due to radiation after dispersal to South America [27]. Porter considers *Sericodes* to be the most closely related genus to *Larrea*; thus, the occurrence in Coahuila, Mexico, and not in South America, of the monotypic taxon *Sericodes greggii* Gray provides support for his view of a North American origin of *Larrea*. However, his treatment of the *Sericodes–Larrea* relationship requires further chemical investigation especially in light of the recent report that *Sericodes* is n = 15 (Lidia Poggio, unpublished data) whereas *Larrea* is x = 13. In contrast to Porter's interpretations, however, Hunziker considers the primarily South American genus *Bulnesia* (n = 13) to be most closely related to *Larrea* [25]. A third view (B. L. Turner, private communication) suggests that although the genus itself may have originated in South America, the species *L. tridentata* may have become established in North America from a South American progenitor and subsequently gave rise to *L. divaricata* in South America.

Although our data do not resolve the controversy regarding the origin of *Larrea*, they do bear upon the nature of the polyploidy in *L. tridentata*. The lack of chemical differences between the diploid, tetraploid and hexaploid races of *L. tridentata* in North America provides strong evidence that the latter two are autoploids.

Table 1. Chromatographic data for flavonoid aglycones from *Larrea tridentata* and *L. divaricata*

Compound*	R_f's (×100)† BeAW	25% HOAc	Polyamide column fractions‡	Presence and relative quantity‖ *L. tridentata*	*L. divaricata*	Colors UV	UV/NH_3
1 Gossypetin 3,7,3′-trimethyl ether¶	52	38	39–91	++++	–	Blue–green	Yellow–green
2 Gossypetin 3,7-dimethyl ether	5	38	398–636	++	++§	Blue–purple	Yellow–green
3 Herbacetin 3,7-dimethyl ether¶	27	51	110–183	++++	++§	Blue-green	Yellow–green
4 Quercetin 3,7,3′,4′-tetramethyl ether	99	45	7–37	+++	++	Purple	Purple
5 Quercetin 3,7,3′-trimethyl ether	90	38	7–52	++	++	Purple	Yellow
6 Quercetin 7,3′4′-trimethyl ether	96	15	24–37	++	++	Yellow	Yellow
7 Quercetin 3,7-dimethyl ether	33	34	92–109	+++	+++	Purple	Yellow
8 Quercetin 3,3′-dimethyl ether	28	35	136–183	+++	+++	Purple	Yellow
9 Quercetin 7,3′-dimethyl ether	90	13	70–109	+++	+	Yellow	Yellow
10 Quercetin 3′-methyl ether	17	15	554–925	++	+	Yellow	Yellow
11 Kaempferol 3,7-dimethyl ether	82	45	38–69	++++	++++	Purple	Yellow
12 Kaempferol 3-methyl ether	12	52	311–423	++	++++	Purple	Yellow–green
13 Kaempferol 7-methyl ether	65	13	163–220	+++	++++	Yellow	Yellow
14 Kaempferol	7	16	797–925	+	+	Yellow	Yellow
15 Luteolin 7,3′-dimethyl ether	84	23	24–37	++	++	Purple	Fluorescent yellow
16 Luteolin 3′-methyl ether	15	23	211–243	++	++	Purple	Yellow
17 Apigenin 7-methyl ether	66	39	38–69	++++	++++	Purple	Yellow–green
18 Apigenin	8	31	455–585	++	++	Purple	Yellow
19 Dihydromyricetin 3′,5′-dimethyl ether**	14	83		++	++	Purple	Purple
20 NDGA	15	77	680–925	++++	++++	Purple	Purple
21 Unidentified††	3	41		+	+	Blue–green	Blue–green
22 Unidentified††	82	79		+++	–	Purple	Yellow–green
23 Unidentified††	45	70		–	++++	Purple	Yellow–green
24 Unidentified††	4	34		++++	–	Purple	Yellow

* All compounds except **1**, **2**, **3**, **19**, **21**, **22**, **23**, **24** and **25** were identified by at least UV, MS and cochromatography. † The chromatograms (Whatman 3MM, 46 × 57 cm) were developed in BeAW (C_6H_6–HOAc–H_2O, 6:7:3, upper) [28] in the first dimension and 25% HOAc (HOAc–H_2O, 1:3). ‡ A 7·5 × 100 cm polyamide column (560 g) using $CHCl_3$–MeOH–MeCOEt-2,4-pentanedione (20:10:5:1) as solvent was run collecting 20 ml samples beginning with the first band visible under UV light. ‖ (++++)—very strong; (+++)—strong; (++)—medium; (+)—weak; (–)—absent. ¶ These structures were determined by UV, MS and NMR (see References 10 and 11). § These compounds are produced by the Peruvian populations of *L. divaricata*. ** Structure elucidated by UV, NMR and MS and NMR and MS of its acetate. †† Structures are still under investigation.

Moreover, the lack of variation in the flavonoid chemistry of *L. tridentata* and the detection of considerable variation of the flavonoids of *L. divaricata* from Peru and Argentina suggests a relatively recent origin for the North American populations from a more ancient *L. divaricata*-like South American progenitor.

In summary, because the origin of the disjunction in the *L. divaricata–L. tridentata* complex is still a matter of dispute, especially in light of the occurrence of three ploidy levels in North America and only one in *L. divaricata* in South America, we are presently extending our studies to thoroughly examine not only the external resin from populations over the ranges of these taxa in both North and South America but also the patterns for the flavonoid glycosides and other natural products for both taxa over their complete ranges.

EXPERIMENTAL

Plant material. Leaves and vouchers of *Larrea tridentata* were collected near Fort Stockton, Texas (2*n*), Tucson, Arizona (4*n*) and Las Vegas, Nevada (6*n*). Leaves and vouchers of *L. divaricata* were collected near Cordoba, Argentina.

Table 2. UV data for flavonoid aglycones from *Larrea tridentata* and *L. divaricata**

Compound		MeOH (λ_{max}, nm)	NaOMe (λ_{max}, nm)	$AlCl_3$ (λ_{max}, nm)	$AlCl_3$–HCl (λ_{max}, nm)	NaOAc (λ_{max}, nm)	NaOAc–H_3BO_3 (λ_{max}, nm)
Kaempferol 7-methyl ether	(13)	366	418 *dec*	423	426	369	366
		327*sh*		353	351	327*sh*	326*sh*
		266	269	300	300	265	265
			243	270	267		
Luteolin 7,3′-dimethyl ether	(15)	345	402	391	388	404	346
		267	292*sh*	369*sh*	355	354	267
		250	260	296	291*sh*	288	249
		246*sh*		275	276	263*sh*	241
				267*sh*	262	254	
Luteolin 3′-methyl ether	(16)	346	386	388	384	365	345
		268	328*sh*	366	354	326*sh*	267
		248	272*sh*	295	295	270	247
		242	265	274	276		240
				261	260		
Apigenin 7-methyl ether	(17)	333	382	380	378	378*sh*	332
			295	348	338	344	
		266	266	300	299	265	265
				274	276		
Dihydromyricetin 3′,5′-dimethyl ether	(19)	313*sh*	318	375	360*sh*	321	315*sh*
		287	250	311	308	300*sh*	290
				278			

* All UV spectra were recorded using standard procedures [17]. For spectral data for **1** and **3**, see Ref. [10]; for **2**, see Ref. [11]; for **4**–**12**, see Ref. [7]; and for **14**, see Ref. [17].

Table 3. NMR data for flavonoid aglycones from *Larrea tridentata* and *L. divaricata**

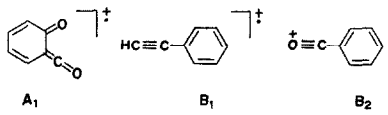
									OMe's		
									C_6D_6		
	H-2	H-3	H-6	H-8	H-2′	H-3′	H-5′	H-6′	CCl_4	7-OMe	3′-OMe	5′-OMe
Kaempferol 7-methyl ether (**13**)	—	—	6·18*d* (J=2)	6·47*d* (J=2)	8·00*d* (J=8)	6·85*d* (J=8)	6·85*d* (J=8)	8·00*d* (J=8)	3·83	3·20 (Δ+0·63)	—	—
Luteolin 7,3′-dimethyl ether (**15**)	—	6·35	6·23*d* (J=2)	6·53*d* (J=2)	7·31*d* (J=2)	—	6·88*d* (J=8·5)	7·39*dd* (J=2,8·5)	3·90	3·23 (Δ+0·70)	3·30 (Δ+0·60)	—
Luteolin 3′-methyl ether (**16**)	—	6·33	6·12*d* (J=3)	6·47*d* (J=3)	7·27*d* (J=2)	—	6·83*d* (J=8)	7·36*dd* (J=2,8)	3·92	—	3·25 (Δ+0·60)	—
Apigenin 7-methyl ether (**17**)	—	6·35	6·22*d* (J=2)	6·52*d* (J=2)	7·78*d* (J=9)	6·88*d* (J=9)	6·88*d* (J=8)	7·78*d* (J=8)	3·90	3·28 (Δ+0·62)	—	—
Dihydromyricetin 3′,5′-dimethyl ether (**19**)	4·93*d* (J=11)	4·17*d* (J=11)	5·92*d* (J=2)	6·08*d* (J=2)	6·67	—	—	6·67	3·84	—	3·45 (Δ+0·39)	3·45 (Δ+0·39)
Acetate† of **19**	5·40*d* (J=12)	5·81*d* (J=12)	6·85*d* (J=2)	6·65*d* (J=2)	6·76	—	—	6·76	3·85	—	3·43 (Δ+0·42)	3·43 (Δ+0·42)

* Spectra were recorded in CCl_4 and C_6D_6 (only OMe signals are recorded for this solvent) on a Varian A-60 or Varian EM-360 spectrometer. Values are given in ppm (δ-scale) relative to TMS as an internal standard. Numbers in parentheses denote coupling constants in Hz; signals are singlets unless otherwise stated: *d*(doublet), *dd*(double doublet). For data for **1** and **3**, see Ref. [10]; for **2**, see Ref. [11]; for **4–12**, see Ref. [7]; and for **14**, see Ref. [17]. † Four singlets were observed for acetoxyl protons at 2·05, 2·31, 2·35 and 2·38 in CCl_4, and at 1·60, 1·68, 2·02 and 2·19 in C_6D_6.

Table 4. MS data for flavonoid aglycones from *Larrea tridentata* and *L. divaricata**

		Fragment†													
Compound		M^+	$M-H^+$	$M-CO^+$	$M-HCO^+$	$M-COMe^+$	A_1+H^+	A_1+	A_1-CO^+	B_1+	B_1Me^+	B_2+	B_2-CO^+	B_2-Me^+	$A_1COMe-CO$
Kaempferol 7-methyl ether	(**13**)	100	12	4	7	10	3					13	4		2
Kaempferol	(**14**)	100	20	11	9		6	1	4	5		20	9		
Luteolin 7,3′-dimethyl ether	(**15**)	100	11	4	16	13	14	3	6	6	7	3	4	2	9
Luteolin 3′-methyl ether	(**16**)	100	6	6	4	13	22	4	5	12	10	2	7	7	
Apigenin 7-methyl ether	(**17**)	100	10		18	9	5	5	7	5		4	2		8

* For MS data of dihydrosyringetin acetate see experimental section; for **1** and **3**, see ref. [10]; for **2** see ref. [11]; for **4–12**, see ref. [7]. MS were recorded on a Dupont 21–491 at 70 eV, source temperature 190° and probe temperature from 200–300°. Values are given in % relative intensity. † Skeletons for A_1, B_1 and B_2 fragments are:



Vouchers specimens are deposited in the Herbarium, The University of Texas at Austin (TEX). All plant material was dried for 3 days in a 50° oven and then extracted.

Extraction, purification and identification. Ground leaf material (250 g) of the hexaploid *L. tridentata* was extracted with 1 l. of 85% aq MeOH for 24 hr. The liquid was removed by filtering, and the leaf material was re-extracted in the same manner. Extracts were combined and evaporated under red. pres. until only H_2O remained. The aq suspension was extracted with Et_2O until the Et_2O layer was colorless. Et_2O extracts were combined and evaporated under red. pres. The syrup obtained (12 g) was chromatographed over a polyamide column (7·5 × 100 cm; 560 g, packed in the elution solvent). The column was eluted with $CHCl_3$–MeOH—MeCOEt-2,4-pentanedione (20:10:5:1). Every third fraction of 20 ml was checked by polyamide TLC with MeOH; fractions were combined to give a total of 28 fractions. Each of the 28 fractions was evaporated and, when necessary, the material obtained was rechromatographed over polyamide using MeOH as the eluting solvent. The compounds were recrystallized from MeOH. Two-D PC and co-chromatography were run using Whatman 3MM paper (46 × 57 cm) with C_6H_6–HOAc–H_2O (6:7:3, upper) [28] and 25% aq HOAc (see Table 1 for R_f values). All spectra analyses were carried out as previously described [7,17,29].

MS of tetraacetate of dihydrosyringetin (**19**). MS (*m/e*): 516 (M^+, 7% relative intensity, 474 ($M-CH_2$=CO, 43%), 432) ($M-2CH_2$=CO, 84%), 390 ($M-3CH_2$=CO, 16%), 372 ($M-2CH_2$=CO–$MeCO_2H$, 100%), 330 ($M-3CH_2$=CO–$MeCO_2H$, 80%), 300 ($M-3CH_2$=CO–$MeCO_2H$–2Me, 16%), 223 (B_2^+, 14%) 195 (A + H–CH_2=CO, 87%), 167 (A + H–CH_2=CO–CO, 57%), 153 (A + H–$2CH_2$=CO, 49%), 149 (B_2–Me–0,91%).

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