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THE DITERPENOIDS FROM THE GENUS *HYPTIS* (LAMIACEAE)

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Abstract – The genus *Hyptis* (family Lamiaceae) is known mainly for the essential oils isolated from the aerial parts of several species. Less known are the diterpenoids, extracted from a limited number of species. In consideration of the interest for the structures of this class of compounds, largely occurring in the whole Lamiaceae family, the present paper means to review and update their chemistry. Also the use of many species of *Hyptis* in folk-medicine is reported.

INTRODUCTION

The genus *Hyptis*, family Lamiaceae (Labiatae) comprises about 400 species, and is one of the largest genera of the family. It is native of Central and South America, including the southern part of United States.^{1,2} Now several species were introduced in Western and Central Africa (for instance Cameroon, Nigeria, Burkina Faso, Ivory Coast), and even in India, China, Thailand and Fiji Islands, where they are cultivated specially for the production of essential oils. Moreover, they are important for the ethnopharmacologic point of view.

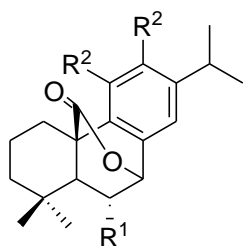
For this reason, a large number of species was investigated for their content of essential oils, and minor attention was given to other constituents. For instance, the occurrence of diterpenoids was reported only in nine species.

CHEMICAL INVESTIGATIONS

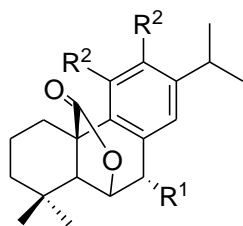
The present paper means to review the isolation and the structures of these products. A total of 66 diterpenoids occurs in the genus, and 26 of them show heterocyclic structures.

acetyl-pisiferic acid methylester **19**.^{16,18} Two not previously described derivatives were identified: diacetyl-epimethylrosmanol **20** and diacetyl-epiethylrosmanol **21**.

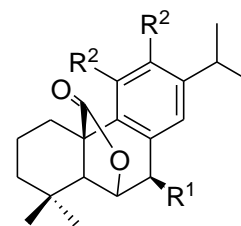
It must be evidenced that the nine abietane **11-21** are not authentic natural products, but derivatives originating from the acetylation/diazomethane treatment: the diterpenes originally occurring before the treatment are carnosol **8**, rosmanol **9**, methylrosmanol **10**, but evidently also ethylrosmanol **22**, isorosmanol **23**, epirosmanol **24**, epimethylrosmanol **25**, epiethylrosmanol **26**, carnosic acid **27**, pisiferic acid **28**, all not acetylated or partially acetylated products. These true natural products **22-28** were not isolated.



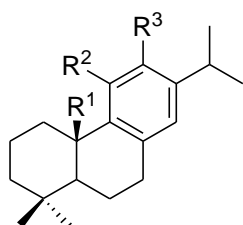
- 8** R¹ = H R² = OH
11 R¹ = H R² = OAc
15 R¹ = OAc R² = OAc
23 R¹ = OH R² = OH



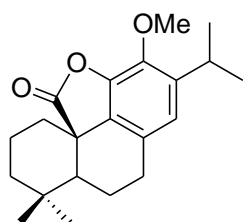
- 9** R¹ = OH R² = OH
10 R¹ = OMe R² = OH
12 R¹ = OAc R² = OAc
13 R¹ = OMe R² = OAc
14 R¹ = OEt R² = OAc
22 R¹ = OEt R² = OH



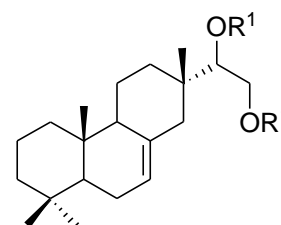
- 16** R¹ = OAc R² = OAc
20 R¹ = OMe R² = OAc
21 R¹ = OEt R² = OAc
24 R¹ = OH R² = OH
25 R¹ = OMe R² = OH
26 R¹ = OEt R² = OH



- 17** R¹ = CO₂H R² = OAc R³ = OAc
18 R¹ = CO₂Me R² = OAc R³ = OAc
19 R¹ = CO₂Me R² = H R³ = OAc
27 R¹ = CO₂H R² = OH R³ = OH
28 R¹ = CO₂H R² = H R³ = OH



29

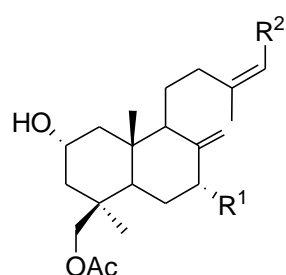


- 30** R¹ = Ac
31 R¹ = H

Many of the diterpenoids isolated from *Hyptis dilatata* show heterocyclic rings of 20,6- and 20,7-lactones. Also the known¹⁹ heterocyclic 20,11-lactone **29** was isolated. All the **8-29** products show the abietane skeleton. Another known compound, diacetyl-esquirolin B **30**²⁰ was also isolated, but it has an isopimarane skeleton (not pimarane, as written in the original paper). Probably, also in this case, the plant contained the non-acetylated esquirolin B **31**.

Seven new products have been isolated from the aerial parts of *Hyptis spicigera* occurring in Mexico,²¹ and popularly known as “hierba del burro”. It is remarkable that these compounds show a different skeleton, as they are labdane derivatives. They were not given trivial names. On the basis of spectroscopic determinations and functional groups chemical modifications they were attributed the following structures.

The first product has the structure **32** of 19-acetoxy-2 α ,7 α ,15-trihydroxy-labda-8(17),(13Z)-diene. The other new products are 15,19-diacetoxy-2 α ,7 α -dihydroxy-labda-8(17),(13Z)-diene **33**; 7 α ,15,19-triacetoxy-2 α -hydroxy-labda-8(17),(13Z)-diene **34**; 19-acetoxy-2 α ,7 α -dihydroxy-labda-8(17),(13Z)-dien-15-al **35**; 19-acetoxy-7 α ,15-dihydroxy-labda-8(17),(13Z)-dien-2-one **36**; 19-acetoxy-2 α ,7 α -dihydroxy-labda-14,15-dinor-labd-8(17)-en-13-one **37**; 2 α ,7 α ,15,19-tetrahydroxy-*ent*-labda-8(17),(13Z)-diene **38**. It is remarkable that product **38** has the *ent*-labdane skeleton, whereas the **33-37** products have the normal labdane backbone.

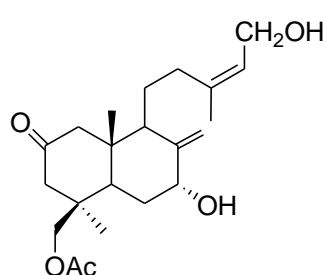


32 R¹ = OH R² = CH₂OH

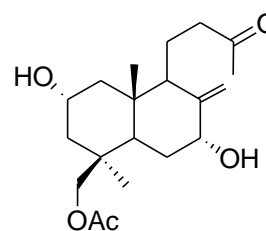
33 R¹ = OH R² = CH₂OAc

34 R¹ = OAc R² = CH₂OAc

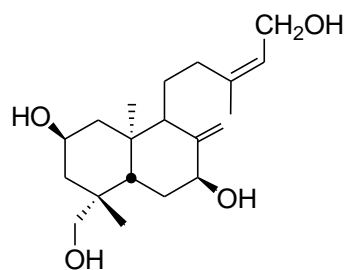
35 R¹ = OH R² = CHO



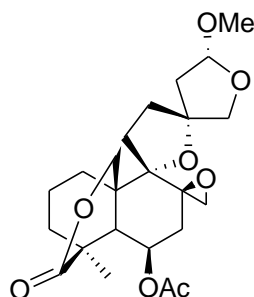
36



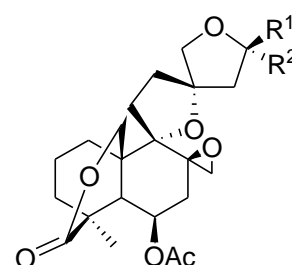
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38



39

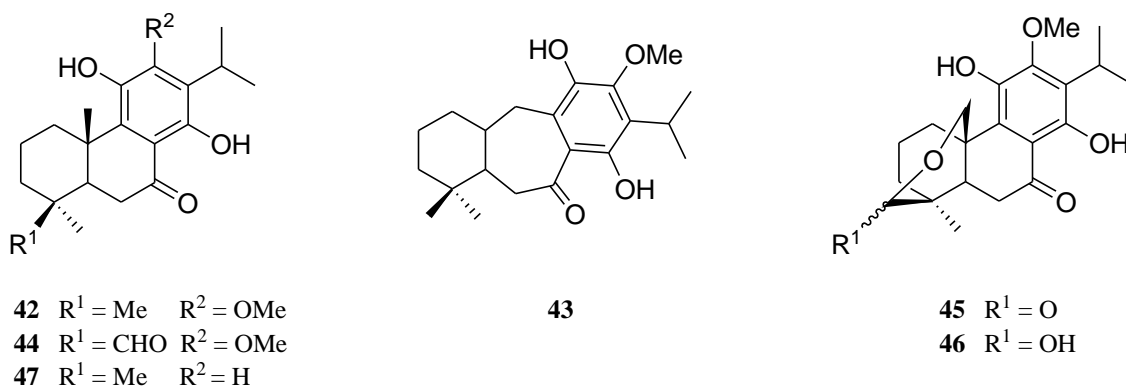


40 R¹ = OMe R² = H

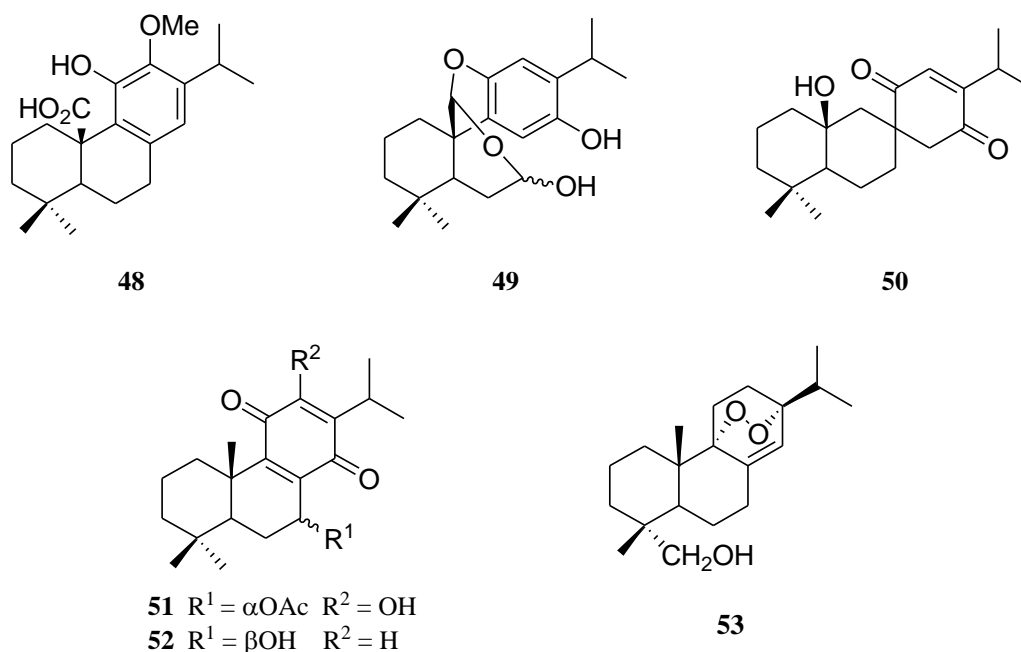
41 R¹ = H R² = OMe

Three diterpenoids, also in this case with the labdane skeleton, have been found in the aerial parts of *Hyptis fasciculata* collected in Brazil.²² The first product was identified as the known²³ methoxynepetaefolin **39**, showing four oxygenated rings, whilst the others are new natural products, 15 β -methoxyfasciculatin **40** and 15 α -methoxyfasciculatin **41**, both also rich in oxygenated rings.

A recent paper²⁴ reports on the investigation of the roots of *Hyptis platanifolia*, again from Brasil. Five abietane derivatives were isolated: two of them are the known inuroyleanol **42**²⁵ and coulterone **43**,²⁵ whilst new products are 19-oxo-inuroyleanol **44**, 11,14-dihydroxy-12-methoxy-7-oxo-8,11,13-abietatrien-19,20 β -olide **45** and 19,20-epoxy-12-methoxy-11,14,19-trihydroxy-7-oxo-8,11,13-abietatriene **46**, the last as a diastereoisomeric mixture at the 19-hydroxy group. No trivial names were given to these new products. Both products **45** and **46** have a lactone or lactol 20,19-ring.



Another species from Northeastern Brazil is *Hyptis martiusii*, popularly known as “cidreira-do-mato”, whose roots were investigated. A paper²⁶ reported the isolation of two known diterpenoids: carnosol **8**¹⁰ and 11,14-dihydroxy-8,11,13-abietatrien-7-one **47**.²⁷ In a second paper²⁸ some new diterpenes were described: 12-O-methyl-carnosic acid **48**, the structurally interesting 7-seco-7(20),11(20)-diepoxy-7,14-dihydroxy-abieta-8,11,13-triene **49**, and a product **50** with a rearranged abietane skeleton, designated as martiusane. In continuation²⁹ two more abietane diterpenes were found: the known 7 α -acetoxy-royleanone **51**³⁰ and the new 7 β -hydroxy-11,14-dioxo-abieta-8,12-diene **52**.

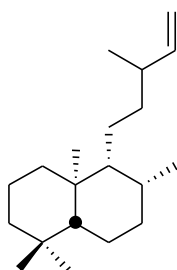
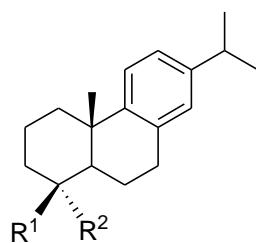
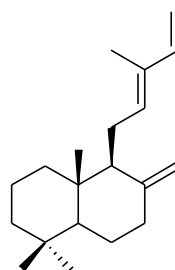
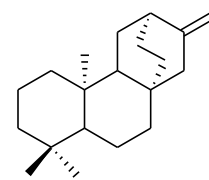
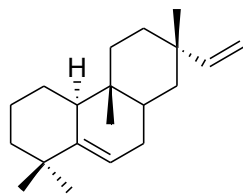
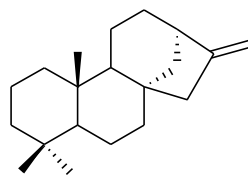
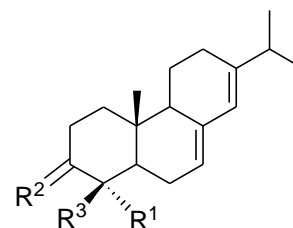
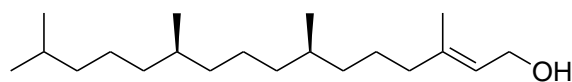
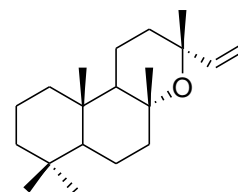


An abietane diterpenoid with high antiplasmodial activity was isolated³¹ from the leaves of *Hyptis suaveolens* collected in Nigeria. It has the structure **53** of 9 α ,13 α -*epi*-dioxiabiet-8(14)-en-18-ol. The same product had been isolated from *Cedrus atlantica*.³²

The **1-53** diterpenoids here listed were isolated from the aerial parts or from the roots or from the whole plant. A large number of investigations on the essential oils of this genus was performed for the

identification of their components, almost exclusively mono- and sesquiterpenes. However in one case also the occurrence of minor amounts of some diterpenes was detected.

This the case of the oil from *Hyptis suaveolens*, largely studied. A first paper³³ on material collected in Venezuela quoted the presence of three unidentified diterpenes. In a sample of the oil from Malaysia the GC analysis indicated the occurrence of six unidentified diterpenes.³⁴ In a sample of oil from Nigeria³⁵ the occurrence of a diterpene hydrocarbon was reported, indicated as 5 β H,8 β H,9 β H,10 α -labd-14-ene **54** but no structural formula was given. Two diterpenes, 8,11,13-abietatriene **55** and 8,11,13-abietatrien-18-ol **56** (syn. dehydroabietol, dehydroabietinol) were identified in the oil from Kumaon, India.³⁶ Particularly rich in diterpenoids was the oil from Cameroon.³⁷ biformene **57**, atisirene **58**, rimuene **59**, abietatriene **55**, phyllocladene **60**, abietinol **61** (syn. abietol), dehydroabietol **56** and the linear diterpene phytol **62** were identified. The oil from North India³⁸ contained abietadiene **63**, abietatriene **55** and dehydroabietol **56**. Many products occurred in the oil from Alfenas (Brazil).^{39,40} abietatriene **55**, abietadiene **63**, abieta-7,13-dien-3-one **64**, abietinol **61**, 4-epi-abietinol **65**,^{41,42} dehydroabietol **56**, manoyloxide **66**. Remarkable differences were observed in the content of diterpenes (and also of monoterpenes and sesquiterpenes) depending on the geographical origin of the oil and on the season of harvesting.

**54****55** R¹ = Me R² = Me**56** R¹ = Me R² = CH₂OH**57****58****59****60****61** R¹ = CH₂OH R² = H,H R³ = Me**63** R¹ = Me R² = H,H R³ = Me**64** R¹ = Me R² = O R³ = Me**65** R¹ = Me R² = H,H R³ = CH₂OH**62****66**

As far as we know, no occurrence of diterpenoids in other oils is reported in the literature.

Concerning the structure of these diterpenoids, it can be remarked that they show the abietane or the labdane skeleton prevalently; only few have different skeleta.

BIOLOGICAL ACTIVITY AND PHARMACOLOGY

The most diffused utilization of species belonging to the *Hyptis* genus is related to their essential oils, obtained, also in industrial scale, from several species. Such oils are largely used in cosmetics and flavouring and as insecticides and insect repellents. Dried whole plants are used for pest control. Oils, parts of plants and extracts find diffused application in ethnopharmacology of tropical countries.

About the biological activities and related pharmacology, wide information is reported in a review² and references therein. Rarely such activities were attributed to single diterpenoids^{2,21,26,29} or to the whole mixtures of terpenoids, but usually to the oils or to the extracts in different solvents. In the case of *H. martiusii*, the cytotoxic and antimitotic activity was tested on the pure diterpenoids.^{26,29} The diterpenoids from *H. spicigera* inhibit the larval growth of the European corn borer.²¹

Therefore, many reports are concerned with activities as expectorant, antihelminthic, antibacteric, antimicrobial, antiviral, antibiotic, antimycotic, antiseptic, antimalaric, antidolorific, anticonvulsive, antioxidant, cytotoxic, anti-tumour. Preparations are used against gastrointestinal disorders, fevers, grippe, cough, asthma, cramps, conjunctivitis, depression, and the most various ailments.

The extract of *H. spicigera* shows antimicrobial, phytotoxic and antifungine properties, and cytotoxic activity on KB cells.^{45,21} The powdered plant is used as insecticide in Africa.⁴³

The ethanolic extract of *H. umbrosa* has a significant antimicrobial activity.⁸ Also the methanolic extract of *H. salzmanii* is active against *Staphylococcus aureus*, *Bacillus subtilis*, *Candida albicans* and *Mycobacterium smegmatis*.⁷ The methanolic extract of *H. albida* is active against *C. albicans* and other Gram-positive and Gram-negative bacteria,⁴⁴ and used in Mexico against gastroenteric diseases.⁴⁵

Some *Hyptis* species are active against schistosomiasis.⁴⁶

The essential oil of *H. mutabilis* has antiulcerogenic activity,⁴⁷ and the essential oil of *H. lanceolata* shows antifungine properties.⁴⁸ Extracts of leaves of *H. mutabilis* are used in Mexico and Brazil against malaria and numberless ailments.^{47,49}

The oil from *H. pectinata* has insecticide⁵⁰ and antiseptic⁵¹ activity. Extracts of *H. pectinata* have antimicrobial, antibacteric activity^{44,51} and are cytotoxic against various cancer cells;⁵¹ the aqueous extract is antinociceptive and antiedematogenic.⁵² It is widely used in Mexico and West Africa.⁵³

The methanolic extract of the roots of *H. fructicosa* shows antibacteric and anti-tumour activity.^{4,54}

Terpenoids from *H. emoryi* have been investigated as antifertilizing agents⁵⁵ and tumour-inhibitors.⁵⁶ A triterpene from *H. rombooides* is cytotoxic in vitro against cells of human hepatome HS-G2.⁵⁷

Extracts of the whole plant of *H. capitata* are reported to be active against HIV, leucemia, many species of cancer, and to have anti-inflammatory, anti-arthritic, anti-diabetic, anti-ulcera, anti-atherosclerosis properties.⁵⁸

H. verticillata has various activities: insecticide, acaricide,⁵⁹ anticancer,⁶⁰ anti-inflammatory, cytotoxic, antimitotic,⁶¹ antimicrobial.⁴⁴

The most investigated species is certainly *H. suaveolens*, largely employed in ethnomedicine of Mexico, Brazil, Central and South America, West Africa, India. Roots, leaves, flowers are commonly used. The oil is active as antimicrobial,^{35,62,63} antibacterial,⁶⁴ fungicide,^{35,48,65} larvicide against *Aedes aegypti*, and also against *Vibrio cholerae*.⁶⁶ A tea prepared from the roots is used as stomachic⁶⁷ in India. The aqueous extract has antinociceptive activity.⁶⁸

A recent paper⁶⁹ reported the anti-inflammatory activity of suaveolic acid (**1**) and suavelol (**2**) occurring in *Hyptis suaveolens* collected in El Salvador; these diterpenoids had been isolated previously³ from the same species.

Table 1 Diterpenes from genus *Hyptis*

No	name	taxa	Ref.
1	suaveolic acid	<i>H. suaveolens</i> (A)	3
2	suavelol	<i>H. suaveolens</i> (A)	3
3	horminone	<i>H. fruticosa</i> (R)	4
4	14-methoxy-taxodione	<i>H. fruticosa</i> (R)	4
5	hyptol	<i>H. fruticosa</i> (R)	6
6	salzol	<i>H. salzmanii</i> (A)	7
7	umbrosone	<i>H. umbrosa</i> (R)	8
8	carnosol	<i>H. dilatata</i> (A)	9
		<i>H. martiusii</i> (R)	26
9	rosmanol	<i>H. dilatata</i> (A)	9
10	methylrosmanol	<i>H. dilatata</i> (A)	9
11	diacetyl-carnosol	<i>H. dilatata</i> (A)	9
12	triacetyl-rosmanol	<i>H. dilatata</i> (A)	9
13	diacetyl-methylrosmanol	<i>H. dilatata</i> (A)	9
14	diacetyl-ethylrosmanol	<i>H. dilatata</i> (A)	9
15	triacetyl-isorosmanol	<i>H. dilatata</i> (A)	9
16	triacetyl-epirosmanol	<i>H. dilatata</i> (A)	9
17	diacetyl-carnosic acid	<i>H. dilatata</i> (A)	9

18	diacetyl-carnosic acid methyl ester	<i>H. dilatata</i> (A)	9
19	acetyl-pisiferic acid methyl ester	<i>H. dilatata</i> (A)	9
20	diacetyl-epimethylrosmanol	<i>H. dilatata</i> (A)	9
21	diacetyl-epiethylrosmanol	<i>H. dilatata</i> (A)	9
22	ethylrosmanol	<i>H. dilatata</i> (A)	9
23	isorosmanol	<i>H. dilatata</i> (A)	9
24	epirosmanol	<i>H. dilatata</i> (A)	9
25	epimethylrosmanol	<i>H. dilatata</i> (A)	9
26	epiethylrosmanol	<i>H. dilatata</i> (A)	9
27	carnosic acid	<i>H. dilatata</i> (A)	9
28	pisiferic acid	<i>H. dilatata</i> (A)	9
29	lactone	<i>H. dilatata</i> (A)	9
30	diacetyl-esquirolin B	<i>H. dilatata</i> (A)	9
31	esquirolin B	<i>H. dilatata</i> (A)	9
32	19-acetoxy-2 α ,7 α ,15-trihydroxy-labda-8(17),(13Z)-diene	<i>H. spicigera</i> (A)	21
33	15,19-diacetoxy-2 α ,7 α -dihydroxy-labda-8(17),(13Z)-diene	<i>H. spicigera</i> (A)	21
34	19,7 α ,15-triacetoxy-2 α -hydroxy-labda-8(17),(13Z)-diene	<i>H. spicigera</i> (A)	21
35	19-acetoxy-2 α ,7 α -dihydroxy-labda-8(17),(13Z)-diene-15-al	<i>H. spicigera</i> (A)	21
36	19-acetoxy-7 α ,15-dihydroxy-labda-8(17),(13Z)-dien-2-one	<i>H. spicigera</i> (A)	21
37	19-acetoxy-2 α ,7 α -dihydroxy-labda-14,15-dinor-labd-8(17)-en-13-one	<i>H. spicigera</i> (A)	21
38	2 α ,7 α ,15,19-tetrahydroxy- <i>ent</i> -labda-8(17),(13Z)-diene	<i>H. spicigera</i> (A)	21
39	methylnepetaefolin	<i>H. fasciculata</i> (A)	22
40	15 β -methoxyfasciculatin	<i>H. fasciculata</i> (A)	22
41	15 α -methoxyfasciculatin	<i>H. fasciculata</i> (A)	22
42	inuroyleanol	<i>H. platanifolia</i> (R)	24
43	coulterone	<i>H. platanifolia</i> (R)	24
44	19-oxo-inuroyleanol	<i>H. platanifolia</i> (R)	24
45	11,14-dihydroxy-12-methoxy-7-oxo-8,11,13-abietatrien-19,20- β -olide	<i>H. platanifolia</i> (R)	24
46	19,20-epoxy-12-methoxy-11,14,19-trihydroxy-7-oxo-8,11,13-abietatriene	<i>H. platanifolia</i> (R)	24
47	11,14-dihydroxy-8,11,13-abietatrien-7-one	<i>H. martiusii</i> (R)	26
48	12-O-methyl-carnosic acid	<i>H. martiusii</i> (R)	28
49	7-seco-7(20),11(20)-diepoxy-7,14-dihydroxy-abieta-8,11,13-triene	<i>H. martiusii</i> (R)	28
50	martiusane	<i>H. martiusii</i> (R)	28
51	7 α -acetoxy-royleanone	<i>H. martiusii</i> (R)	29
52	7 β -hydroxy-11,14-dioxo-abieta-8,12-diene	<i>H. martiusii</i> (R)	29

53	9 α ,13 α - <i>epi</i> -dioxiabiet-8(14)-en-18-ol	<i>H. suaveolens</i> (A)	31
54	5 β H,8 β H,9 β H,10 α -labd-14-ene	<i>H. suaveolens</i> (EO)	35
55	8,11,13-abietatriene	<i>H. suaveolens</i> (EO)	36-40
56	8,11,13-abietatrien-18-ol	<i>H. suaveolens</i> (EO)	36,38-40
57	biformene	<i>H. suaveolens</i> (EO)	37
58	atisirene	<i>H. suaveolens</i> (EO)	37
59	rimuene	<i>H. suaveolens</i> (EO)	37
60	phyllocladene	<i>H. suaveolens</i> (EO)	37
61	abietinol	<i>H. suaveolens</i> (EO)	37,39-40
62	phytol	<i>H. suaveolens</i> (EO)	37
63	abietadiene	<i>H. suaveolens</i> (EO)	38,39-40
64	abieta-7,13-dien-3-one	<i>H. suaveolens</i> (EO)	39,40
65	4- <i>epi</i> -abietinol	<i>H. suaveolens</i> (EO)	39,40
66	manoyloxide	<i>H. suaveolens</i> (EO)	39,40

R = roots. A = aerial parts. EO = essential oil.

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