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Diterpenoids from Roots and Aerial Parts of the Genus *Stachys*

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Abstract: The occurrence of diterpenoids from roots and aerial parts of the species of the genus *Stachys* (Lamiaceae, Labiatae) is reviewed. The presence of these diterpenoids in other taxa and their biological properties have been also reviewed.

Keywords: Diterpenoids; Lamiaceae*, Stachys;* roots; aerial parts; biological properties.

The family Labiatae (Lamiaceae) is widespread in tropical and subtropical regions, but the chief centre is the Mediterranean region. A rich genus is *Stachys*, occurring in about 300 species as annual or perennial herbs or small shrubs. The stem vary from 50–300 cm (20–120 in) tall, with simple, opposite, triangular leaves, 1–14 cm (0.39–5.5 in) long with serrate margins. In most species, the leaves are softly hairy. The flowers are 1 to 2 cm (0.39 to 0.79 in) long, clustered in the axils of the leaves on the upper part of the stem. The corolla is 5-lobed with the top lobe forming a 'hood', varying from white to pink, purple, red or pale yellow. The name is derived from the Greek word σταχυς (*stachys*), meaning "an ear of grain", and refers to the fact that the inflorescence is often a spike, whereas one of the common name, woundwort, derives from the past use of certain species for the treatment of wounds. The genus is present in Europe, Asia, Africa, Australasia and North America. Several species are cultivated as ornamentals such as *S. byzantina* that is a popular decorative garden plant or as food (Chinese artichoke, *S. affinis*) [1-6]. Many species have been investigated, and many kinds of secondary metabolites have been isolated, mainly flavonoids, iridoids, terpenoids, from the aerial parts and the roots.

Recently the occurrence of diterpenoids in the essential oils from *Stachys* has been reviewed [7]; the present review is restricted to the chemistry of the diterpenoids, that have been isolated from aerial parts and roots of some species.

The first species to be investigated in order to seek for diterpenoids was *Stachys annua*, collected in Moldavia. A first paper [8] of the Moldavian researchers in 1969 reported the occurrence of three compounds in the aerial parts, a diacetate and two monoacetates, that by saponification with

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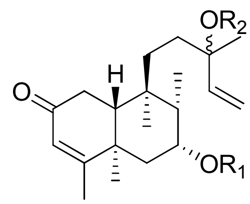
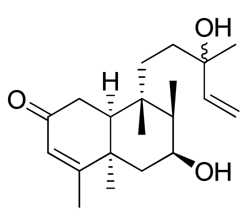
alkali yielded the same ketodiol $C_{20}H_{32}O_3$ diterpenoid, called stachysolone and, the structure of this product was elucidate three years later as (**1**) in a second paper [9]; it is a bicyclic compound and has the neoclerodane skeleton, a ketogroup at C-2, a secondary hydroxy group at C-7, a tertiary hydroxy group at C-13. By acetylation it gives back the diacetyl (**2**), the 7-monoacetyl (**3**) and the 13-monoacetyl (**4**) derivatives originally occurring in the plant. Its stereochemistry was further studied [10].



1 R_1 = H R_2 = H
2 R_1 = Ac R_2 = Ac
3 R_1 = Ac R_2 = H
4 R_1 = H R_2 = Ac

Continuing the investigation of *S. annua*, three new similar diterpenoids were isolated and called as annuanone (**5**) [11, 12], stachylone (**6**) [11, 13] and stachone (**7**) [11, 13]. It is worthy of remark that annuanone (**5**) has a *cis* (5α,10α) linkage of the rings instead of the usual *trans* (5α, 10β) present in the other diterpenoids occurring in this species. The configuration of (**6**) and (**7**) at C-4 was not surely proved. Also the configuration at C-13 was not indicated for the (**1**-**7**) compounds. All these compounds have the *neo*-clerodane skeleton. Compounds **5**, **6** and **7** were later detected in several other species of *Stachys* of the flora of Ukraine [14] (Table 1).



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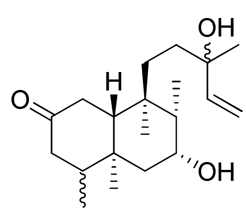

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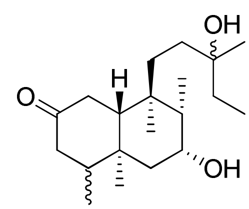

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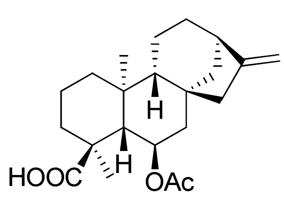
The same researchers investigated the species *Stachys silvatica* and isolated [15] from the aerial parts a new diterpenoid, stachysic acid (**8**). It is a tetracyclic compound with an *ent*-kaurane skeleton. The same plant contained also the alcohols 6β-hydroxy-*ent*-kaur-16-ene (**9**) and 6β,18-dihydroxy-*ent*-kaur-16-ene (**10**). All the products show the unsaturation at C-16.



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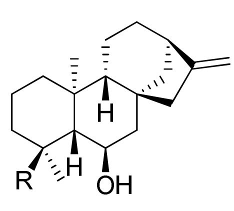
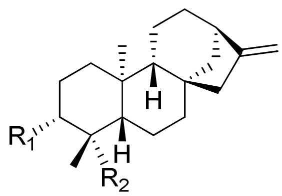


9 R = CH_3
10 R = CH_2OH

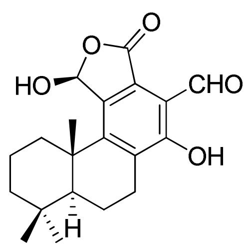
Three diterpenoids with *ent*-kaurane skeleton were isolated [16] from *Stachys lanata* (now indicate as *Stachys byzantina* [3]). They are the acetoxy-acid (**11**), previously isolated from *Helichrysum dendroideum* [17], the new hydroxy-acid (**12**) and the already known (Table 1) 3α,19-dihydroxy-*ent*-kaur-16-ene (**13**).

The investigation of the aerial parts of *Stachys recta*, a species growing in Italy, yielded [26] the three acetylderivatives (**2**), (**3**), and (**4**) of stachysolone (**1**), previously isolated from *Stachys annua* [9]. The improved NMR analysis was useful for confirming their stereochemistry, with the exception of C-13.

The roots of the species *Stachys officinalis* (synonimus *Betonica officinalis*), collected in Ukraine, yielded [27] a diterpene lactone named betolide that was assigned the structure (**14**), with a novel transposed tricyclic skeleton similar to abietane but substituted at C-11, C-12 and C-13, that therefore does not conform to the isoprene rule. The structure was confirmed by X-ray analysis.



11 R_1 = OAc R_2 = COOH
12 R_1 = OH R_2 = COOH
13 R_1 = OH R_2 = CH_2OH



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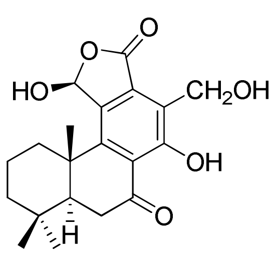
A second investigation of the roots of *Stachys officinalis* was performed [28] on material cultivated in the Botanic Garden of the University of Shizuoka, Japan. A new diterpene betonicolide (**15**) was isolated, structurally similar to betolide (**14**). Also four diterpene glucosides were isolated, betonicosides A (**16**), B (**17**), C (**18**) and D (**19**). Their aglycone (**20**) is identical with the product obtained [27] by $NaBH_4$ reduction of betolide (**14**). Betolide (**14**) was later found in other species of *Stachys* [29] (Table 1).



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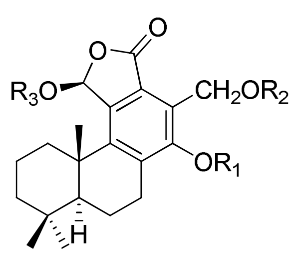
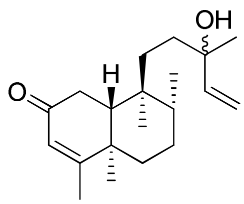


16 R_1 = Glu R_2 = H R_3 = Glu
17 R_1 = Glu R_2 = H R_3 = H
18 R_1 = H R_2 = H R_3 = Glu
19 R_1 = H R_2 = Glu R_3 = H
20 R_1 = H R_2 = H R_3 = H

Stachysolone (**1**) and its 13-monoacetylderivative (**4**) have been also isolated from *Stachys aegyptiaca* collected near Cairo [30].

A species harvested in Cyrenaica, *Stachys rosea*, yielded [31] two new neoclerodane diterpenoids, roseostachenone (**21**) and roseostachone (**22**). A reinvestigation of the plant [32] led to the isolation of two new neoclerodanes, roseostachenol (**23**) and roseotetrol (**24**), and of the known 13-*epi*-sclareol (**25**) (see Table 1). Also for the (**21**-**24**) compounds the configuration at C-13 was not proved. Compounds **21** and **23** were later found in other species (Table 1).



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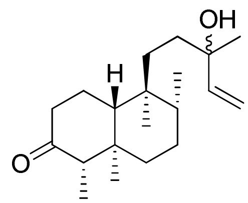

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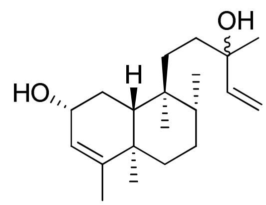

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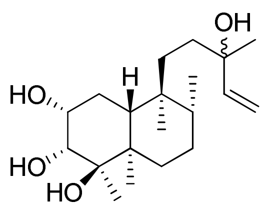

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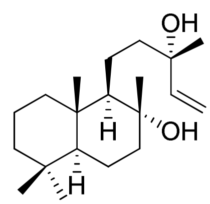

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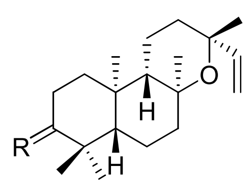
The investigation of *Stachys mucronata*, collected in the island of Karpathos (Greece), gave [44] two *ent*-labdane diterpenoids, ribenone (**26**) and ribenol (**27**). Both products had been isolated from other plants (see Table 1), but never from *Stachys* species.



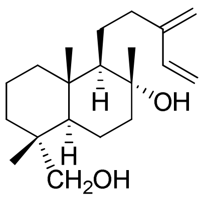
26 R = O
27 R = αOH, βH

The species *S. plumosa*, native of the Balkan peninsula but cultivated by the Botanic Garden of the University of Milano, yielded three new labdane diterpenoids [58]. Their structures are very interesting. The first product showed the identical spectroscopic and physical data of 6-deoxyandalusol, a laevorotatory compound occurring in *Sideritis arborescens* [59]: however the rotatory power of the new product was identical but dextrorotatory. Since the absolute configuration of the diterpenoid from *Sideritis arborescens* had been proved to belong to the *ent*-labdane series and must be indicated now as (-)-6-deoxyandalusol, the new product is its enantiomer and belongs to the *normal*-labdane series and therefore must indicated as (+)-6-deoxyandalusol (**28**). The second product was proved to be the enantiomer of (-)-13-epijabugodiol (*ent*-labdane series) occurring in *Sideritis arborescens* ssp. *pauli* [60]: therefore it is (+)-13-epijabugodiol (**29**) and belongs to the *normal*-labdane series. The third product was given the trivial name (+)-plumosol: its absolute configuration was not proved, and the tentative structure (**30**) (*normal*-labdane series) was suggested. (+)-6-Deoxyandalusol (**28**) was later found in *Stachys ionica* and *S. distans* [61].

Table 1. Diterpenoids Isolated from Genus *Stachys* and their Occurrence in other Genus

No	Name	Taxa	
1	stachysolone	*S. annua*	[8],[9],[10]
		S. aegyptiaca	[30]
2	diacetyl- stachysolone	*S. annua*	[9]
		S. recta	[26]
3	7-monoacetyl-stachysolone	*S. annua*	[9]
		S. recta	[26]
4	13-monoacetyl-stachysolone	*S. annua*	[9]
		S. recta	[26]
		S. aegyptiaca	[30]
5	annuanone	*S. annua*	[11],[12],[14]
		S. atherocalix,	[14]
		S. balansae	[14]
		S. iberica	[14]
		S. inflata	[14]
		S. palustris	[14]
		S. silvatica	[14]
6	stachylone	*S. annua*	[11],[13],[14]
		S. atherocalix,	[14]
		S. balansae	[14]
		S. iberica	[14]
		S. inflata	[14]
		S. palustris	[14]
		S. silvatica	[14]
7	stachone	*S. annua*	[11],[13],[14]
		S. atherocalix,	[14]
		S. iberica	[14]
		S. inflata	[14]
		S. palustris	[14]
		S. silvatica	[14]
8	stachysic acid	*S. silvatica*	[15]
9	6β-hydroxy-*ent*-kaur-16-ene	*S. silvatica*	[15]
10	6β,18-dihydroxy-*ent*-kaur-16-ene	*S. silvatica*	[15]
11	3α-acetoxy-19-kaur-16-en-oic acid	*S. lanata*	[16]
		Helichrysum dendroideum	[17]
12	3α-hydroxy-19-kaur-16-en-oic acid	*S. lanata*	[16]
13	3α,19-dihydroxy-*ent*-kaur-16-ene	*S. lanata*	[16]
		Beyeria leschenaultia	[18]
		Goodenia strophiolata	[19]
		Gochnatia polymorpha ssp. *polymorpha*	[20]
		Aristolochia rodiguesii	[21]
		Jamesoniella tasmanica	[22]
		Cacalia pilgeriana	[23]
		Helichrysum dendroideum	[24]
		Laetia thamnia	[25]
14	betolide	*S. officinalis*	[27],[28]
		S. germanica	[29]
		S. silvatica	[29]
		S. thracica	[29]
		S. plumosa	[29]

		Betonica bulgarica	[29]
		Betonica scardica	[29]
15	betonicolide	*S. officinalis*	[28]
16	betonicoside A	*S. officinalis*	[28]
17	betonicoside B	*S. officinalis*	[28]
18	betonicoside C	*S. officinalis*	[28]
19	betonicoside D	*S. officinalis*	[28]
21	roseostachenone	*S. rosea*	[31]
		Amoora stellato-squamosa	[33]
		Aristolochia chamissonis	[34]
		Viguiera tucumanensis	[35]
		Agelas nakamurai	[36]
22	roseostachone	*S. rosea*	[31]
23	roseostachenol	*S. rosea*	[32]
		Aristolochia chamissonis	[34]
24	roseotetrol	*S. rosea*	[32]
25	13-*epi*-sclareol	*S. rosea*	[32]
		Cistus incanus ssp. *creticus*	[37]
		Gnaphalium pellitum	[38]
		Gnaphalium graveolens	[38]
		Pseudognaphaliun cheiranthifolium	[39]
		Salvia sclarea	[40]
		Egletes viscosa	[41]
		Coleus forskohlii	[42]
		Pseudognaphaliun heterotrichium	[43]
26	ribenone	*S. mucronata*	[44]
		Solidago misouriensis	[45]
		Sideritis lotsyi	[46]
		Excoecaria agallocha	[47],[48]
		Avicenna officinalis	[49]
27	ribenol	*S. mucronata*	[44]
		Sideritis canariensis	[50]
		Sideritis varoi	[51]
		Sideritis hirsuta ssp. *nivalis*	[52]
		Sideritis varoi ssp. *cuatrecasasii*	[53]
		Sideritis varoi ssp. *nijarensis*	[54]
		Excoecaria agallocha	[48]
		Cistus clusii	[55]
		Sideritis javalambrensis	[56]
		Cistus creticus	[57]
28	(+)-6-deoxyandalusol	*S. plumosa*	[58]
		S. ionica	[61]
		S. distans	[61]
29	(+)-13-epijabugodiol	*S. plumosa*	[58]
30	(+)-plumosol	*S. plumosa*	[59]
31	phytol nonadecanoate	*S. byzanthina*	[62]
		Jasminum ssp.	[63]



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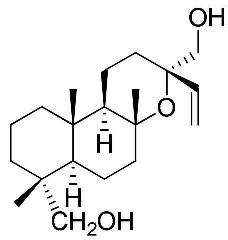

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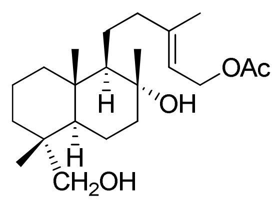

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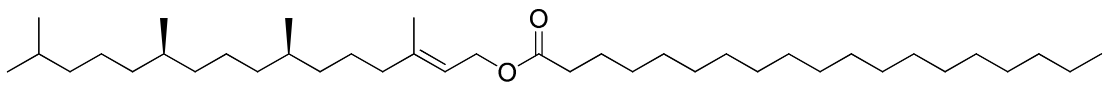
A last paper on aerial parts reported [52] the occurrence of a linear diterpenoid, the ester of phytol with nonadecanoic acid (**31**), in *Stachys byzanthina* growing in Iran, previously isolated in the jasmine flowers [63].



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It is worthy to be remarked that the aerial parts of several species of *Stachys*, investigated by our group [64], were found to contain no diterpenoids. This is the case of *S. germanica* (from Sicily), *S. ocymastrum* (from Sicily), *S. tournefortii* (from Crete), *S. cretica* subsp. *cretica* (from Crete), *S. glutinosa* (from Northern Italy), *S. floridana* (from South Carolina, USA), *S. recta* (from Lybia). The last case is particularly remarkable, as *S. recta* collected in Italy did contain diterpenoids [26].

No diterpenoids had been found also in the aerial parts of *S. palaestina* and *S. libanotica* collected in Lebanon [65].

In total, 30 diterpenoids were isolated, 25 beeing new compounds. They show the labdane or kaurane skeleta, and some (**14**-**19**) a novel unprecedented skeleton.

Biological activity and pharmacology

Many species of *Stachys* are used in ethnomedicine under the form of extracts, decoctions, ointments and plants of this genus have long been applied to treat genital tumors, sclerosis of the spleen, inflammatory tumors and cancerous ulcers [66]. Modern investigations proved the presence of several biological activities in aerial parts and roots. In some cases the activity was attributed to isolated products, mainly flavonoids and phenylethanoid glycosides. As far as we know from literature screening, in no case a biological activity was attributed to diterpenoids.

Preparations from many species are reported as cholagogue, hypotensive, cardioprotective, analgesic, anxiolytic, antipyretic, immunostimulating, antinephritic, antiallergic, antiinflammatory, antioxidant, antimicrobic, antibacteric [67-70]. Further informations can be found in reviews like [71] and [72].

Some of the compounds isolated form species of *Stachys* have shown several biological properties.

3α,19-Dihydroxy-*ent*-kaur-16-ene (**13**) was evaluated for cytotoxicity against human prostate (22Rv1, LNCaP), colon (HT29, HCT116, SW480, SW620), and breast (MCF-7) tumor cells at concentrations ranging from 6 to 50 µg/mL. The kaurene showed activity in all cell lines tested, with the prostate cells demonstrating the most sensitivity [25].

In the course of studies on the isolation of bioactive compounds from the roots of *Coleus forskohlii*, a traditional herb in India, 13-epi-sclareol (**25**) was isolated, and was showed to have antiproliferative activity in breast and uterine cancers in vitro. The antiproliferative activity of 13-epi-sclareol is comparable to Tamoxifen in terms of IC50 and also showed concentration dependent increased apoptotic changes in the breast cancer cell line, MCF-7 [42]. 13-Epi-sclareol (**25**) showed a good antibacterial activity against several bacteria [43, 73]. The interaction of 13- epi-sclareol (**25**) with the bacterial respiratory chain was analyzed. The compound inhibited oxygen consumption of intact Gram-positive cells, but not with Gram-negative bacteria. The compound inhibited NADH oxidase and cytochrome c reductase activities, while coenzyme Q reductase and the cytochrome c oxidase activities were not affected. These results suggest that the target site of 13-epi-sclareol is located between coenzyme Q and cytochrome c. Using cytoplasmic membrane fractions, the results of the analysis of the enzyme activities associated with the respiratory chain complexes were the same for both Gram-positive and Gram-negative bacteria, indicating that the compound has no access to the cytoplasmic membrane of intact Gram-negative bacteria. Thus, the Gram-negative envelope may act as a physical barrier that prevents the access of this compound to the site of action [74].

Ribenone (**26**) was tested to evaluate its activity its activity against *Leishmania donovani* and was showed to inhibit growth with significant antileishmanial activity [75, 76]. On the other hand 13-epi-sclareol (**25**) and ribenol (**27)** had moderate activity aginst *Leishmania donovani* promastigotes [77].

Ribenone (**26**) and ribenol (**27**) were tested as possible anti-tumor promoters. Ribenone (**26**) exhibited remarkable inhibitory effects on EBV-EA activation and preserved a high viability of Raji cells whereas ribenol (**27**) was shown to be less active [78]. Ribenol (**27**) isolated from the leaves and from the fruits of *Cistus creticus* subsp. *creticus*, was found to be active against human leukemic cell lines [79] and several tumor cell lines [57].

Ribenone (**26**), isolated from the mangrove *Avicennia officinalis*, did not show antifungal activities against *Rhizopus oryzae* and *Aspergillus niger* and neither exhibited antibacterial activity against *Bacillus subtilis* [49].

Ribenol (**27**) was shown to have a moderate antibacterial activity against the Gram-positive bacteria *Staphylococcuis aureus* and the Gram-negative bacteria *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, *Acinetobacter anitratus* and *Proteus mirabilis* [80].

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