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Biological Activity of Diterpenoids Isolated from Anatolian Lamiaceae Plants

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Abstract: In this study, antibacterial, antifungal, antimycobacterial, cytotoxic, antitumor, cardiovascular, antifeedant, insecticidal, antileishmanial and some other single activities of diterpenoids and norditerpenoids isolated from Turkish Lamiaceae plants, are reviewed. The diterpenoids were isolated from species of *Salvia*, *Sideritis*, and *Ballota* species growing in Anatolia. Fifty abietanes, ten kaurenes, seven pimaranes, six labdanes with their biological activities were reported. While twenty five diterpenoids showed antibacterial activity, eight of which showed activity against fungi. The most cytotoxic one was found to be taxodione **(44)** isolated from species of *Salvia*. Antifeedant, insecticidal and insect repellent activity of kaurenes, antimycobacterial activity and cardioactivity of abietanes and norabietanes together with labdanes were also reported.

Keywords: Biological activity; Diterpenoids, Lamiaceae, *Salvia*, *Sideritis*, *Ballota*, Antibacterial, Antifungal, Antimycobacterial, Cytotoxic, Cardiovascular and Insecticidal Activities.

1. Introduction

Flora of Türkiye has more than 12.000 species of plants, represented by 173 families and 1225 genera and over 2650 endemic species. In Türkiye, Labiatae (Lamiaceae) family is the most endemic species containing family, represented by 45 genera and 550 species with over 735 taxa [1, 2]. From this family, 28 genera are widely distributed and over 240 species are endemic to Türkiye. Many of Lamiaceae family plants have been used in Anatolia as folk medicines [3] to treat various health problems such as common cold, throat infections, psoriasis, seboreic eczama, hemorrhage, menstrual disorders, miscarriage, ulcer, spasm and stomach problems since ancient time. Their constituents, particularly diterpenoids and triterpenoids have been found to be antiseptic, antibacterial, anti-inflammatuar, cytotoxic, cardioactive etc. [4, 5]. Although there are some studies by several groups on the Lamiaceae family plants growing in Türkiye, this diverse family is still waiting to be explored. But, the essential oils of Anatolian Lamiaceae plants have been extensively investigated by Prof. Başer [6] and his group. The most avaliable data for Anatolian Lamiaceae plant species, especially on their

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diterpenoids, can be found on *Salvia* species. They have been studied by Ulubelen and Topçu chemically and when possible for their biological activity for over thirty years [4, 5]. The second most studied Lamiaceae family plant for diterpenic constituents growing in Türkiye, is *Sideritis* species. However, considering that only 15 species, from 46 species and 10 taxa, have been studied so far, many are still waiting to be investigated. The other chemically studied Lamiaceae plants [1, 2] are *Stachys, Phlomis, Ballota, Teucrium, Ajuga, Nepeta, Lavandula* and *Scutellaria* species by several Turkish groups. But, biological activity studies on their isolated diterpenic constituents are very limited. To our best knowledge, more than 200 new diterpenoids and 300 known diterpenoids were isolated from plants growing in Türkiye and biological activity data are avaliable only for 110 of the isolated diterpenoids from Turkish species on Web of Science database till the year of 2006. In this study, all activities of the isolated diterpenoids from Turkish plants are reported. However, there are increasing number of biological activity studies on Lamiaceae plant extracts rather than their constituents or at least their diterpenoids in the last decade.

2. Biological Activities of Diterpenoids

2.1 Antibacterial activity

The most biological activity data are avaliable on the abietane diterpenoids from Turkish plant species. The abietane diterpenoids generally showed activity against *Staphylococcus aureus*. 2,3-Dehydrosalvipisone **(1)** and 7-oxoroyleanone **(2),** from *Salvia sclarea*, displayed activity only against *S. aureus* [7]. A series abietanes, which were isolated from *S. hypargeia* and named hypargenins were screened against standard bacteria. Among them, hypargenin A **(3)** and hypargenin B **(4)** were found to be active against *S. aureus* and *K. pneumonia* while hypargenin C **(5)** showed activity against *S. aureus* and *B. subtilis* [8]. The other abietane hypargenin D **(6)**, isolated from *Salvia hypargeia* [8], showed activity only against *B. subtilis* while hypargenin F **(7)** was found to be active against *B. subtilis, S. epidermidis* and *P. aureginosa* [8]. The pisiferic acid **(8)** derivatives, O-methyl pisiferic acid **(9)** [9] and O-methyl pisiferic acid methyl ester **(10)** [9] from *Salvia bleapharochelana,* showed activity against *B. subtilis* and *E. coli*, respectively. The widely found abietane diterpenoids in Turkish *Salvia* species ferruginol **(11)** [4, 5, 9] , horminone **(12)** and 7-acetyl horminone **(13)** [4, 5, 9, 10,11], sugiol **(14)** and 1-oxo-ferruginol **(15)** [9] showed good activity against *S. aureus*, *S. epidermidis* and *B.subtilis,* the latter was also found to be slightly active against *P. mirabilis.* The rearranged diterpenoid candidissiol **(16)** [12] displayed good activity against *S. epidermidis* and *P. mirabilis*, while the other rearranged diterpenoid microstegiol **(17)** [11, 13] was found to be slightly active against *B. subtilis.* Forskalinone **(18)** [14], isolated from *Salvia forskahlei*, was reported to be slightly active against *S. epidermidis* and *E. faecalis*.

Multicaulin **(19)**, 12-demethylmulticauline **(20)**, multiorthoquinone **(21)**, 2-demethylmultiorthoquinone **(22)** and 12-methyl-5-dehydroacetylhorminone **(23)**, isolated from *Salvia multicaulis*, have been tested against bacterial strains. While the new compound **(19)** showed very high activity against *S. aureus, E. coli*, *P. mirabilis* and β-hemolytic *Streptococcus*, the other new compound **(20)** showed moderate activity against *K. pneumonia*, *β-hemolytic Streptococcus* and *P. aeruginosa* [15].

Table 1. Antibacterial activity data of diterpenoids isolated from Turkish Lamiaceae plants

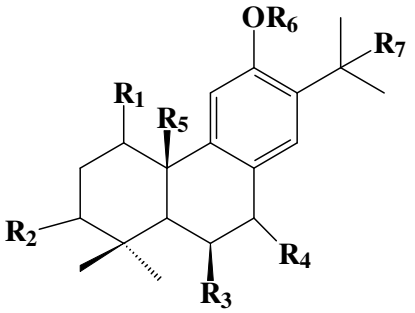
Compounds	*S.aureus*	*S.epidermidis*	*B.subtilus*	*P.mirabilis*	*E.faecalis*	*P.aureginosa*	*K.pneumonia*	*E.coli*
Abietanes								
1	10.5	NT	NT	NA	NT	NT	NT	NT
2	54.0 [a]	NT	NT	NA	NT	NT	NT	NT
3	15.6 [a]	NA	NA	NT	NT	NA	15.6 [a]	NT
4	125.0 [a]	NA	NA	NT	NT	NA	125.0 [a]	NT
5	125.0 [a]	NA	15.6 [a]	NT	NT	NA	NA	NT
6	NA	NA	62.5	NT	NT	NA	NA	NT
7	125 [a]	62.5 [a]	NA	NT	NT	125 [a]		
9	NA	NA	6.5 [a]	NA	NA	NA	NA	NA
10	NA	NA	NA	NA	NA	NA	NA	6.5 [a]
11	>250 [a]	>250v	>250 [a]	NT	NT	NT	NT	NA
12	6.5 [a]	1.5 [a]	1.5 [a]	NA	NA	NA	NA	NA
13	10.0 [a]	6.0 [a]	3.0 [a]	NA	NA	NA	NA	NA
14	NA	NA	>600	NA	NA	NA	NA	NA
15	15.6 [a]	15.6 [a]	15.6 [a]	>250	NA	NA	NA	NA
16	NA	8.0 [a]	NA	8.0 [a]	NA	NA	NA	NA
17	NT	NT	>250 [a]	NT	NT	NT	NT	NT
18	NA	670 [a]	NA	NA	168 [a]	NA	NA	NA
19	0.2 [a]	NT	NT	1.4 [a]	NA	NA	NA	0.7 [a]
20	NA	NT	NT	NA	NA	15.6 [a]	15.6	NA
21	0.1	NT	NT	NA	2.0 [a]	0.5 [a]	NA	NA
22	NA	NT	NT	NA	NA	NA	NA	4.6
23	NA	NT	NT	NA	NA	NA	7.2 [a]	NA
24	NT	16.8 [a]	32.9 [a]	NT	NT	NT	NT	NT
25	>128 [a],*							
Labdanes								
26	48.2 [a]	NA	NT	NA	NT	16 [b]	22 [b]	NA
27	13.7 [a]	NT	NT	NA	NT	NT	NT	NT
28	25.0 [a]	NT	25.0 [a]	NT	25 [a]	25.0 [a]	25 [a]	50.0 [a]
29	25.0 [a]	NT	NT	NT	25 [a]	50.0 [a]	25 [a]	50.0 [a]
30	25.0 [a]	NT	25.0 [a]	NT	25 [a]	50.0 [a]	25 [a]	50.0 [a]
Pimaranes								
31	9.0 [a]	18.0 [a]	9.0 [a]	NA	NA	NA	NA	NA
32	12 [b]	NA	20 [b]	NA	NA	NA	NA	NA
34	250 [c]	250 [c]	NT	NT	NT	NT	>2.0 [c]	>2.0 [c]
33+34	24 [b]	NA	NT	NT	NT	14 [b]	24 [b]	NA
35	NA	NT	NT	3.6 [a]	3.6 [a]	NA	NA	NA
Kaurenes								
36	NA	NT	NA	>625 [c]	>625 [c]	>625 [c]	NA	>625 [c]
37	>625 [c]	NT	>625 [c]	>625v	NA	NA	NA	NA
38	NA	NT	NA	NA	NA	NA	>625	NA
39	>300 [c]	NT	NA	NA	>300 [c]	>300 [c]	>300 [c]	>300 [c]
40	NA	NT	>625 [c]	NA	NA	NA	NA	NA

[a]MIC values as µg/mL [b]Zone diatemeter as mm [c]MIC_{50} (mg/mL);*methicillin resistant *S. aureus*.NT: Not tested, NA: Not active.

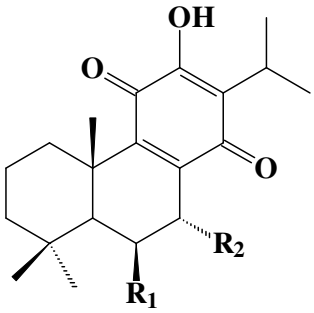
The new norditerpenoid multiorthoquinone **(21)** was reported to have strong activity against β-hemolytic *Streptococcus, E. faecalis* and *P. aeruginosa*, and 2-demethyl multiorthoquinone **(22)** was active only against a gram negative bacteria *E.* coli. The compound **(23)** was found to be active only against *K. pneumonia* [15], the two abietane diterpenoids (**18)** and **(21)** had an effect on *E. faecalis*. The abietane diterpenoid bractealine **(24),** isolated from *S. bracteata*, [16] showed activity against *S. epidermidis* and *B. subtilis*.

The oxidized natural abietanes such as ferruginol **(11)**, royleanone **(25)**, sugiol **(14)** taxodione were synthesized by a Japanese group and their activities were reported against methicilin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Entrococcus* (VRE) [17].

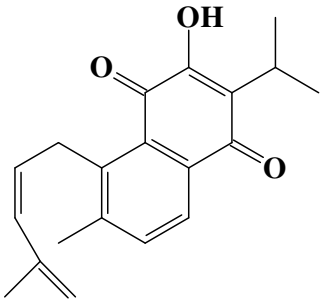
Figure 1. Bioactive abietane diterpenoids from Turkish Lamiaceae plants



	R_1	R_2	R_3	R_4	R_5	R_6	R_7
3	=O	H	OH	=O	Me	H	H
4	H	H	H	=O	Me	H	OH
5	H	H	=O	=O	Me	H	H
8	H	H	H	H	COOH	H	H
9	H	H	H	H	COOMe	H	H
10	H	H	H	H	COOMe	Me	H
11	H	H	H	H	Me	H	H
14	H	H	H	=O	Me	H	H
15	=O	H	H	H	Me	H	H



	R_1	R_2
2	H	=O
12	H	OH
13	H	OAc
25	H	H
43	OH	H



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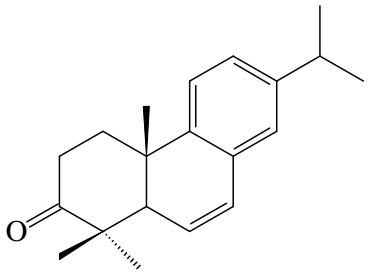

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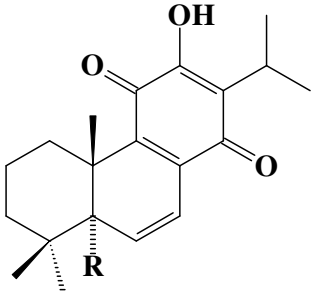
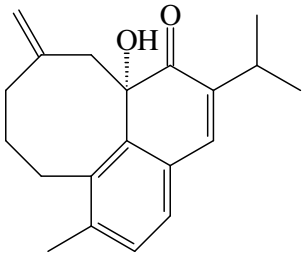


R

7 **OH**
64 **H**

Figure 1. continued



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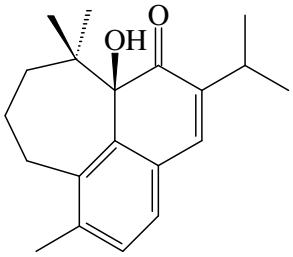

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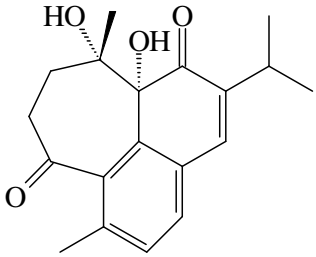

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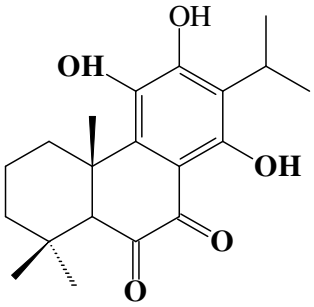

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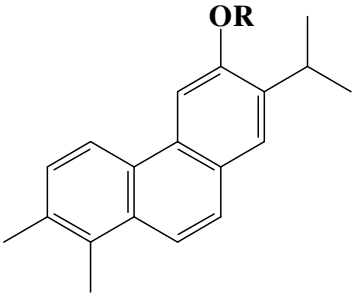
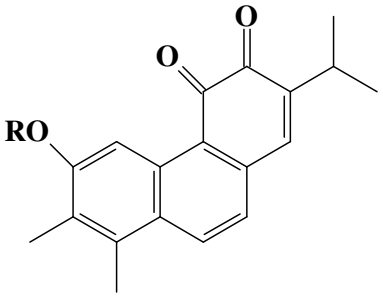
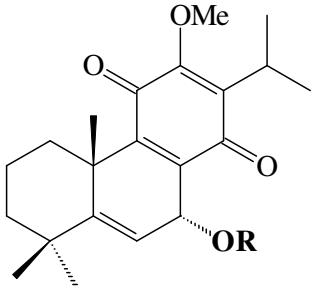


	R
19	**Me**
20	**H**



	R
21	**Me**
22	**H**



	R
23	**Ac**
41	**H**

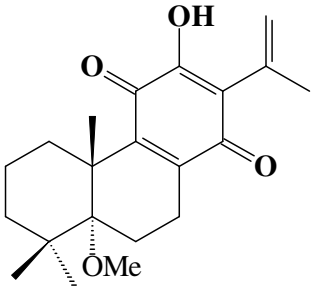


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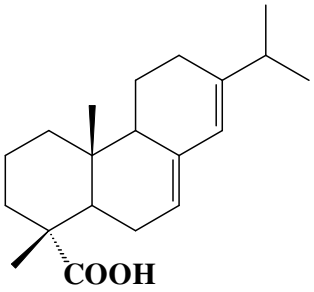
Figure 1. continued



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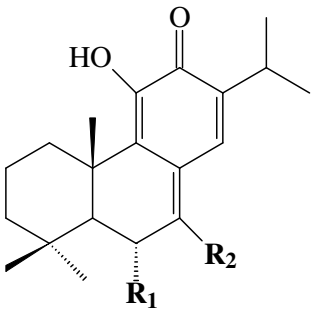
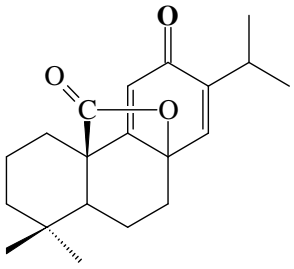


	R_1	R_2
44	**=O**	**H**
55	**OH**	**OH**



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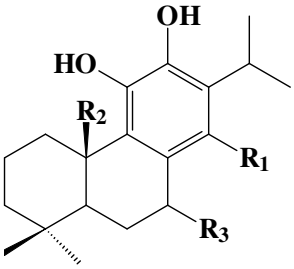
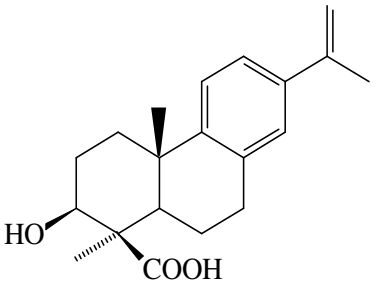


	R_1	R_2	R_3	Double bond
49	**H**	**COOH**	**H**	
50	**OH**	**Me**	**H**	**Δ_6**
45	**H**	**Me**	**=O**	**Δ_5**



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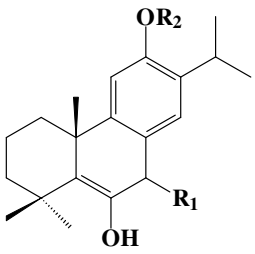

	R_1	R_2
51	**=O**	**Me**
54	**H**	**H**

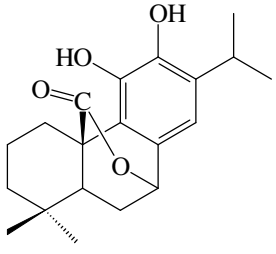

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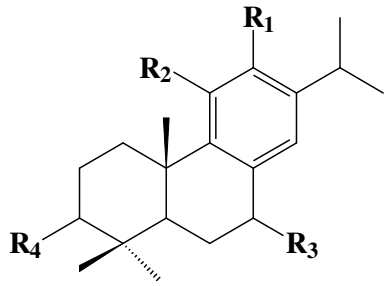
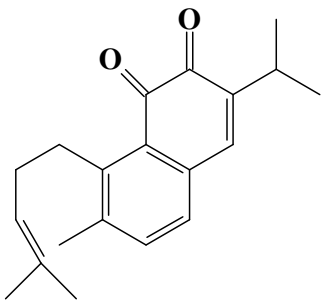
Figure 1. continued



	R_1	R_2	R_3	R_4
53	**H**	**H**	**H**	**=O**
59	**OMe**	**OH**	**=O**	**H**
66	**H**	**H**	**=O**	**H**



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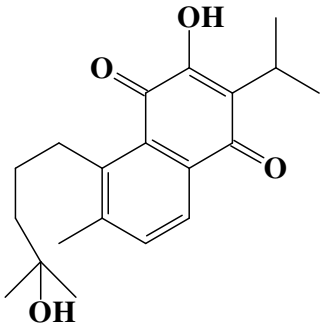

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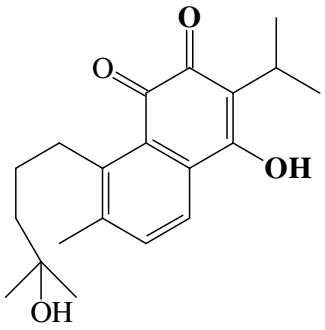

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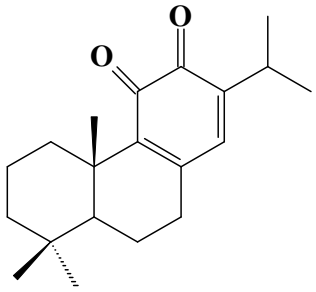

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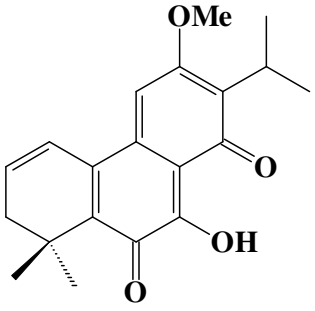

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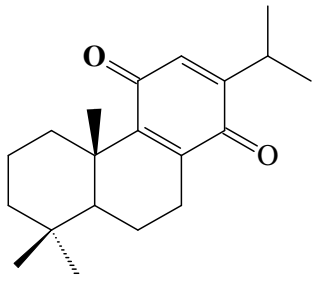

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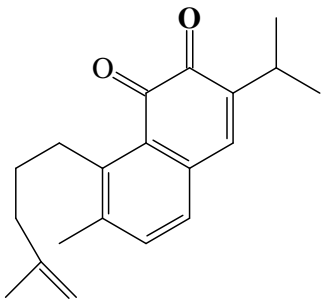

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The labdane diterpenoids, isolated from Turkish Lamiaceae plants, were found to be antibacterial agents. The antibacterial activity of sclareol **(26)** [7] against *S. aureus, P. aureginosa* and *K. pneumonia* has been reported while manool **(27)** was found to be active only against *S. aureus*, which were isolated from species of *Salvia.* The compounds hispanolone **(28)** [18, 19] dehydrohispanolone **(29)** [18] and ballonigrine **(30)** [18, 19]**,** isolated from *Ballota* species, showed activity against *S. aureus, B. subtilis, P. aureginosa* and *E. coli*.

The pimarane diterpenoid 6β-hydroxyisopimaric acid **(31)** [20], isolated *from Salvia caespitosa*, displayed strong activity against *S. aureus*, *S. epidermidis* and *B. subtilis*. Another pimarane diterpene sandrocopimaric acid **(32)** was found to be active more or less against *B. subtilis*, *S. aureus, β-hemolitic Streptococcus, Kl. pneumonia, and C. albicans,* however this study was carried out on the isolated sample from *Juniperus excelsa* extract [21].

The labdane diterpenoid manoyloxide **(33)** and 13-*epi*-manoyl oxide **(34)** and their derivatives were obtained from some Turkish *Salvia* [22, 23], and *Sideritis* species, such as manoyloxide from *Salvia staminea* [22], and ent-2-α-hydroxy-13-*epi*-manoyl oxide from *Sideritis perfoliata* [24]. When 13-*epi*-manoyl oxide **(34)** and manoyl oxide **(33)** were investigated against *S. aureus, S. epidermidis, S. hominis, K. pneumoniae* and *E. coli* by a Greek group [25], 13-*epi* isomer was found to be active against *Staphylococci*. Some manoyl oxide derivatives, 11β-hydroxymanoyl oxide and 8,13-di*epi*manoyl oxide were isolated from *S. candidissima* Vahl. ssp. *occidentalis* Hedge, but no activity studies were carried out on them [23].

A new pimarane diterpene salvipimarone **(35)** isolated from *Salvia multicaulis*, showed activity against *P. mirabilis* and *E. faecalis* [15].

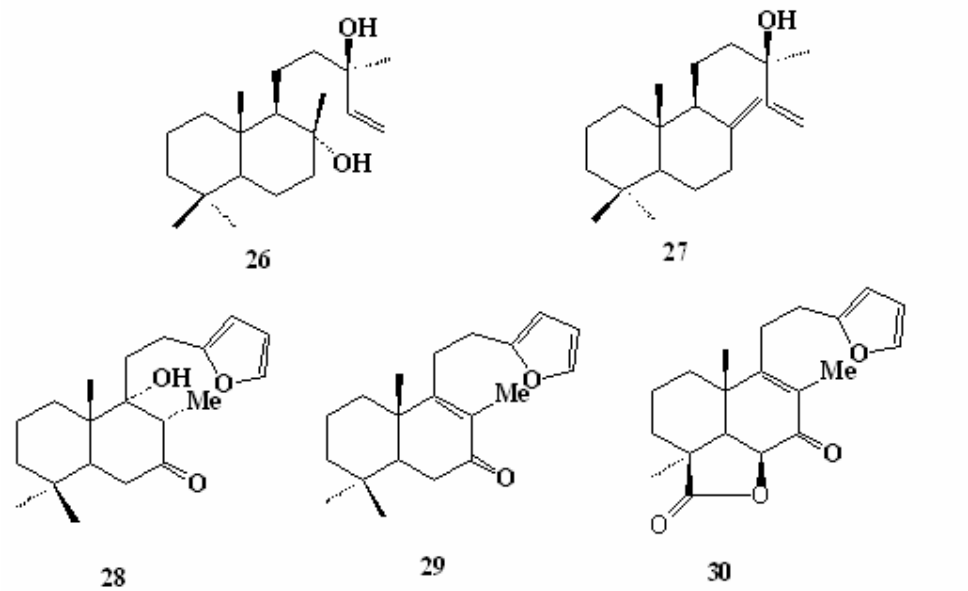
2.2. Antimycobacterial Activity

Since some *Salvia s*pecies, particularly fully aromatic abietane containing ones have been used in the treatment of tuberculosis in folk medicine, especially in China, fully aromatic norabietanes multicaulin **(19)**, 12-demethylmulticaulin **(20)**, multiorthoquinone **(21),** 2-demethylmultiorthoquinone **(22)**, and two abietanes 12-methyl-5-dehydroacetylhorminone **(23)**, 12-methyl-5-dehydrohorminone **(41)** and the pimarane diterpenoid salvipimarone **(35)** were evaluated against *Mycobacterium tuberculosis* strain H37Rv, and all tested abietanes/norabietanes showed strong antituberculosis activity with the MIC values of 5.6 μg/mL, 0.46 μg/mL, 2.0 μg/mL, 1.2. μg/mL, 0.89 μg/mL, 1.2 μg/mL, respectively, and salvipimarone as well, with a MIC value of 7.3. μg/mL [15]. Against *M. tuberculosis,* abietane diterpene hypargenin F **(7),** isolated from *Salvia hypargeia* [8] was also found to be active. The labdane diterpene sclareol **(26),** isolated from *Salvia sclarea* (clary sage) also showed antituberculosis activity with a MIC value of 6.0 μg/mL [7] while sandracopimaric acid **(32)** showed moderate activity with a MIC value of 15.0 μg/mL [21].

2.3. Antifungal activities

Labdane diterpenoids hispanolone **(28)** [18, 19]**,** dehydrohispanolone **(29)** [18] and ballonigrine **(30)** [18, 19], isolated from *Ballota inaequidens* and *B. saxatilis* subsp. *saxatilis* were reported as antifungal agents against *Candida albicans* and *C. krusei*. The abietane diterpenoids 2,3-dehydrosalvipisone **(1)** and 7-oxo-royleanone **(2)** [7] isolated from *Salvia sclarea* and pimarane diterpenoid sandracopimaric acid **(32)** showed moderate activity against *Candida albicans* [21]. The pisiferic acid **(8)** and its derivatives isolated from *Salvia blepharochlaena* were not tested against *C. albicans.* However, antifungal activity of pisiferic acid **(8)** against rice blast fungus has already been reported [26] as well as carnosic acid 12-methyl ether **(25)** against *Alternalia* fungi [27].

Figure 2. Bioactive labdane diterpenoids from Turkish Lamiaceae plants



In general, *Sideritis* diterpenes which are formed mainly from ent-kauranes were not showed high antibacterial activity against standard bacteria, however 7α,18-dihydroxykaur-16-ene was found to be selectively active against *E. faecalis* and *B. subtilis by Fraga et al*. [28]. Kaurene diterpenoids linearol **(36)**, foliol **(37)**, siderol **(38)**, 7-epicandicandiol **(39)** and kaurane diterpenoid epoxyisolinearol **(40)** were reported to be slightly antibacterial diterpenoids which were isolated from five *Sideritis* species by our group [29-34] (Table 1). The acetone extract and ten ent-kaurane diterpenes isolated from *Sideritis stricta* were tested against standard bacterial and fungal strains, but they were shown very weak or no activity, although 7-epicandicandiol was shown relatively better activity against *E. coli* and *S. aureus* [34].

In a recent study, the ent-kaurene diterpenes siderol, linearol and epicandicandiol, isolated from *Sideritis sipylea* Boiss., also previously isolated several Turkish *Sideritis s*pecies, were investigated against the bacteria including a fungus *C. albicans.* In this study, the only 7-epicandicandiol was found to be active against *S. aureus, B. subtilis* and *C. albicans* [35]. The results of this study were correlated with our results on the investigated *Sideritis* ent-kauranes [33, 34].

Table 2. Antifungal activity data of diterpenoids isolated from Turkish Lamiaceae plants

Fungus	1	2	8	12	28	29	30	32
Candida albicans	5.3[a]	6.7[a]	*NT*	NA	3.1[a]	1.5[a]	3.1[c]	5[b]
Candida krusei	NT	NT	85[d]	NT	6.2[c]	NT	6.2[c]	NT
Pyricularia oryzae	NT	NT	85[d]	NT	NT	NT	NT	NT

[a]MIC values as µg/mL [b]Zone diatemeter as mm [c]MIC_{50} (mg/mL) [d]Inhibition % spore germination at a dosage 100µg/mL. NT: Not tested, NA:Not active

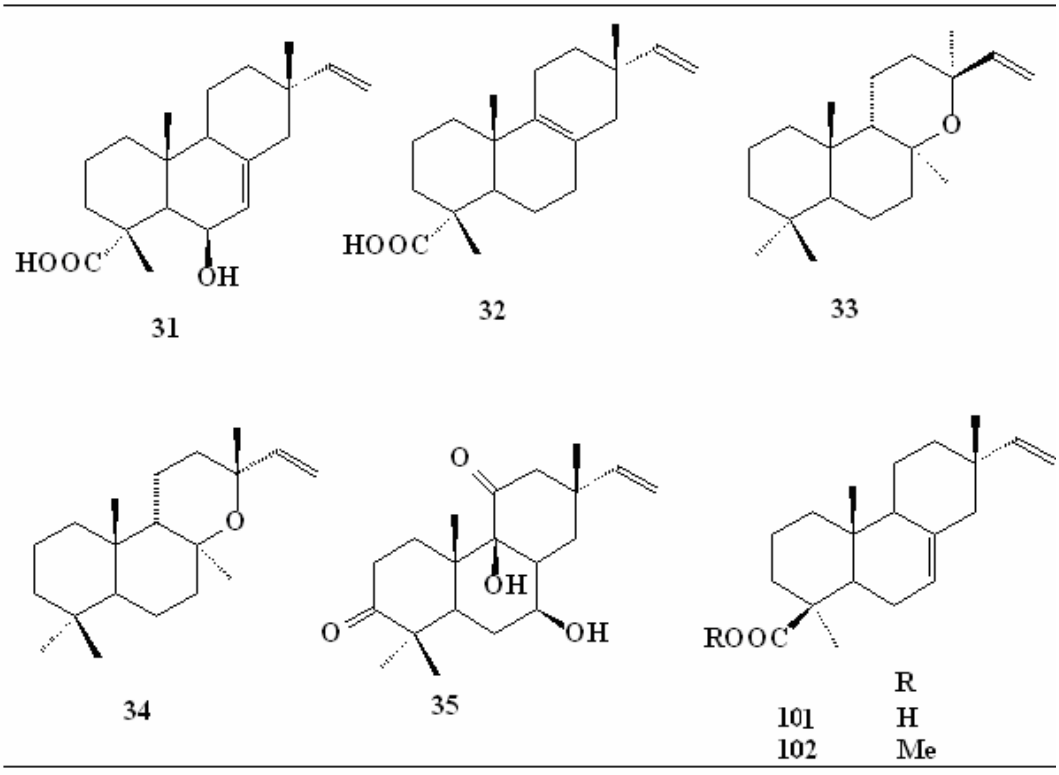
2.4. Cytotoxic and Antitumor Activities

Cytotoxic activity is one of the most searched activities of *Salvia* species, including particularly di- and triterpenoid constituents, by our group [4, 13, 22, 36, 37], and the most studied species is *S. hypargeia* for this purpose which is highly rich in abietane diterpenoids (22). The antitumor activities of abietane diterpenoids horminone **(12)**, 6β-hydroxyroyleanone **(43)**, royleanone **(25)** and taxodione **(44)** which have been commonly found in Turkish *Salvia* species, have been reported as well as salvinolone **(45),** 3β-hydroxyabieta-8,11,13,15-tetraen-18-oic acid **(46)** and abietic acid **(47)** [4]. 6α-hydroxysalvinolone **(54)**, 6-hydroxytaxodone **(55)**, aethiopinone (**56**), microstegiol **(17)**, ferruginol **(11)**, saprorthoquinone **(57)**, 11,12-dioxoabieta-8,13-diene **(58)**, taxodione **(44)**, cryptojaponol **(59)**, 1-oxo-salvibretol **(60)**, hypargenin A **(3)**, hypargenin D **(6)** isolated from several *Salvia species* [4, 13, 22, 36], were tested against human breast cancer (BC1), human lung cancer (LU1), human colon cancer (COL2), drug resistance (KB and KB-VI), human prostate cancer (LNCaP) and mouse lymphocytic leukemia (P388) (Table 3) [36].

The kaurene diterpenoids 7-epicandicandiol **(39)**, sidol **(61)**, siderol **(38)**, sideridiol **(62)** and linearol **(36)**, isolated from *Sideritis lycia* and some other Turkish *Sideritis* species [29-33] were tested against KB, P-388, COL-2, hTERT RPE, LU1, LNCAP and A2780 ovarian cancer cell lines. Only 7-epicandicandiol **(39)** showed slight potential cytotoxic activity [38].

There are some DNA damaging and cytotoxic activity studies [38, 39] continuing or completed (in press) on the diterpenic constituents of *Salvia* and *Sideritis* species by our group as well as other genera of Lamiaceae plants growing in Anatolia.

Figure 3. Bioactive pimarane diterpenoids from Turkish Lamiaceae plants



2.5. Cardiovascular activity

Since *Salvia* species, especially Chinese sage *S. milthiorrhiza* has been used in the treatment of coronary heart diseases, Prof. Ulubelen group also investigated cardiovascular properties of several *Salvia* extracts (*S. amplexicaulis, S. eriophora* and *S. syriaca*) and their constituents *in vivo*, on Wistar Albino rats [5, 40-42]. The crude extract *of S. eriophora* and isolated eleven diterpenoids ferruginol **(11)**, aethiopinone **(56)**, 4,12-dihydroxysapriparaquinone **(63)**, 6,7-didehydroroyleanone **(64)** and 4,14-dihydroxysaprorthoquinone **(65),** horminone, acetylhorminone, salvipisone, 12-hydroxysapriparaquinone, 3,12-dihydroxysapri-paraquinone-1-ene, salvilimbinol, were tested [40] for cardiovascular activity. Among the tested abietanes, compounds **65, 56, 11, 63** and **64** as well as the crude extract showed antihypertensive activity, especially ferruginol, aethiopinone and 4,12-dihydroxysapriparaquinone by significantly reducing arterial blood pressure, and this activity is considered probably due to the vasorelaxation activity [5]. Besides some steroids, ferruginol and other diterpenoids isolated from *S. syriaca* [41] and *S. amplexicaulis* [42] were also tested for cardioactivity, and in both
experiments ferruginol and another abietane 7-oxo-abieta-9,12,14-triene were found to be active. In the three experiments, active compounds showed very similar results to the positive controls propranolol and regitine [5, 40-42].

2.6. Antifeedant, Insecticidal and Insect Repellent Activities

Antifeedant activity of *ent*-kaurane diterpenoids, isolated from Turkish *Sideritis* species [43, 44], were screened against the final stadium larvae of the *Lepidoptera*. Among them, sideroxol **(67),** isolated from most of the studied *Sideritis* species**,** caused significant antifeedant activity against *Spodoptera frugiperda*, and another ent-kaurane foliol **(36),** also common in *Sideritis* species was found to be a potent phagostimulant for *Spodoptera littoralis* [43]. *Ent*-kaurene diterpenoids, 7-epicandicandiol **(39)**, 18-acetylsideroxol **(68)** and acetone extract of *Sideritis trojana* showed toxicity against the insects *Acanthoscelides obtectus* and *Sitophilus granarius*, while 7-epicandicandiol diacetate **(69)** showed toxicity only against *Ephestia kuehniella* [44]. The acetone extracts of *S. lycia* and linearol **(36)** were found to be active against *Tetranychus urticae, Bemicia tabaci, Sitophilus granarius and Lasioderma serricorne*, and our insect anti-feedant and insect repellant activity studies have been continuing on the diterpenic constituents of *Sideritis, Teucrium* and *Ajuga* species.

2.7. Other Biological Activities

In this part, various activities of diterpenes, isolated from Lamiaceae plants, most from Anatolian Lamiaceae plants are given, although their assays were carried out especially by foreign scientists.

Table 3. Cytotoxic activity data of diterpenoids isolated from Turkish Lamiaceae plants

Compounds	BC1	LU 1	COL 2	KB	KB-VI	LNCaP	P 388	hTERT RPE	A 2780
3	>20	>20	>20	>20	>20	>20	>5	NT	NT
6	12.6	>20	12.3	>20	>20	>20	>5	NT	NT
11	>20	>20	9.7	>20	>20	17.1	16.3	NT	33.3
17	>20	>20	>20	>20	>20	>20	3.0	NT	NT
36	NT	>20	>20	>20	NT	>20	>20	>20	>20
38	NT	>20	>20	>20	NT	>20	>20	>20	>20
39	NT	17.9	11.8	13.3	NT	14.9	>20	NT	9.0
44	1.2	5.1	0.7	3.4	4.1	0.7	0.3	NT	9.0
54	4.7	4.2	10.1	9.7	5.6	*4.0*	>5	NT	NT
55	>20	>20	9.0	>20	>20	12.9	>5	NT	NT
56	NT	NT	NT	NT	NT	NT	NT	NT	NT
57	9.2	16.4	3.3	>20	9.1	>20	2.3	NT	NT
58	>20	>20	>20	>20	>20	>20	>5	NT	NT
59	NT	>20	>20	>20	NT	>20	>20	NT	34.2
60	NT	>20	>20	>20	NT	>20	>20	NT	22.3
61	NT	>20	>20	>20	NT	>20	>20	>20	15.6
62	NT	>20	>20	>20	NT	>20	>20	>20	>20
Ellipticine	0.2	0.02	0.3	0.04	0.3	0.8	0.1	0.3	NT

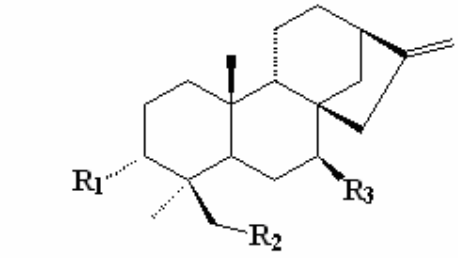
Data are given ED_{50} values in µg/mL, BC1, human breast cancer; LU 1, human lung cancer; COL 2, human colon cancer; KB, originally derived from human nasopharyngeal cancer; KB-VI, multidrug-resistant KB; LNCaP, human prostate cancer; P 388, mouselymphoctic leukemia; NT: Not tested, NA: Not active

The two new abietane diterpenoids, 7-hydroxy-12-methoxy-20-nor-abieta-1,5(10),7,9,12-pentaen-6,14-dione **(99)**, and abieta-8,12-dien-11,14-dione (12-deoxyroyleanone) **(100)** , isolated from *Salvia cilicia* [45], were tested against both promastigote and amastigote forms of *Leishmania donovani* and *L. major*. The compounds showed moderate activity against amastigote forms of two *Leishmania* species [45].

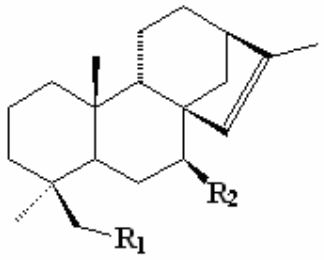
The common diterpenoid abietic acid **(47)** [46] was found to be inhibitor of soybean 5-lipoxygenase with IC_{50} of 29.5±1.29 µM. Because of this result, abietic acid is considered that may inhibit human 5-lipoxygenase and potentially be used in the treatment of allergy, asthma, arthritis and psoriasis [46]. The aldose reductase inhibitory effect of sugiol **(14)** was reported by a Japanese group [47]. Aethiopinone has been evaluated for toxicity, anti-inflammatory, analgesic, antipyretic, and haemostatic activities by Rodriguez group [48]. The results showed that strong anti-inflammatory, peripheral and central analgesic properties for aethiopinone.

The antioxidant activity of sage extract and abietane diterpenoid carnosic acid **(49)** was also reported. Many of Lamiaceae plants, such as rosemary, oregano, thyme and sage have been used as culinary herbs, and their extracts or constituents were added to the foods as antioxidant agents [49]. There are increasing number of studies on the antioxidant activity of *Salvia* extracts, however, till today, antioxidant activity studies on Turkish Lamiaceae plants were carried out on their essential oils or the extracts, rather than pure compounds. We have targeted to evaluate pure diterpenoids for this purpose, by iniatiating from abietane diterpenes of *Salvia* species [50].

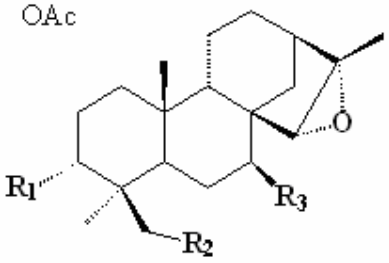
Figure 4. Bioactive kaurane diterpenoids from Turkish Plant species



	R_1	R_2	R_3
36	OH	OAc	OH
37	OH	OH	OH
39	H	OH	OH
61	OAc	OH	OH
69	H	OAc	OAc



	R_1	R_2
38	OH	OAc
62	OH	OH



	R_1	R_2	R_3
40	OH	OAc	OH
67	H	OH	OH
42	H	OAc	OH

3. Conclusions

Biological activities of diterpenoids isolated from Lamiaceae (Labiatae) plants have been studied by many groups in the world, and various activities of the isolated diterpenes were reported. Regarding activity results of diterpenes from Lamiaceae plants, each class of diterpenes can be considered potential compounds at least for one or two specific activities. Considering completed results and some preliminary assays on the investigated diterpenes from Anatolian Lamiaceae plants we can make some conclusions as follows;

For abietane diterpenes, cytotoxic, antioxidant, and acetylcholinesterase/ butyrylcholinesterase inhibitory properties seem more promosing while fully aromatic abietanes (norabietanes) can be announced potential antituberculostatic drugs as well as antitumor agents. *Ajuga* and *Teucrium* species and other neo-clerodane containing plants should be searched for their insecticidal properties, even *Sideritis* species being rich in ent-kaurane diterpenes were found to be more promosing in recent investigations for this purpose. As antibacterial agents, except a few diterpenes, there is no remarkable results to discover a new natural agent. For antiviral activity, it is not easy to classify diterpenes at the moment, however labdanes and abietanes have better potential. Some species such as *Phlomis, Micromeria, Scutellaria,* even *Sideritis* species which are more rich in phenolic compounds including

flavones should be focused to evaluate for their anti-oxidant potential rather than other activities. The possibility for discovery and development of non-toxic drugs from plants is important. These compounds and future studies by the bioassay guided fractionation may serve as useful templates for further biological evaluation and structure modifications.

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