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Biological Activities of Diterpenoids Isolated from Anatolian Lamiaceae Plants II

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Abstract: In this review article, biological activity studies on diterpenoids isolated from Lamiaceae family plants in Türkiye were updated. The studies conducted in the past twenty years (between 2006-2025) were examined, and it was observed that mainly cytotoxic and acetylcholinesterase and butyrylcholinesterase inhibitory activity tests were carried out on diterpenoids, obtained from the Lamiaceae family plants. However, despite the decreasing number of studies, antibacterial, antifungal, cytotoxic, antitumor, cardiovascular, antiviral, antiplasmodial, and insecticidal activities have been investigated. In this review article, 34 abietane diterpenoids from *Salvia* species, 13 kaurane diterpenoids from *Sideritis* species, and 3 labdane, and 1 pimarane diterpenoids were isolated from different sources, and their biological activities data were reported.

Keywords: *Salvia*; *Sideritis*; *Teucrium*; cytotoxic activities; anticholinesterase activities; insecticidal activities.

1. Introduction

Flora of Türkiye is an extremely valuable ecological habitat, where it contains approximately 12000 taxa which 4000 are endemic, belonging to 173 families, discovery new species or subspecies for each year [1-2]. The Lamiaceae family is the 6th largest family in the world and the 3rd largest family in Türkiye in terms of both endemic species and the number of species. Approximately 620 species (800 taxa) of the Lamiaceae family are distributed in Türkiye, and the endemism rate is 44%. The species are mostly distributed in the Mediterranean phytogeographic region, and the endemism rate in this region is 61% [1-5]. These rich plant species are an important and widespread part of the Lamiaceae family and their species in the flora of Türkiye.

This review article includes the studies carried out between the year of 2006 and 2025 of the biological activity studies on diterpenoid type compounds obtained from Lamiaceae plants grown in Anatolia updated of our previous study [6]. Although it has been used to treat various health problems such

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as cold, throat infections, psoriasis, seborrheic eczema, bleeding, low ulcers in folk medicine. However, such a rich diversity species, diterpenoid isolation and biological activity studies are extremely limited in the studies carried out in Türkiye and this revolution has been revealed with the gradually decreasing groups of these areas [6].

This study reports the isolated diterpenoids from the extracts of plant species of the Lamiaceae family grown in Anatolia, and biological activities of them against various cancer cell lines, and anticholinesterase, cardiovascular, antiviral, and insecticidal properties

2. Biological Activities of Diterpenoids

2.1. Antibacterial, Antimycobacterial and Antifungal Activity Studies

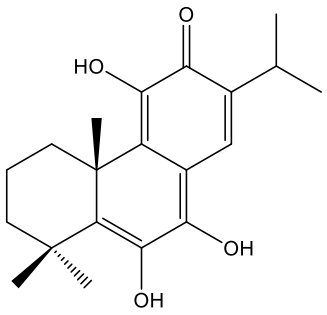
The acetone and methanol extracts of *Sideritis tmolea* P.H. Davis collected from Ödemiş-Bozdağ, İzmir and investigated by Çarıkçı et al. The acetone and methanol extracts of the species *S. tmolea* and an *ent*-kaurene diterpenoid siderol (**1**) were tested against the gram-negative bacteria *Escherichia coli* (ATCC 29995) and the gram-positive bacteria *Staphylococcus aureus* (ATCC 6538P). As reported in the previous studies, siderol (**1**) and the extracts showed a very weak–antibacterial activity [1, 7, 8]. The compounds were also tested against *Mycobacterium smegmatis*, and *Mycobacterium tuberculosis* H37Ra (ATCC 25177), and a yeast *Candida albicans* (ATCC 10239), however no activity was observed.

Another Lamiaceae family plant is the genus *Teucrium* representing in Türkiye by 58 taxa. A *Teucrium* species *T. pruinosum* Boiss. was studied by Aydoğan et al. for the first time [9], its extract afforded three iridoid glycosides, two phenylethanoids, seven flavonoids, a sesquiterpenoid, three abietanes, and five *neo*-clerodane diterpenoids. A subsequent study on another *Teucrium* species *T. divaricatum* Heldr. subsp. *divaricatum* was published again by Aydoğan et. al [10]. The two new *neo*-clerodane diterpenoid glycosides teudivaricoside A and teudivaricoside B, as well as the known compounds teucvidin, 2-deoxychamaedroxide, teuflin, teucrin G, teuflidin teuchamaedryn B, 6*β*-hydroxyteuscordin, teucrin F, 6-epi-teucrin A, teucrin A, isoteuflidin, dihydroteugin, and montanin E were isolated from *Teucrium divaricatum* subsp. *divaricatum*. All diterpenoid compounds were tested against gram negative and positive bacteria, and *Candida albicans* [10].

2.2. Cytotoxic Activities

Topçu et al. [11] reported the cytotoxic activities of ethanol, methanol, acetone, and dichloromethane extracts of sixteen *Salvia* species, including *S. amplexicaulis* Lam., *S. aucheri*, Benth., *S. bracteata* Banks & Sol., *S. candidissima* Vahl, *S. heldrechiana* Boiss. ex Benth., *S. hypargeia* Fisch. et Mey., *S. napifolia* Jacq., *S. tomentosa* Mill.) *S. cassia* G. Samuelsson ex Rech. f., *S. eriophora* Boiss. & Kotschy ex Boiss., *S. pilifera* Montb. & Auch., *S. recognita* Fisch. & Mey.), *S. staminea* Montb. & Auch. ex Benth., *S. triloba* L. (syn. *S. fruticosa* Mill.), *S. heldrechiana* Boiss. ex Benth., and *S. syriaca* L., against A2780 human ovarian cancer cell line. The IC_{50} values of the extracts ranged from 15.5. μg/mL to 41.7 μg/mL against the tested cell line, and the extract of *S. eriophora* Boiss. & Kotschy ex Boiss did not show any activity to the A 2780 cell line. Due to the nature of bioassay-guided fractionation methodology, the authors were selected to evalaute the highest active extract which was *S. hypargeia* Fisch & Mey (IC_{50}: 15.5 μg/mL), then the authors isolated four diterpenoids, one triterpene, and one fatty acid compound from the acetone extracts of the root of this species. The isolated three abietane and one rearranged abietane diterpenoids namely, 5,6-didehydro-7-hydroxytaxodone (**2**), 14-deoxycoleon U (6-hydroxysalvinolone) (**3**), demethylcryptojaponol (**4**), and salvicanaric acid (**5**) were also tested against A2780 cell line, and the most active compounds were determined as 14-deoxycoleon U (6-hydroxysalvinolone) (**3**) (IC_{50}: 3.9 μg/mL), and demethylcryptojaponol (**4**) (IC_{50}: 1.2 μg/mL). While the subfraction of *S. hypergeia* was shown activity as IC_{50}: 13.4 μg/mL, the other isolated compounds, 5,6-didehydro-7-hydroxytaxodone (**2**) and salvicanaric acid (**5**) had the IC_{50} values 18.80 and 15.00 μg/mL, respectively. The other abietane diterpenoids cryptojaponol (**6**) and taxodione (**7**) were used for comparison purposes and their IC_{50} values were determined as 34.2 μg/mL and 9 μg/mL, respectively. Interestingly the fatty acid mixture which was

isolated from the *S. hypergia* root acetone extracts showed the highest activity with the IC_{50}: 0.6 µg/mL (See Table 1).



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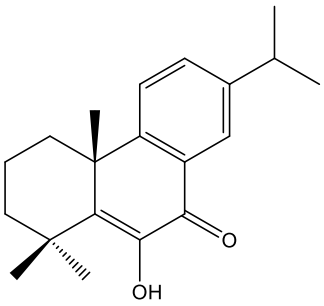

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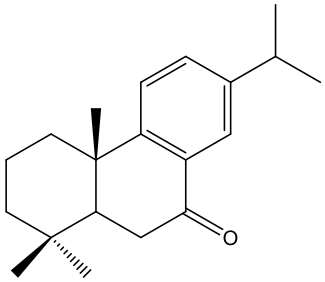

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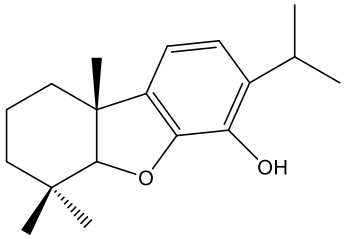

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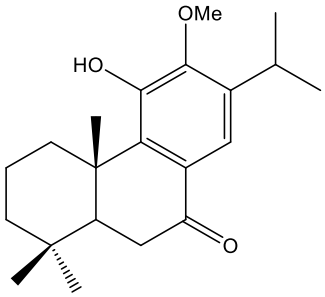

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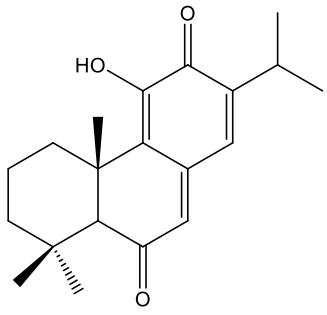

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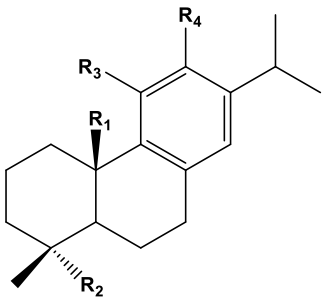

	R_1	R_2	R_3	R_4
8	**CH_3**	**CH_3**	**H**	**H**
11	**CH_3**	**CH_3**	**H**	**OH**
15	**CHO**	**CH_3**	**H**	**OH**
25	**COOH**	**CH_3**	**OH**	**OH**

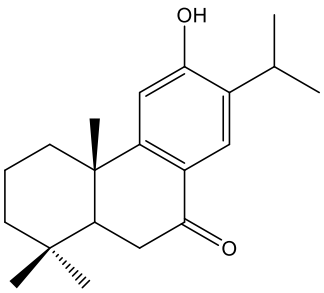

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Figure 1. Bioactive abietane diterpenoids from Turkish Lamiaceae plants

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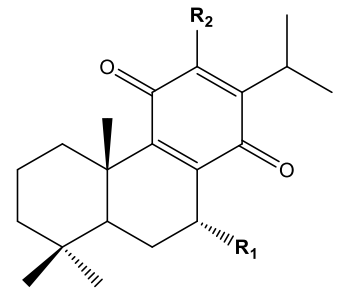
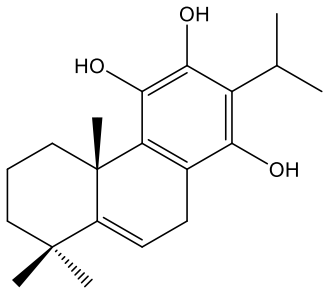


	R1	R2	Double Bond
9	**H**	**OH**	**Δ6**
10	**=O**	**OH**	
36	**OAc**	**OH**	
49	**OAc**	**OH**	



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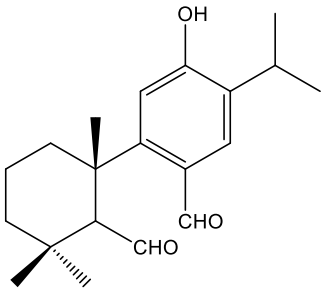

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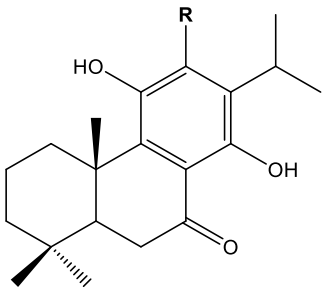
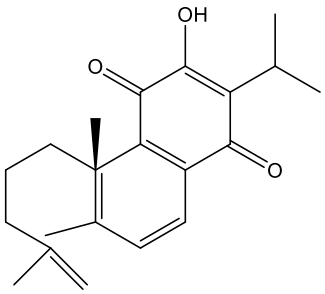


	R
14	**OMe**



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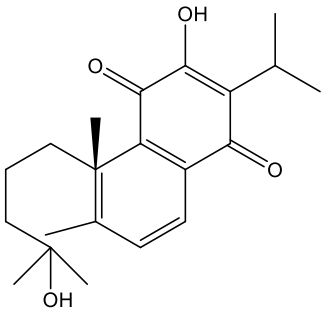

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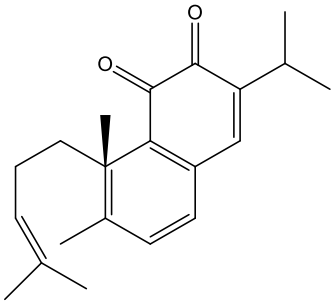

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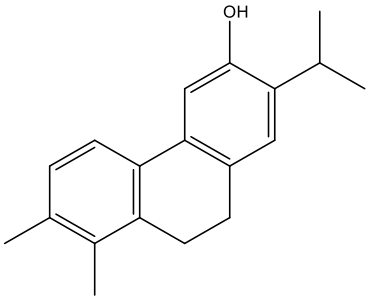

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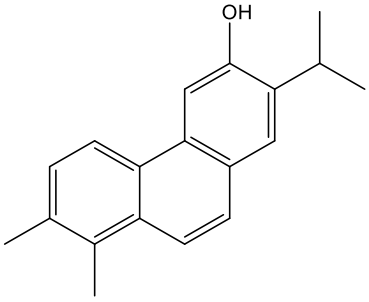

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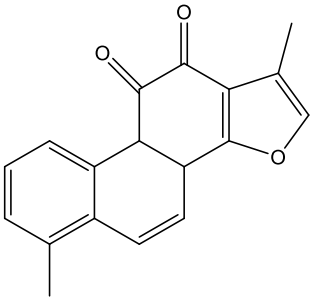

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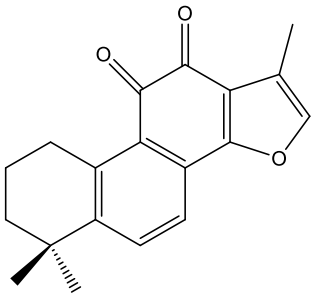

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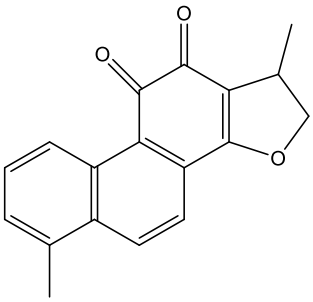

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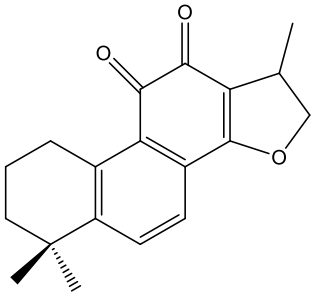

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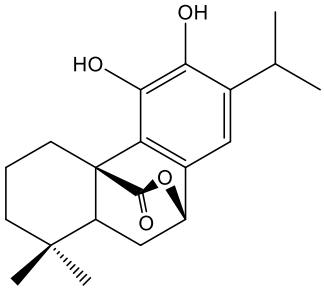

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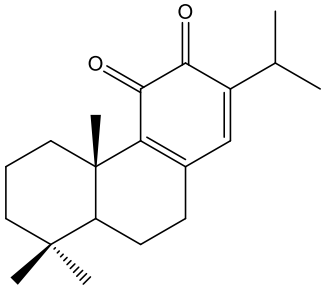

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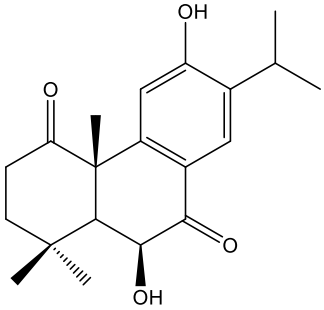

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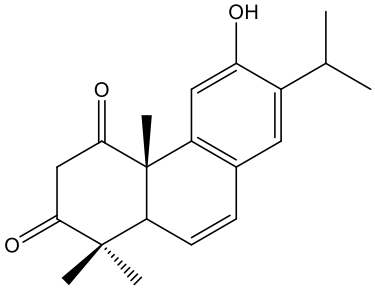

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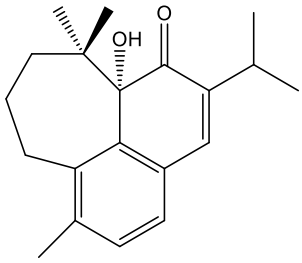

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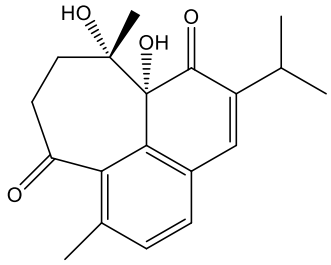

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Figure 1. Bioactive abietane diterpenoids from Turkish Lamiaceae plants

Topçu et al. [11] investigated cytotoxic and apoptic effects of sixty-three compounds which are isolated from some *Salvia* species including phenolics, abietane diterpenoids, triterpenoids and steroids. In this study, they reported cytotoxic activities of nineteen abietane diterpenoids; abieta-8,11,13-triene (**8**), 6,7-dehydroroyleanone (**9**), 7-acetylroyleanone (**10**), ferruginol (**11**), sugiol (**12**), cryptanol (**13**), inuroyleanone (**14**), pisiferal (**15**), salvipisone (**16**), 12-hydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial (**17**), 4-hydroxysapriparaquinone (**18**), 12-hydroxyabieta-1,3,5(10), 8, 11, 13-hexaene (**19**), 12-demethylmulticauline (**20**), tanshinone I (**21)**, tanshinone IIA (**22**), dihydrotanshinone I (**23**), cryptotanshinone (**24**) carnosic acid (**25**) and carnosol (**26**) against healthy PDF (Primary Dermal Fibroblast) cell line, HT-29 (colon cancer) and MCF-7 (breast cancer) cell lines. All the tested abietane diterpenoids, except for inuroyleanol, tanshinone IIA, and cryptotanshinone, were found to be toxic on healthy cell lines PDF, HT-29 and MCF-7 (See Table 1). Among the tested abietane diterpenoids 6,7-dehydroroyleanone (**9**), pisiferal (**15**), 7-acetylroyleanone (**10**), ferruginol (**11**), cryptotanshinone (**24**), carnosic acid (**25**) and carnosol (**26**) showed strong cytotoxic activity against the tested cell lines.

Ulubelen et al. [13], reported a review article entitled "Screening some plants for their antiproliferative compounds" in 2011, and similar compounds were reported by Kandemir et al. [12].

The cytotoxic activity data against human breast cancer (BC 1), human lung cancer (LU2), human colon cancer (COL 2), human epidermoidal carcinoma in mouth (KB), vinblastine-resistant KB-VI, hormone-dependent human prostate cancer (LNCaP), as well as P388 and ASK cells in culture [1, 13, 14] of the abietane diterpenoids 6-hydroxysalvinolone (**3**), ferruginol (**11**), taxodione (**7**), of saprorthoquinone (**27**), 11,12-dioxo-abieta-8,13-diene (**28**), hypargenin A (**29**) and hypargenin D (**30**) were summarized (Table 1).

Kılıç et al [15] reported cytotoxic activities of isolated *ent*-kaurane diterpenoids from *Siderits lycia*. The acetone extract of *S. lycia*, and the isolates linearol (**31**), sidol (**32**) and 7-*epi*-candicandiol (**33**), siderol (**1**) and sideridiol (**34**) were tested against a cultured KB (human epidermoid carcinoma), P-388 (mouse leukemia), COL-2 (human colon cancer), hTERT RPE (human retinal pigmented epithelial cancer), LU1 (human lung cancer), LNCaP (hormone-dependent human prostate cancer) and A2780 (human ovarian cancer) cell lines. The *ent* kaurane diterpenoid 7-*epi*-candicandiol (**33**) was found to be the most active diterpenoid against cancer cell lines with ED_{50} values: KB (13.3 μg/mL), COL-2 (11.8 μg/mL), LU1 (17.9 μg/mL), LNCaP (14.9 μg/mL) and A2780 (9.0 μg/mL), the ED_{50} values of the others compounds were observed > 20 μg/mL. Linearol (**31**) was not tested on the cancer cell lines except for A2780.

On the other hand, four new *neo* clerodane diterpenoids namely, isoteusandrin B, teusandrin H, teusandrin I and teusandrin J were isolated from the non-polar fraction of aerial parts of *T. sandrasicum* O. Schwarz, and they tested against MRC-5; normal human lung fibroblasts cell line (ATCC®CCL-171 TM), HeLa; human endometrial carcinoma cell line, DU-145; human prostate cancer cell line (ATCC®HTB-81) [16].

2.4. Antiviral Activity

Antiviral activity properties of linearol (**31**), sidol (**32**), isosidol (**35**) and the acetone extract of *Sideritis lycia* were test on human parainfluenza virüs type (HPIV-2) Verol Cells in order to determine the antiviral activity potential of the extract and ent-kaurene diterpenoids. While the CD_{50} values of the test compounds were determined as 29.32 ± 3.32 μg/mL, 27.27 ± 3.10 μg/mL, 14.64 ± 2.01 μg/mLand 2.91 ± 1.20 μg/mL respectively, the ED_{50} values of linearol (**27**), isosidol (**31**) and *S. lycia* Boiss. Et. Heldr. Apud. Bentham acetone extrract were found to be as 12.72 ± 2.80 μg/mL, 7.27 ± 1.59 μg/mL and 1.13 ± 0.25 μg/mL, respectively. Antiviral index (AI) were calculated by the ratio of CD_{50}/ ED_{50} values and calcualted for linearol (**31**), isosidol (**35**) and the acetone extract of *S. lycia* as 2.31, 2.01, 2.58, respectively. While the AI index of linearol (**31**), isosidol (**35**) and the acetone extract of species shows remarkable antiviral activity, sidol did not show any plaque inhibition, thus it is determined as inactive on HPIV-2 Vero Cells [15].

2.5. Antiplasmoidal and Antiinflammatory Activities

The *neo*-cloredane diterpenoids and abietane diterpenoids, isolated from *Teucrium pruniosum* Boiss. were tested for antimicrobial, antiplasmoidal, and anti-inflammatory activities which are. Among them 7-*O*-acetylhorminone (**36**) showed strong activity against chloroquine-sensitive (D6) and chloroquine-resistant (W2) strains of *Plasmodium falciparum* with IC_{50} values of 7.1 and 12.0 μM, respectively [9].

The anti-inflammatory activity data of 7-*O*-acetylhorminone (**36**) were reported in the same study *via* *i*NOS inhibition with an $IC5_0$ value of 0.55 ± 0.07 μM [9].

2.6. Acetylcholinesterase (AChE) and Butrylcholinesterase (BChE) Inhibition Activities

Only seven studies have been published on Acetylcholinesterase (AChE) and Butrylcholinsterease (BChE) Inhibition Activities of diterpenoids of Lamiaceae family species growing in Turkey flora between 2007 and 2025. The first study was conducted by Çulhaoğlu et al [17] about the bioactive components of *Salvia chrysophylla* Stapf. The authors have reported only one diterpenoid in this study. It was determined that the isolated diterpenoid scleraol (**33**) showed only approximately 60% inhibition against AChE and BChE at a concentration of 200 ug/mL, and they declared that this effect was a weak inhibitory activity value when compared to the positive control galantamine.

Topçu et al. continued their work in this field, and they have published several reports on *Salvia staminea* Montbret et Aucher ex Bentham, *S. bracteata* Banks et sol., *S. heldreichiana* Boiss. ex Bentham. *S. aucheri* Bentham var. *auche*ri, *S. kronenburgiii* Rech. fil., *S. verticillata* subsp. *amasiaca* Bornm., *S. poculata* Nab., *S. syriaca* L., *S. pilifera* Montbret & Aucher ex Bentham, *S. eriophora* Boiss. et Kotschy, *S. macrochlamys* Boiss. & Kotschy, *Salvia staminea* Montbret et Aucher ex Bentham, *S. macrochlamys* Boiss. As a result of these tests, AChE and BChE inhibitory activity values of *Salvia staminea* extract were determined as 55.17% and 79.95% at 200 ug/mL concentration value, respectively, and it was evaluated as the most active extract. There upon, the authors continued their studies on this species and microstegiol (**37**), 1-oxo-salvibretol (**38**), ferruginol (**11**), taxodione (**7**) and manoyloxide (**39**) [18,19] compounds were examined in terms of AchE and BChe inhibitory activities. In the experiments carried out at 200 μM concentrations of these compounds, only taxodione (**7**) showed activity with 74.97% ± 2.20 and Ferruginol with 74.97% ± 2.20 in AChE inhibition activity values, while the others did not show any significant inhibition against AChE. When compared with the sesquiterpenoids, triterpenoids and flavonoids tested in the study, it was determined that diterpenoids showed the highest activity against BChE. Taxodione (**7**) showed the highest inhibitory activity value with 91.25% ± 1.41, followed by Ferruginol with 88.61% ± 0.60 and then microstegiol (**37**) and 1-oxo-salvibretol (**38)**. (see Table 2).

Table 1. Cytotoxic activity results of diterpenoids against a panel of cancer cell lines[a]

Compounds	BC1	KB[a]	KB-IV	P-388[a]	COL-2[a]	hTERT [a]RPE	LU 1[a]	LNCaP[a]	A2780[a]	PDF[b]	HT-29[a]	MCF-7[a]
Kaurene Diterpenoids												
7-*Epi*candicandiol (**33**)		13.3		>20	11.8	NT	17.9	14.9	9.0	NT	NT	NT
Sidol (**32**)	NT	>20	NT	>20	>20	>20	>20	>20	15.6	NT	NT	NT
Siderol (**1**)	NT	>20	NT	>20	>20	>20	>20	>20	>20	NT	NT	NT
Sideridiol (**34**)	NT	>20	NT	>20	>20	>20	>20	>20	>20	NT	NT	NT
Linearol (**31**)	NT	NT	NT	>20	NT	NT	NT	NT	>20	NT	NT	NT
Abietane Diterpenoids												
Abieta-8,11,13-triene (**8**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	135.68	>1000	>1000
Acetylroyleanone (**10**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	149.11	65.92	55.87
Ferruginol (**11**)	>20	>20	>20	>5	9.47	NT	>20	>20	NT	147.60	121.87	69.02
6α-Hydroxysalvinolone (**3**)	4.7	4.2	5.6	>5	10.1	NT	4.2	4.0	3.9 [d]	NT	NT	NT
Taxodione (**7**)	1.2	3.4	4.1	0.3	0.7	NT	5.1	0.7	34.2 [d]	NT	NT	NT
Saproorthoquinone (**27**)	9.2	>20	9.1	2.3	3.3	NT	16.4	>20	NT	NT	NT	NT
11,12-Dioxo-abieta-8,13-diene (**28**)	>20	>20	>20	>5	NT	NT	>20	>20	NT	NT	NT	NT
Hypargenin A (**29**)	>20	>20	>20	>5	NT	NT	>20	>20	NT	NT	NT	NT
Hypargenin D (**30**)	12.6	>20	>20	>5	12.3		>20	>20	NT	NT	NT	NT
Cryptanol (**13**)	NT	NT	NT	>20	NT	NT	NT	NT	NT	122.40	154.54	669.44
Inuroyleanol (**14**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	>1000	363.61	127.73
Psiferal (**15**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	76.82	>1000	>1000
Salvipisone (**16**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	84.03	>1000	>1000
12-Hydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial (**17**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	95.55	251.83	108.26
4-Hydroxysapri paraquinone (**18**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	266.17	33.68	242.55
12-Hydroxy-abieta-1,3,5(10),8,11,13-hexaene (**19**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	155.68	36.63	30.88

12-Demethylmulticauline (**20**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	140.11	90.67	113.95
Tanshinone I (**21**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	189.44	>1000	104.67
Tanshinone IIA (**22**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	>1000	>1000	30.98
Dihydrotanshinone (**23**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	7.80	48.62	11.32
Cryptotanshinone (**24**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	>1000	50.14	145.97
Carnosic acid (**25**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	53.03	82.78	71.32
Carnasol (**26**)	NT	NT	NT	NT	NT	NT	NT	NT	NT	28.69	111.10	85.38
6,7,11-trihydroxy-12-oxo-abieta-5,7,9,13-tetraen[d] ()	NT	NT	NT	NT	NT	NT	NT	NT	18.8	NT	NT	NT
Demethylcryptojaponol [d]	NT	NT	NT	NT	NT	NT	NT	NT	1.2	NT	NT	NT
Salvicanaric acid[d]	NT	NT	NT	NT	NT	NT	NT	NT	15.0	NT	NT	NT
	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT
Ellipticine (positive control)	0.2 [c]	0.02 [c]	0.04[a]	0.1 [c]	0.04 [a]	0.3 [a]	0.1 [a]	0.8 [a]	-			

[a]Compounds were initially tested at a concentration of 20 μg/mL, and followed by dose-response studies, as required to the yield ED_{50} values (μg/mL) [15]

[b]Concentrations were reported as μM [12].

[C]Concentrations are given as ED50 values in μg/mL [13]

[d]Concentrations are given as IC50 values in μg/mL [11]

BC1:human breast cancer; KB: originally derived from human nasopharyngeal cancer cells; KB-IV:multidrug-resistant KB cells; P388:mouse lymphocytic leukemia cells COL2:human colon cancer cells; hTERTRPE; hTERT-immortalized retinal pigment epithelial cells; LU1:human lung cancer cells; LNCap:human prostate cancer cells; A2780:human ovarian cancer cells;PDF: primary dermal fibroblast cells; HT-29:colon cancer cells; MCF-7: Human breast cancer cells

Table 2. Acetylcholinesterase (AChE) and Butrylcholinesterase (BChE) Inhibitory activities of Diterpenoids reported the years of 2006-2025 from Anatolia flora.

Compound	AChE Inhibition %	BChE Inhibition %
Abietane Diterpenoids		
Microstegiol (**37**)[b]	7.23	34.85
1-Oxosalvibretol (**38**)l[b]	NA	73.63
Ferruginol (**11**)[b]	74.97	88.13
Taxodione (**7**)[b]	83.41	88.13
Manoyloxide (**39**)[b,c]	16.75[c]	26.60
Tanshinone IIA (**22**)[d,e]	32.34[d]/>100[e]	66.26 [d] /1.12 [e]
Dihydrotanshinone (**23**)[d,e]	64.54 [d] /1.50 [e]	87.19 [d] /0.50 [e]
Tanshinone I (**21**)[d,e]	31.29 [d] /38.12 [e]	33.01 [d] /27.67 [e]
Carnosic acid (**25**)[d,e]	37.99 [d] /31.83 [e]	.48 [d] /4.12 [e]
Carnosol (**26**)[d,e]	47.60 [d] /11.15 [e]	57.99 [d] /3.92 [e]
Cryptanshinone (**24**)[d,e]	17.46 [d] />100 [e]	35.16 [d] /28.41 [e]
Kaurene Diterpenoids		
Diacetylstanol (**45**)[f]	NA[g]	175.8 [f]
Eubol (**44**) [f]	NA[g]	23.2 [f]
Eubotriol (**50**) [f]	NA[g]	98.1 [f]
Sideroxol (**42**) [f, h]	14.5 f/1.27[h]	25.0 [f]/0.024[h]
7-Epi-candicandiol (**33**) [f,h]	22.8 [f]/0.23[h]	21.1 [f]/0.022[h]
Ent-7α-acetoxy-16β,18-dihydroxy-kaurane (44)[h]	1.89[h]	1.19[h]
Epoxyisolinearol (**41**)[h]	0.87[h]	0.43[h]
Sideridiol (**34**)[h]	8.04[h]	3.67[h]
Siderol (**1**)[h]	0.69[h]	0.65[h]
Linearol (**31**)[h]	2.66[h]	0.15[h]
Sidol (**32**)[h]	0.92[h]	0.05[h]
Pimarane Diterpenoid		
14α-Acetoxy-18-hydroxy-isopimara-8,15-diene-7-10 (**47**)[j]	17.8[j]	120 [j]
Labdane Diterpenoid		
Sclareol[a] (**46**)	62	64
Galanthamine[b]	82.41[h]	75.54 [e]
Galanthamine[d,e]	76.08 [d] /5.13 [e]	67.52 [d] /8.19 [e]
Galanthamine[f]	73.9 [f]	50.9 [f]
Galanthamine[h]	0.0037	0.041

[a]200µg/mL [11]
[b]200 µM [18]
[c]200 µM [19]
[d:]Inhibition % at 10 µg/mL [20]
[e]:IC_{50} values as µg/mL[20]
[f]:IC_{50} values as µM [A4-16 23]
[g] >200 µM [16, 23]
[h]Concentrations were given as mM [24]
[j]IC_{50} values as µg/mL [29,31]

Tanshinone I (**21**), tanshinone IIA (**22**), dihydrotanshinone I (**23**), cryptotanshinone (**24**) carnosic acid (**25**) and carnosol (**26**) were evaluated for their inhibition potential against AChE and BChE enzymes. They reported the experimental inhibitory effects on acetyl- and butyryl-cholinesterase of dihydrotanshinone I (**21**), (IC50: 1.50 ± 0.02 and 0.50 ± 0.01 µg/mL, respectively), the success of

dihydrotanshinone I (**21)**, were idefined as carnosol (IC50: 11.15 ± 0.05 ve 3.92 ± 0.03 μg/mL) and carnosic acid (IC50: 31.83 ± 0.65 ve 4.12±0.04 μg/mL [20].

A new *ent*-kaurane diterpenoid, *ent*-7a-acetoxy-16β,18-dihydroxy-kaurane (7-acetyldistanol) (**40**) and the known compounds *ent*-3β,7α-dihydroxy,18-acetoxy-15β,16α-epoxykaurane (epoxyisolinearol) (**41**), sideroxol (**42**), sideridiol (**34**), siderol (**1**), 7-epicandicandiol (**33**), foliol (**43**), linearol (**31**) and sidol (**32**) were isolated from *Sideritis congesta*. 7-Acetyldistanol (**40**) *ent*-3β,7α-dihydroxy,18-acetoxy-15β,16α-epoxykaurane (epoxyisolinearol) (**41**), sideroxol (**42**), siderol (**1**), 7-epicandicandiol (**33**), linearol (**31**) and sidol (**32)** showed remarkable activity against both AChE and BChE. On the other hand, Carikci et al [22] reported the occurrence of the diterpenoids and phenolic constituents from *S. hololeuca.* Boiss & Heldr. Apud Bentham and tested AChE and BChE inhibitory activity. Among diterpenoids, siderol (**1**), eubol (**44**), eubotriol (**50**) exhibited weak AChE inhibitory activity, while 7-epicandicandiol (**33**) exhibited high activity especially against BChE comparable with the standard compound galanthamine as decribed by Topçu et al. [21, 22]. Similarly, acetylcholinesterase and butyrylcholinesterase inhibitory activity were also evaluated for eubol (**44**), sideroxol (**42**), and 7-*epi*-candicandiol (**33**) from *Sideritis arguta* and their results were in agreement with all of the other studies [21, 28].

2.7. Antioxidant Activity

Antioxidant activity potential of the isolated kaurene diterpenoids 7-acetyldistanol (**40**) and the known compounds *ent*-3β,7α-dihydroxy,18-acetoxy-15β,16α-epoxykaurane (**45**), sideroxol (**42**), sideridiol (**34**), siderol (**1**), 7-epicandicandiol (**33**), linearol (**31**) and sidol (**32**), obtained *Sideritis congesta,* and evaluated based on a series activity tests, namely the *β*-carotene bleaching method, free radical scavenging activity, DPPH, and superoxide anion radical scavenging activity test assays. When the results were compared with the positive controls α-tocopherol and BHT (butylated hydroxy toluene) none of the *ent*-kaurane diterpenoids showed antioxidant activity. However, the acetone extract of *S. congesta* showed very strong antioxidant capacity when compared with positive controls (See Table 3) [17, 21, 24].

The antioxidant activity evaluations of other *Salvia* species such as *Salvia chrysophylla*, Stapf [17], *Salvia staminea* [18], *Salvia cerino-pruinosa* Rech. F. var. *cerino-prunosa* [25], *Salvia marashica* [23].

From those species the isolated diterpenoids, sclareol (**46**), ferruginol (**11**), 7-acetylroyleanone (**10**), 6,7-deyhydroroyleanone (**9**), inuroyleanol (**14**) and 12-hydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial (**17**) were tested to determine their antioxidant capacity. Among those compounds, inuroyleanol (**14**), 7-acetylroyleanone (**10**), 6,7-dehydroroyleanone (**9**), and ferruginol (**11**) showed the highest activity in the ABTS, DPPH and CUPRAC assays (See Table 3).

In another investigation of Kolak et al., the antioxidant activities of the diterpenoids ferruginol (**11**) and taxodione (**7**) were studied using complementary methods including *β*-carotene bleaching, DPPH free radical scavenging activity, ABTS cation radical scavenging activity and CUPRAC assays. Taxodione (**7**) was determined as the highest active diterpenoid in all assays (see Table 3) [27].

Sclareol (**46**) was also isolated from *Teucrium orientale* subsp. *orientale* from Iran, and similar data were reported by Alviri et al. [26].

Two Nepeta species (*Nepeta obtusicrena* Boiss. Et Kotschy Ex Hedge and *Nepeta sorgerae* Hedge et Lamond) were collected from Nemrut Mountain (East Anatolia) and afforded two diterpenes. Obtusicrenone was obtained from *Nepeta obtusicrena* and sorgerolone was obtained *Nepeta sorgerae* for the first time and They showed low antioxidant activity. Although their AChE enzyme inhibition of the extracts and two diterpenoids was very promising [29, 30].

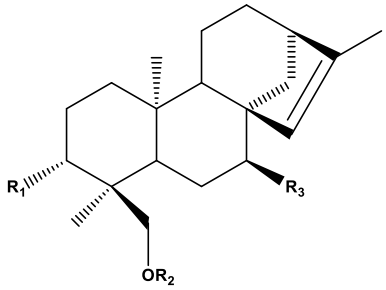
Table 3. Antioxidant activity data of diterpenoids reported the years of 2006-2025 from Anatolia

Compound	DPPH assay	ABTS assay	O_2 assay·	CUPRAC	β-Carotene-Linoleic assay
Abietane Diterpenoids					
Ferruginol (**11**)[a/d]	99.68/33.80 [d]	5.39/6.61 [d]	>100	49.83 [d]	NT
Taxodione (**7**)[a]	40.64	2.37	>100	NT	NT
7-Acetylroyleanone (**10**) [d]	12.17	27.64	NT	35.55	NT
6,7-Dehydroroyleanone (**9**) [d]	16.84 [d]	55.73	NT	28.56	NT
Inuroyleanol (**14**) [d]	2.21 [d]	5.11[d]	NT	7.12 [d]	NT
12-Hydroxy-6,7-secoabieta-8,11,13-triene-6,7-dial (**17**)	>1000	54.94	NT	72.40	NT
Kaurane Diterpenoids					
Ent-7α-acetoxy-16β,18-dihydroxy-kaurane (**45**)[c]	94.52	NT	303.53	NT	94.52
Epoxyisolinearol (**41**)[c]	NA	NT	337.52	NT	195.17
Sideroxol (**42**)[c]	NA	NT	388.30	NT	NA
Sideridiol (**34**)[c]	NA	NT	273.85	NT	NA
Siderol (**1**)[c]	NA	NT	298.95	NT	NA
7-E*pi*-candicandiol (**33**) [c,e]	NA	NT	514.38[c]/NA[e]	NT	53.82/43.1[e]
Linearol (**31**)	NA	NT	571.05	NT	271.70
Sidol (**32**)	NA	NT	548.14	NT	355.82
Pimarane Diterpenoid					
14α-Acetoxy-18-hydroxy-isopimara-8,15-diene-7-10 (**47**)[b]	NT	NT	NT	NA	59.5
Labdane Diterpenoid					
Manoyl oxide (**39**)	NA	NA	NA	NA	NA
Sclareol (**46**)	129.3	NT	NT	NT	NT
α-Tocopherol[a/c]	12.26[a]/41.33 [c]	4.87[a]	44.60[a]/17.27 [c]	9.34[d]	4.88 [c]
BHT[a/c]	54.03[a]/84.41 [c]	2.91[a]	87.59[a]/144.27[c]	5.12[d]	84.41[c]

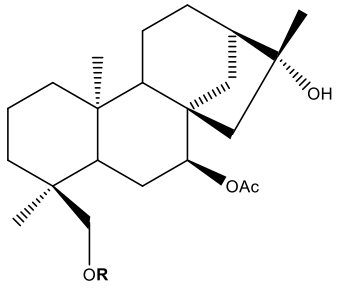
[a]IC_{50} values were given as μg/mL [27]
[b]IC_{50} values were given as μg/mL [28, 29]
[c]IC_{50} values were given as μM [24]
[d]IC_{50} values were given as μg/mL [25]

2.6. Insecticidal Activity

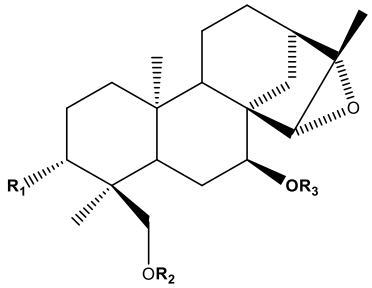
Insecticidal activities of *ent*-kaurene diterpenoids isolated from *Sideritis condensata* and *Sideritis lycia* were reported by Kiliç et al [15, 31]. Topical application and contact toxicity assays were caried out on the *S. lycia and S. condesata* extracts and the isolated diterpenoid linearol (**31**) against *Tetranychus urticae, Bemicia tabaci, Sitophilus granaries, Ephestia kuehnilla* and *Lasioderma serricorne Lasioderma.* The diterpenoid linearol (**31**) was found to be active against the tested larvae reported earlier on other *ent*-kaurene diterpenoids, 7-epicandicandiol **(33)**, and 18-acetylsideroxol **(48)**. This studies proof that *ent*-kaurene diterpenoids enriched extracts of *Sideritis lycia*, *Sideritis condensata* and *Sideritis trojana* could be used as insecticidal agent [1, 15, 31-33]



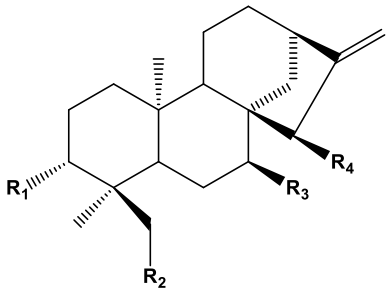
	R_1	R_2	R_3
1	H	H	OAc
34	H	H	OH
35	OAc	H	OH



	R
40	OH
45	OAc



	R_1	R_2	R_3
41	OH	OAc	H
42	H	H	H



	R_1	R_2	R_3	R_4
31	OH	OAc	OH	H
32	OAc	OH	OH	H
33	H	OH	OH	H
43	OH	OH	OH	H
44	H	OH	OAc	OH
50	H	OH	OH	OH

Figure 2. Bioactive kaurene diterpenoids from Anatolian Lamiaceae species

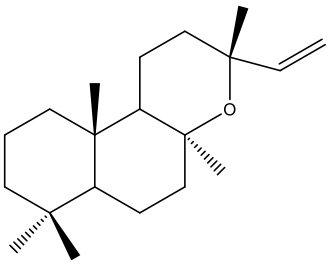
2.7. Cardiovascular Activity

The most prescribed drug group in the current treatment of hypercholesterolemia is the statin group of drugs that act via the HMG-CoA reductase inhibitor mechanism. For this purpose, *Salvia multicaulis* Vahl. extract and abietane diterpenoids isolated from this plant were investigated for their HMG-CoA reductase inhibitory properties. 6,7-Dehydroyleanone (**9**), ferruginol (**11**), 7-acetylhorminone (**36**), horminone (**49**), 7-acetylhorminone (**36**) mixture (1:1), psiferal (**15**), 12-demethylmulticauline (**20**), 12-hydroxyabieta-1,3,5(10), 8, 11, 13-hexaene (**19**) [20], isolated from this species, showed inhibition potential of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The HMG-CoA Reductase inhibition % of the compounds were reported as 28.50 ± 0.13, 18.11 ± 0.10, 84.15 ± 0.10, 76.26 ± 0.14, 35.29 ± 0.05 and 2.26 ± 0.21, respectively. The higher inhibitions were observed for 7-acetylhorminone (**36**), horminone (**49**)-7-acetoxyhorminone (**36**) mixture (1:1) and their IC_{50} values determined as 52.3 ± 0.78 μg/mL, and 63.6 ± 1.21 μg/mL, respectively [34].

2.8. Other Biological Activities

Topçu et al have reported the urease and tyrosinase activity of tanshinone I (**21)**, tanshinone IIA (**22**), dihydrotanshinone I (**23**), cryptotanshinone (**24**) carnosic acid (**25**) and carnasol (**26)** and their activities were reported as μg kojic acid or thiourea activity/mg compound. In this report, the urease inhibition activity of the compounds was found to be as tanshinone IIA (**22**) (16.12. ±0.21), tanshinone I (**21**) (174.73±0.19), cryptotanshinone (**24**) (103.05 ±0.21,0.11) carnosic acid (**25**) (62.12 ±0.07) and

carnasol (**26**) (26.60 ±0.03) and the positive control of thiourea (75.14 ± 1.34). Regarding the tyrosinase activity only tanshinone I (**23**) (372.86 ± 2.47) and carnosic acid (**25**) (45.93±0.71) showed antityrosinase activity among the tested compounds. The other diterpenoids were found to be not active on this assay **[**20].



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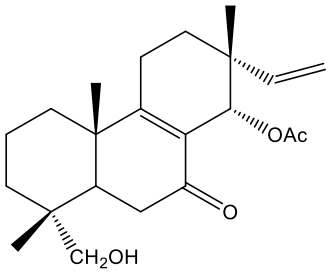

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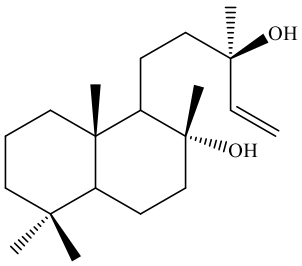

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Figure 3. Bioactive Labdane and Pimarane type diterpenoids from Anatolian Lamiaceae species

3. Conclusions

In this study, the first of which we had previously done, the review on the biological activity studies of diterpenoids isolated from Lamiaceae (Labiatae) plants growing in Türkiye, was updated with studies conducted between 2006 and 2025. The most important element that stands out in this study which is an update of the previous review article study with the data of the past 20 years, is that there is a dramatic decrease in the isolation and structure determination studies of the Lamiaceae family in Türkiye.

It was observed that only a few groups conducted studies in this field, which are eligible to be discussed in this study. During this period, a great-decrease was observed in antibacterial and antifungal activity studies, probably due to the limited biological activity data observed except for a few studies [35, 36], while it was determined that the interest in cytotoxic activity studies was maintained. On the other hand, an increase was observed in enzyme inhibition studies, especially in acetylcholinesterase and butyrylcholinesterase activity studies, during this period. In particular, it has been demonstrated by Topçu et al. that abietane-type diterpenoids obtained from *Salvia* species [37] might be a significant potential source in the treatment of neurodegenerative diseases. When evaluated through a similar mechanism, considering the potential antioxidant capacities of diterpenoids, Lamiaceae species still have many members waiting to be investigated in terms of the isolation of their diterpenoids and the study of their structure-activity relationships.

Another significant result is the antiviral activity studies on the *Sideritis lycia* species as conducted in parallel with the traditional use of Lamiaceae species for colds and flu as given in this context investigation the effects of the species in this family is the utmost importance. COVID-19 pandemic has once again underscored the relevance of such research, mentions the substantial opportunities for further studies in this field. More over insecticidal activity studies on the *Sideritis* genus have revealed that many other topics about *Sideritis* species have a huge potential for this specific area.

It has to be pointed out that the majority of drugs available on the market are natural or natural based therefore it is important to conduct activity-focused studies using bioactivity-guided fractionation

of species belonging to the Lamiaceae family, to identify active compounds to create new semisynthetic derivatives, and to accelerate the process with computer-aided drug design studies. In conclusion, we claim that the genus *Sideritis* has strong potential as a natural resource for the cosmetics, cosmeceuticals, food and veterinary, and pharmaceutical industry applications due to their biological activities and safety issues [38].

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