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Chemical Composition and *In Silico* Acetylcholinesterase Inhibitory Activity of Essential Oils of Six Apiaceae Species from South-East Morocco

Omayma Bouzekri [1], Sabah Elgamouz [1], Khalil El khatabi [1], Ali Amechrouq [1], Mohammed Aziz Ajana [1], Mohammed Bouachrine [1], Tahar Lakhlifi [1], Mostafa El Idrissi [1], M'barek Choukrad [1,*]

[1] Molecular Chemistry and Natural Substances Laboratory, Moulay Ismail University, Faculty of Sciences, B.P. 11201, Zitoune, Meknes, Morocco; m.choukrad@umi.ac.ma (M.C.);
* Correspondence: m.choukrad@umi.ac.ma ; (M.C);

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Abstract: This work aims to investigate the chemical composition of essential oils extracted from the seeds of six wild Moroccan Apiaceae species (*Ammodaucus leucotrichus* Coss & Dur, *Carum carvi* L., *Coriandrum sativum* L., *Cuminum cyminum* L., *Foeniculum vulgare* Mill., and *Petroselinum crispum* (Mill.) Fuss.,), and study the potential of the main compounds of the obtained essential oils as Acetylcholinesterase inhibitors. The essential oils thus obtained were analyzed and identified by the GC-Ms. To determine the similarities and dissimilarities between the chemical composition of the essential oils of the six species, we performed the Principal component analysis (PCA) and Agglomerative Hierarchical Clustering (AHC). The main compounds of the selected plants were studied for their docking behavior against acetylcholinesterase using surflex-docking. The GC-Ms results showed that the major components present in the *A.leucotrichus* Coss, *C.carvi*, *C.sativum*, *C.cyminum*, *F.vulgare*, and *P.crispum* were respectively Perrillaldehyde, Carvone, Linalool, Cuminaldehyde, Estragole, and Apiol. Regarding the in silico study of the main compounds, Cuminaldehyde as the major component of *C. cyminum* L., essential oil indicated a strong Acetylcholinesterase inhibitory activity. These presented findings suggest that the essential oil of *C. cyminum* may be a novel alternative source of acetylcholinesterase inhibitor.

Keywords: Apiaceae species; essential oil; GC-MS; ACP; molecular docking; acetylcholinesterase inhibitors.

1. Introduction

Alzheimer's disease (AD) is a progressive neurological disorder characterized by memory and behavioral problems [1, 2]. One of the main side effects of this pathology is the deficiency of cholinergic neurons in the brain of patients [3]. Acetylcholinesterase (AChE) inhibitors have become the most widely prescribed class of drugs for the treatment of Alzheimer's disease (AD) [2, 4] because they stop the conduction of nerve impulses by rapidly hydrolyzing the neurotransmitter acetylcholine (ACh) into acetate and choline in cholinergic synapses [5, 6]. The most prescribed inhibitors for AChE are related to alkaloids (galantamine and rivastigmine) [7–9]. Therefore, the search for other inhibitors from natural plants has become a necessity in the pharmaceutical field. Essential oils (EOs) extracted from medicinal

plants are attracting special attention. They have been extensively used for medicinal purposes [10]. Essential oils are a mixture of different bioactive components [11]. The existence of a diversity of chemical compounds gives (antispasmodic, antioxidant, insecticidal antipathogenic, and cytotoxic properties to the EOs [12–17]. Generally, the main constituents determine the essential oil characteristics, although compounds at lower concentrations can also confer important properties to the oil [18]. Recently, some EOs have been investigated for their anti-acetylcholinesterase activity and have shown significant acetylcholinesterase inhibitory activity [19]. The Apiaceae family is very widespread around the world [20]. The species of this family are characterized by a high content of phenolic and essential oils [6, 21]. This family provides many plants that are used for a diversity of purposes, including medicine. Currently, plants in this family have shown promising efficacy in the central nervous system [6].

The abundance of plants in nature provides a potential source of acetylcholinesterase inhibitors used as a promising strategy for treating neurological disorders such as Alzheimer's disease [22]. In this work, a comparative study of the chemical composition of essential oils extracted from the seeds of six wild Moroccan Apiaceae species (*Ammodaucus leucotrichus* Coss & Dur, *Cuminum cyminum* L. *Coriandrum sativum* L., *Foeniculum vulgare* Mill., *Carum carvi* L. and *Petroselinum crispum* (Mill.) Fuss.). The species were collected from the southeast of Morocco. And to report promising plant species as AChE inhibitors, the major components of the six species have been tested for AChE inhibitory activity by evaluating the interactions of acetylcholinesterase (AChE) with the selected molecules by molecular docking.

2. Materials and Methods

2.1. Plant material and isolation of essential oil.

Six plants from the Apiaceae family were collected from the region Draa-Tafilalet: *Ammodaucus leucotrichus* Coss & Dur. (Kammoune sofi), *Cuminum cyminum* L. (Kamoune) (31°07'10 "N 5°09'58 "W) *Coriandrum sativum* L. (Kazboure), *Petroselinum crispum* (Mill.) Fuss (Maadnousse) (31°53'45.2" N 4°22'34.5" W), *Carum carvi* L. (Karouia) and *Foeniculum vulgare* Mill. (Bessbass): (31°20'47.2"N 4°19'49.9"W). The seeds were dried in obscurity. The extraction of essential oils was done using the hydrodistillation method with a Clevenger apparatus. 100 g of seeds were coarsely powdered and extracted, while the hydrodistillation was done for 3 hours. The yield (%) was calculated as the volume (mL) of extracted essential oil per 100 g of plant material. The obtained essential oil was dried over anhydrous sodium sulfate and conserved at 4°C in amber glass vials until analysis.

2.2. Analysis of essential oil by GC-MS.

The constituents of the essential oils were analyzed by the GC-Ms method. GC-Ms analyses were performed using Thermo Scientific ISQ Series Quadrupole GC-MS System. The GC instrument was equipped with TG-1MS capillary column (30m×0.32 mm, film thickness: 0.25µm). The carrier gas was helium (He: 1.5mL/min). Temperature program: for the first 5min the oven temperature was held at 40°C and programmed to increase at a rate of 4°C/min until reached a temperature of 200°C, then from 200 to 300°C at a rate of 30°C/min and maintained isothermally for 10 minutes. The mass spectrometer was operating in EI mode at 70 eV. The split ratio was 20:1. The injected volume: 1µl of the dilute sample (in cyclohexane

1:100, v/v), Injector, and detector temperature were held at 250°C. The chemical components of the essential oils were identified using the built-in libraries (Nist Co. and Wiley Co., USA) (the Reverse Match Factor RSI > 600) [23, 24].

2.3. Principal component analysis (PCA) and agglomerative clustering (AHC).

The PCA and AHC were carried out with the aim of highlighting in graphical form the maximum amount of information contained in the data table of the chemical composition of the six studied species from the Apiaceae family. These statistical studies were carried out using XLSTAT Version 2016. The PCA was carried out using Pearson-type matrices. The AHC dendrograms were performed with dissimilarity matrices calculated in Euclidean distance, and the method of aggregation chosen systematically is Ward's method.

2.4. In silico study.

2.4.1. Receptor.

The crystal structure of acetylcholinesterase (PDB code: 1EVE, resolution: 2.5Å), was obtained from the protein databank. The 1EVE protein is classified as a Serine Hydrolase underclass of enzymes and involves one chain A. This chain was employed for macromolecule preparation of a sequence length of 543. The original ligand for 1EVE is 1-benzyl-4-[(5,6-dimethoxy-1-indanon-2-yl)methyl]piperidine.

2.4.2. Molecular docking.

Molecular docking is a powerful technique that explores the binding interactions and predicts a ligand's optimal conformation and protein target [25]. The Surflex-Dock module in SYBYL was used for this study. The protein structure was prepared by eliminating water molecules and adding polar hydrogen atoms. The docking analyses were performed by Discovery studio 2016 and PyMol software [26, 27]. For validating the reliability of Surflex-Dock docking prediction of selected ligands, the AutoDock vina method of PyRx [28] was used. The docked findings were assessed based on the total score and binding affinity. The binding conformations between the receptor and the selected molecules with the highest-dock scores and lowest binding energies were further studied and compared.

3. Results and Discussion

3.1. Chemical composition of Eos.

The yield of each essential oil varied among the species are shown in Figure 1. *C. cyminum* recorded the highest yield (4.78%), followed by *A. leucotrichus* (4.26%), while the lowest values were recorded by *C. sativum* with 0.25%. The chemical profile of the oils, retention indices (RI), and the percentage areas of the oil constituents are summarized in Table 1. The identified compounds in essential oils varied from 16 to 32, with percentages ranging from 98.95% to 99.99%. *Ammodaucus leucotrichus* Coss & Dur. essential oil contains 16 compounds that account for 99.15% of the total oil composition and are distinguished by oxygenated monoterpenoids with Perrillaldehyde (74.71%) followed by D-Limonene (17.57%) and α-Pinene (1.68%) as major components. In *Carum carvi* L, we record 29 constituents representing 99.87% of the total oil composition, characterized by the dominance of ketones

and esters. Carvone (33.10%)as major components, followed by Apiol (22.47%) and Piperitone (16.94%). *Coriandrum sativum* L. presents 29 compounds with 99.18% of the total essential oil composition characterized by Linalool (54.46%), Lyratyl acetate (7.44%), and Neryl acetate (9.48%). An essential oil extracted from *Cuminum cyminum* L., 28 compounds were identified, corresponding to 98.95% of the total oil composed mainly of monoterpenoids (hydrocarbons and oxygenated). The sesquiterpenoids were found in traces. Cuminaldehyde (24.43%), followed by β-Pinene (16.76%) and γ-Terpinen-7-al (15.79%), were the main constituents. The essential oil of *Foeniculum vulgare* Mill. contains 32 constituents (99.99% of the total oil). Phenylpropanoids stood out, followed by monoterpene hydrocarbons. Estragole (34.75%) was the main component, followed by α-Pinene (13.72%) and L-Fenchone (12.13%). *Petroselinum crispum* (Mill.) Fuss. essential oil presented 30 compounds (99.84%), with the dominance of phenylpropanoids and monoterpene hydrocarbons, while sesquiterpenoids and oxygenated monoterpenoids were recorded in lower amounts. Apiole (23.45%) was the major constituent, followed by α-Pinene (18.98%) and β-Pinene (15.6%).

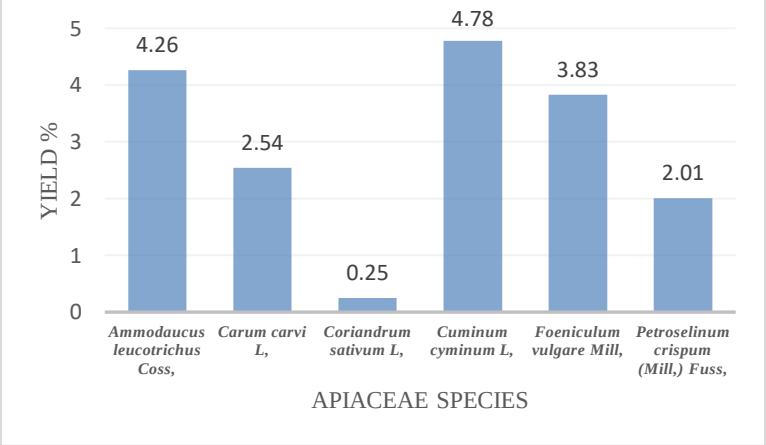


Figure 1. Essential oils yields

Table 1. GC–MS analysis of Chemical composition of essential oils of the six studied species

Components	RT	RI(DIMS)[1]	Apiaceae species					
			Ammodaucus leucotrichus	*Carum carvi*	*Coriandrum sativum*	*Cuminum cyminum*	*Foeniculum vulgare*	*Petroselinum crispum*
β-Thujene	7.97	925.9	----	----	----	0.45	0.08	0.34
α-Pinene	8.26	934.5	1.68	0.11	----	1.51	13.72	18.98
Camphene	8.84	947.4	0.14	----	----	----	0.32	0.22
Sabinene	9.76	967.9	----	1.51	----	1.73	2.05	11
β-Pinene	9.93	973.1	0.78	0.08	----	16.76	1.51	15.6
Myrcene	10.40	983.1	0.30	0.25	----	1.30	2.19	----
δ-2-Carene	10.66	997.7	----	0.12	----	----	----	----
α -Phellandrene	11.00	999.1	0.10	0.57	----	----	0.40	0.51
3-Carene	11.02	1007.2	1.01	----	----	0.15	----	----
α-Terpinene	11.38	1010.9	----	----	----	----	0.03	----
Cosmen	11.78	----	----	----	1.78	----	----	----
o-Cymene	11.85	1032	0.06	----	----	13.06	----	----
D-Limonene	11.89	1023.7	17.57	11.80	----	----	3.17	0.89
1,8-Cineole	12.13	1022.4	----	----	----	0.24	----	----
Lyratyl acetate	12.14	----	----	----	7.44	----	----	----
β-Ocimene	12.56	1038.4	----	----	----	----	0.9	0.11
γ-Terpinolene	12.97	1079.3	----	0.21	----	----	----	----
γ-Terpinene	13.02	1050.3	----	----	5.21	10.89	1.47	----
α-Terpinolene	13.96	1085	----	----	0.36	----	0.14	0.25
cis-Linalool oxide	13.72	1065.1	----	----	0.47	----	----	----
cis-Sabinene hydrate	13.83	1056.3	----	----	----	----	0.08	----
trans-p-Mentha-2,8-dienol	14.06	1107.0	----	----	----	----	----	----

Components	RT	RI(DIMS)[1]	Apiaceae species					
			Ammodaucus leucotrichus	*Carum carvi*	*Coriandrum sativum*	*Cuminum cyminum*	*Foeniculum vulgare*	*Petroselinum crispum*
Neryl alcohol	14.36	1216.2	----	----	0.98	----	----	----
p-Cymenene	14.39	1073.7	----	0.11	----	----	----	0.18
cis-Myroxide	14.47	1132	----	0.82	----	----	----	----
L-Fenchone	14.47	1072.8	----	----	----	----	12.13	----
Linalool	14.88	1086.3	----	----	54.46	0.08	1.76	----
Cosmene	15.13	----	----	----	----	----	----	0.23
cis-Sabinene hydrate,	15.23	1056.3	----	0.15	0.24	----	----	----
trans-p-2-Menthen-1-ol	15.78	1114.4	----	0.08	----	----	----	----
Pinene hydrate	15.88	1107.8	----	----	----	----	0.08	----
(E)-Limonene oxide	16.15	1122.7	----	0.20	----	----	----	----
3,6,6-Trimethylnopinan-2-ol	16.51	1114.4	----	0.21	----	----	----	----
Camphore	16.69	1125.0	----	3.17	0.36	----	0.42	----
trans-Verbenol	16.69	1133.7	----	----	----	----	----	0.05
(+)-2-Bornanone	16.73	1120	----	----	5.87	----	----	----
1,3,4-trimethyl-3-cyclohexen-1-carboxaldehyde	17.17	1198	----	----	----	0.22	----	----
Santolina alcohol	17.31	1035	----	0.11	----	----	----	----
L-Perillaldehyde	17.34	----	0.21	----	----	----	----	----
trans-2-Caren-4-ol	17.66	1109	----	0.34	----	----	----	----
Cumic aldehyde	17.79	1212.6	0.22	----	----	----	----	----
4-Carvomenthenol	17.81	1192	----	0.12	0.49	0.14	0.12	----
3,9-Epoxy-p-menth-1-ene	17.98	1187	----	0.29	----	----	----	----
Cryptone	18.34	1156.7	----	----	----	----	----	0.07
3-p-Menthen-7-al	18.37	1166	----	----	----	1.74	----	----
α-terpinenol	18.47	1175.6	----	----	0.77	0.20	----	----
cis-Myrtenal	18.47	1170.8	----	----	----	----	----	1.48
trans-Dihydrocarvone	18.53	1184.9	----	5.70	----	----	----	----
Estragole	18.64	1200	----	----	----	----	34.75	----
Perrilla aldehyde	19.14	1252.1	74.71	----	----	----	----	----
Dihydrocarveol	19.39	1181.9	----	0.11	----	----	----	----
2,2-Dimethyl-3,4-octadienal	19.40	1109	----	----	----	1.72	----	----
cis-Carveol	19.49	1206.4	----	0.22	----	----	----	----
Bornyl acetate	19.81	1270.2	0.06	----	----	----	----	----
Neodihydrocarveol	19.90	1181.9	----	0.10	----	----	----	----
Perilla alcohol	20.10	1282.1	0.62	----	----	----	----	----
Cuminaldehyde	20.34	1212.6	----	----	0.28	24.43	0.05	----
Geraniol	20.40	1238.9	----	----	3.37	----	----	----
Carvone	20.40	1218.0	----	33.10	----	----	----	----
Piperitone	20.72	1232.7	----	16.94	----	----	----	----
Anisaldehyde	21.01	1222.7	----	----	----	----	0.03	----
Phellandral	21.33	1250.1	----	----	----	0.27	----	----
Anethole	21.67	1264.7	----	----	----	----	11.70	----
α-Terpinen-7-al	21.72	1283	----	----	----	5.19	----	----
γ-Terpinen-7-al	21.92	1290	----	0.26	0.36	15.79	0.04	----
p-Cymen-7-ol	22.05	1270.1	----	----	----	0.61	----	----
Geranyl acetate	22.28	1361.4	----	----	0.34	----	----	----
Myrtenyl acetate	22.58	1305.6	----	----	0.26	----	----	----
Jasmone	23.09	1368.9	----	----	0.38	----	----	----
Methyl perillate	23.10	----	1.48	----	----	----	----	----
1,4-p-Menthadien-7-ol	23.16	1325	----	----	----	0.20	----	----
α-Copaene	23.87	1375.5	----	----	----	----	0.11	----
Azulene	23.95	----	----	----	----	----	----	0.33
β-Cubebene	24.31	1383.5	----	----	----	----	0.05	----
Neryl acetate	24.38	1343.8	----	----	9.48	----	----	----
Eugenol acetate	24.39	1484.5	----	----	----	----	0.04	----
γ-Decalactone	24.83	1426.9	0.17	----	----	----	----	----

Components	RT	RI(DIMS)[1]	Apiaceae species					
			Ammodaucus leucotrichus	*Carum carvi*	*Coriandrum sativum*	*Cuminum cyminum*	*Foeniculum vulgare*	*Petroselinum crispum*
t-β-Farnesene	25.15	1449.3	----	----	0.41	----	----	----
Caryophyllene	25.32	1419.3	----	----	0.24	----	----	0.29
β-Pinene epoxide	25.35	1159	----	----	----	0.20	----	----
Methyleugenol	25.44	1376.1	----	----	----	----	11.19	----
α-Bergamotene	25.69	1410.3	----	----	----	----	----	0.08
(E)-β-Famesene	26.35	1449.3	----	----	----	0.32	0.04	0.66
trans-Verbenyl isovalerate	26.60	----	----	----	0.38	----	----	----
β-Cedrene	27.03	1417.7	----	----	----	----	----	0.22
4-epi-α-Acoradiene	27.09	----	----	----	----	0.19	----	----
2-Dodecanal	27.20	1389.2	----	----	0.46	----	----	----
Germacrene D	27.28	1475.9	----	----	----	----	0.49	0.05
Cuminic acid	27.30	----	----	----	----	0.62	----	----
β-Dihydroagarofurane	27.55	1502	----	----	----	----	----	0.07
β-Bisabolene	28.05	1499.9	----	----	----	----	----	0.11
Myrtenoic acid	28.13	----	----	----	----	0.57	----	----
δ-Cadinene	28.38	1513.9	----	----	----	----	0.15	----
β-Sesquiphellandere e	28.57	1522	----	----	----	----	----	0.07
Kessane	28.80	----	----	----	----	----	----	0.06
Myristicin	29.23	1494.4	----	0.49	1.53	----	----	17.19
Elemicin	29.85	1521.4	----	0.23	----	----	----	2.51
(-)-Spathulenol	29.92	1566.4	----	----	0.82	----	----	----
15-Copaenol	30.03	1550	----	----	----	----	----	0.10
γ-Asarone	30.31	----	----	----	----	----	0.44	----
β-Caryophyllene epoxide	30.51	1570.0	----	----	----	0.13	----	----
Allyltetramethoxybenzene	30.85	----	----	----	----	----	----	4.32
Carotol	31.08	1592.8	----	----	----	0.24	----	0.42
Chamazulene	32.51	1710.0	0.04	----	----	----	----	----
Apiol	33.67	1682	----	22.47	----	----	0.34	23.45
Hexahydrofarnesyl acetone	37.18	1832.9	----	----	0.27	----	----	----
Pentylcurcumene	39.70	1913	----	----	0.24	----	----	----
Geranyl-α-terpinene	40.88	----	----	----	0.37	----	----	----
Pentenylcurcumene	41.03	1980	----	----	1.56	----	----	----
The total identified components			99.15	99.87	99.18	98.95	99.99	99.84
Monoterpenes hydrocarbons			21.64	14.76	7.35	45.85	25.98	48.31
Oxygenated monoterpenoids			77.3	61.92	85.55	52.22	14.68	1.6
Sesquiterpenes hydrocarbons			0.04	----	0.65	0.51	0.84	1.81
Oxygenated Sesquiterpenoids			----	----	1.71	0.37	----	0.65
Diterpenes hydrocarbons			----	----	1.93	----	----	----
Others			0.17	23.19	1.99	----	58.49	47.47

GC–MS = Gas chromatography–mass spectroscopy. RT = Retention time. RI= retention indices in DIMS—dimethylsilicone as Stationary phase. (-) absence

3.2. Principal component analysis for the chemical composition of the six plants studied from the Apiaceae family (PCA).

The analysis of the links between the chemical composition of the essential oils of the six plants: *Ammodaucus leucotrichus* Coss. & Dur., *Carum carvi* L., *Coriandrum sativum* L., *Cuminum cyminum* L., *Foeniculum vulgare* Mill. and *Petroselinum crispum* (Mill.) Fuss., was carried out using the method (PCA), only the discriminating variables were taken into account. To carry out this analysis, two first factorial axes were chosen. Figure 2 shows the dispersion of the six plants in the plane formed by these two axes in relation to the selected variables

explains: 49.69% of the variability, including 25.66% on the first axis and 24.04% on the second axis.

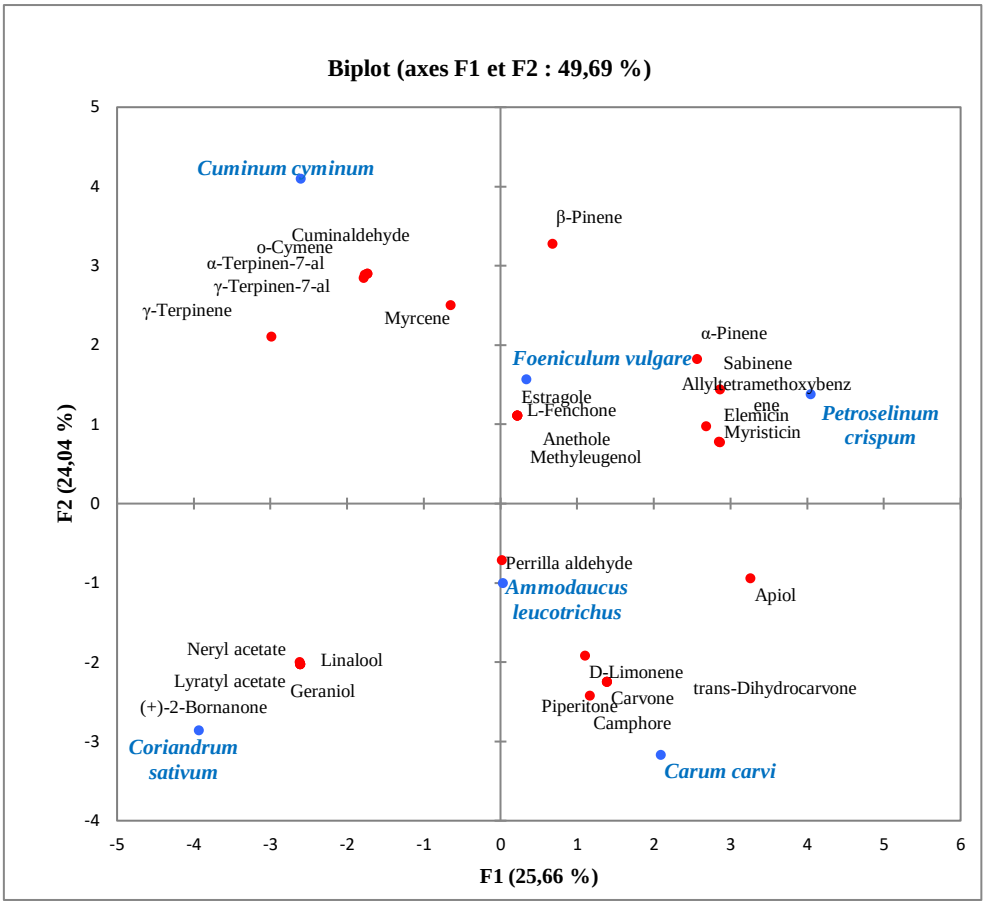
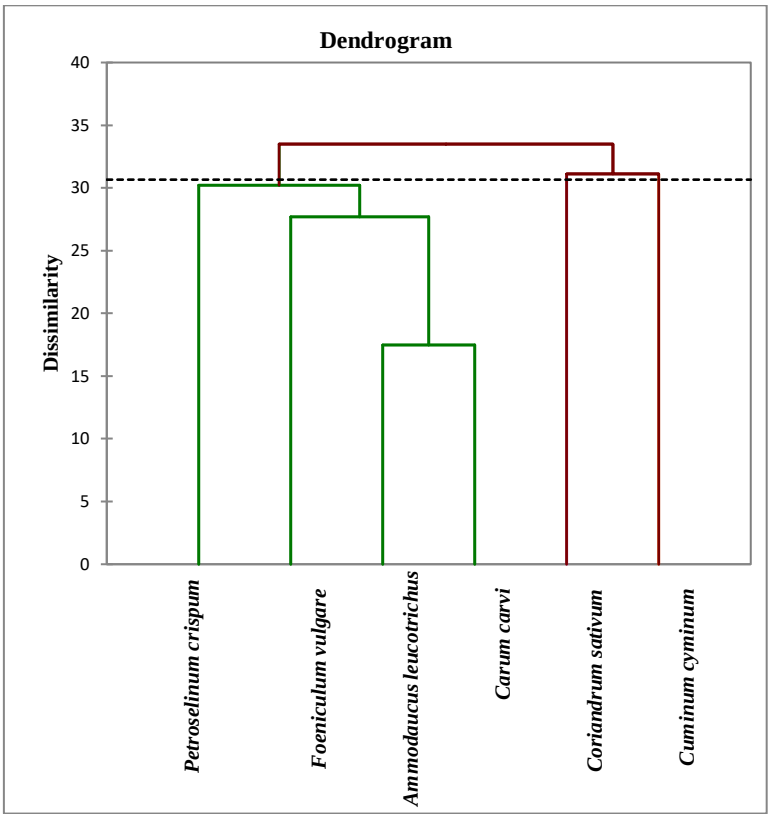


Figure 2. Principal component analysis (PCA) for the common compounds between the six plants studied from the Apiaceae family.



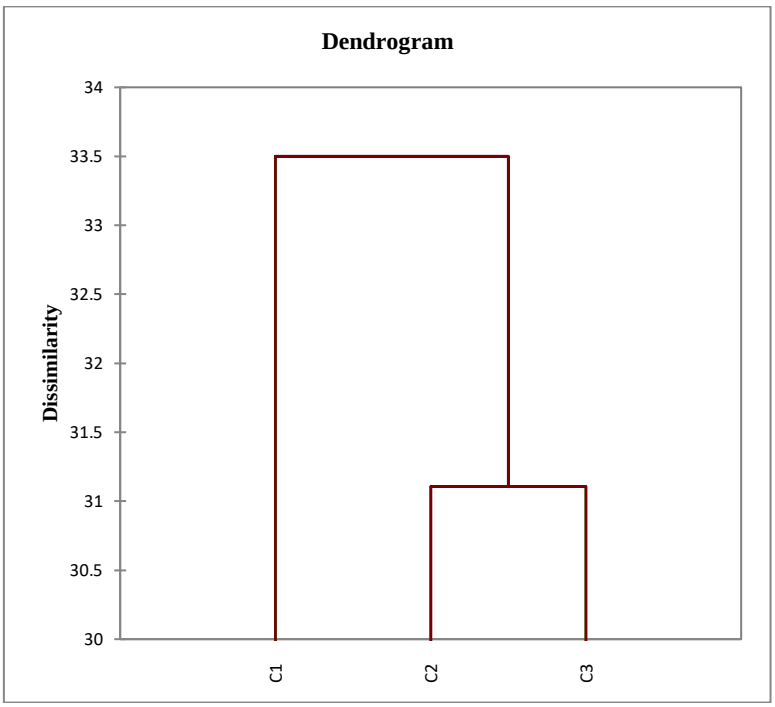


Figure 3. Dendrograms obtained from the analysis of the common compounds between the six plants studied from the Apiaceae family

This figure shows the separation of three groups in the two-axis systems regroups plants with a similar chemical composition. The group formed by *Ammodaucus leucotrichus* Coss & Dur., *Carum carvi* L, *Foeniculum vulgare* Mill., and *Petroselinum crispum* (Mill.) characterized by the presence of D-Limonene, α-Pinene, β-Pinene and Apiol. In this group *Ammodaucus leucotrichus* Coss. & Dur and *Carum carvi* L. are the closest. This group is close to the group formed by *Cuminum cyminum* L, by the presence of α-Pinene, β-Pinene, and Sabinene. The group formed by *Cuminum cyminum* L., is characterized by a high rate of Cuminaldehyde. This group is close to the group formed by Coriandrum sativum L., by the presence of Linalool, Cuminaldehyde, γ-Terpinene, and γ-Terpinen-7-al. In Figure 3, the dendrograms constructed from the chemical data have visualized the links between the six studied plants. The analyzed species were found to be clustered into three major groups, with (*Ammodaucus leucotrichus* Coss. & Dur, *Carum carvi* L, *Foeniculum vulgare* Mill, and *Petroselinum crispum* (Mill.)) being grouped on the first group, Cuminum cyminum L. in the second group and *Coriandrum sativum* L. in the third group. The first cluster is subdivided into two distinct subgroups. *P. crispum* and the second subgroup were formed by *F. vulgare* while *A. leucotrichus* and *C. carvi* were closely related to each other in the third sub-cluster.

Table 2. Total score and binding energy values of main compounds of the studied Apiaceae species.

Apiaceae species	Main compounds	Total score	Binding energy (kcal/mol)
		Surflex-Dock	Autodock vina
Carum carvi L	Carvone	2.2213	-5.6
Coriandrum sativum L	Linalool	4.4251	-4.5
Cuminum cyminum L	Cuminaldehyde	3.3755	-5.5
Foeniculum vulgare Mill,	Estragole	2.6465	-7.3
Petroselinum crispum (Mill,) Fuss	Apiol	2.3160	-5.9
Ammodaucus leucotrichus Coss, & Dur	Perrillaldehyde	2.0508	-5.5

3.3. Molecular docking.

The total score, binding affinity, binding types, and active amino acid residues of the selected compounds in the target protein were investigated using molecular docking. The six main compounds (Carvone, Linalool, Cuminaldehyde, Estragole, Apiol, and Perrillaldehyde) of the studied Apiaceae species were docked into the binding site of the acetylcholinesterase, and their affinity was tested. Table 2 shows the total score and binding affinity values of the six compounds selected.

The highest total scores with the best energies (lowest energy level) of compounds originating from the contribution of several interactions with the acetylcholinesterase were observed for 3 compounds (Linalool, Cuminaldehyde, and Estragole). Consequently, the chosen molecules were prioritized and proceeded to a detailed analysis, as shown in Figures 4, 5, 6.

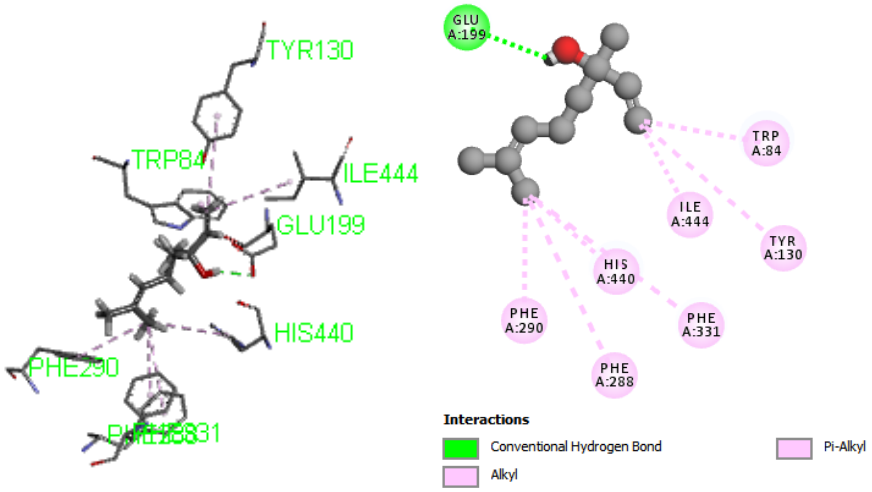


Figure 4. Interactions between Linalool and acetylcholinesterase.

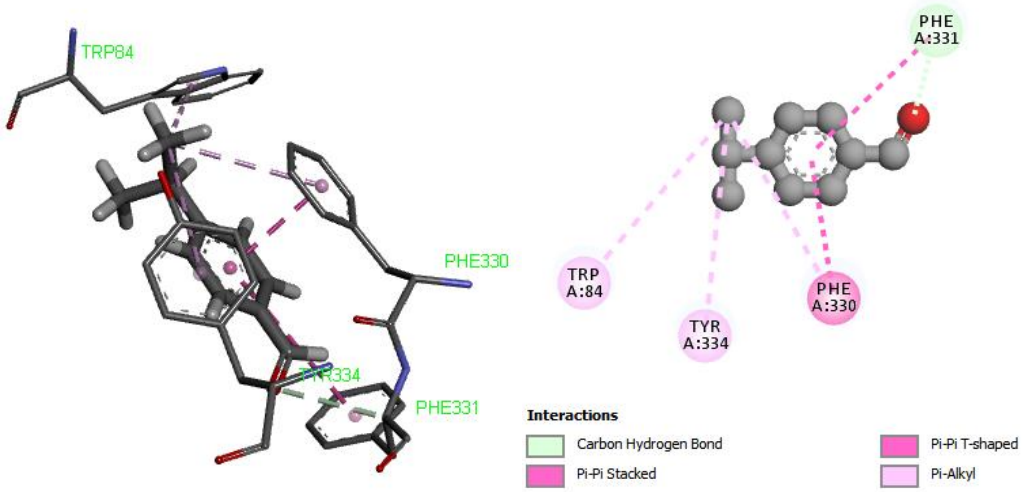


Figure 5. Interactions between Cuminaldehyde and acetylcholinesterase

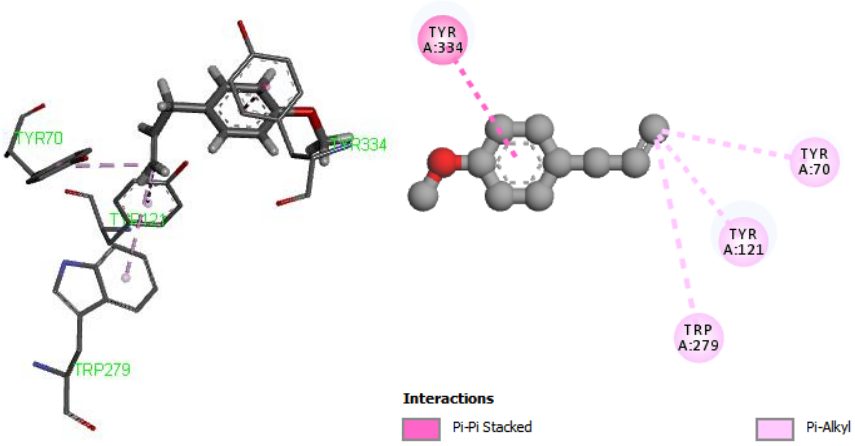


Figure 6. Interactions between Estragole and acetylcholinesterase

Based on the further analysis of the docking results, a hydrogen bond could also be observed for the Linalool binding process, as shown in Figure 4. The hydrogen bond was generated with residue Glu199, while the aliphatic chain was in hydrophobic contact with His440, Ile444, Tyr130, Trp84, Phe331, Phe290, and Phe288.

The docking conformation of Cuminaldehyde was able to provide significant interactions such as carbon-hydrogen bond and hydrophobic, as shown in Figure 5. The carbon-hydrogen bond was generated with residue Phe331, while the phenyl and aliphatic chain were in hydrophobic contact with Phe330, Trp84, and Tyr334, respectively.

Estragole is involved in hydrophobic interactions, as shown in Figure 6. The π-π stack formed by the phenyl moiety on the left side of Tyr334 is beneficial to the binding, while the aliphatic chain was in π-alkyl contact with Trp279, Tyr121, and Tyr70.

Cuminaldehyde was able to be docked deeply inside the binding site of the acetylcholinesterase, resulting in a favorable binding interaction as well as better docking energy. The docking findings support the potential of Cuminaldehyde to be further developed as a novel inhibitor of acetylcholinesterase.

4. Conclusions

The interest in natural bioactive compounds that can preserve human health and inhibit enzymes involved in neurological diseases has increased [29]. Therefore, our work aimed to investigate six wild Moroccan Apiaceae species through essential oil chemical composition analysis, to compare the chemical compounds of the studied species. We opted to study the interactions of this species' major compounds with the acetylcholinesterase enzyme. *Cuminum cyminum* L showed a greater yield (4.78%) than the species studied for essential oil yields. The three major compounds, Linalool, Cuminaldehyde, and Estragole, have shown the highest total scores with the best energies for the interactions with the acetylcholinesterase. Cuminaldehyde, the major component of this essential oil, indicated a strong Acetylcholinesterase inhibitory activity. Moroccan wild *Cuminum cyminum* L could be investigated as a promising neuroprotective agent through functional properties of the main compound.

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Conflicts of Interest

The authors declare no conflict of interest

References

1. Sharma, N.; Tan, M.A.; An, S.S.A. Mechanistic Aspects of Apiaceae Family Spices in Ameliorating Alzheimer's Disease. *Antioxidants* **2021**, *10*, 1571, https://doi.org/10.3390/antiox10101571.
2. Samadi, A.; Estrada, M.; Pérez, C.; Rodríguez-Franco, M.I.; Iriepa, I.; Moraleda, I.; Chioua, M.; Marco-Contelles, J. Pyridonepezils, new dual AChE inhibitors as potential drugs for the treatment of Alzheimer's disease: Synthesis, biological assessment, and molecular modeling. *European journal of medicinal chemistry* **2012**, *57*, 296–301, https://doi.org/10.1016/j.ejmech.2012.09.030.
3. Marucci, G.; Buccioni, M.; Ben, D.D.; Lambertucci, C.; Volpini, R.; Amenta, F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology* **2021**, *190*, 108352, https://doi.org/10.1016/j.neuropharm.2020.108352.
4. Amin, K.M.; Abdel Rahman, D.E.; Abdelrasheed Allam, H.; El-Zoheiry, H.H. Design and synthesis of novel coumarin derivatives as potential acetylcholinesterase inhibitors for Alzheimer's disease. *Bioorganic Chemistry* **2021**, *110*, 104792, https://doi.org/10.1016/j.bioorg.2021.104792.
5. Zarrad, K.; Hamouda, A.B.; Chaieb, I.; Laarif, A.; Jemâa, J.M.B. Chemical composition, fumigant and anti-acetylcholinesterase activity of the Tunisian Citrus aurantium L. essential oils. *Industrial crops and products* **2015**, *76*, 121–127, https://doi.org/10.1016/j.indcrop.2015.06.039.
6. Karakaya, S.; Yılmaz, S. V.; Koca, M.; Demirci, B.; Sytar, O. Screening of non-alkaloid acetylcholinesterase inhibitors from extracts and essential oils of Anthriscus nemorosa (M.Bieb.) Spreng. (Apiaceae). *South African J. Bot* **2019**, *125*, 261–269, https://doi.org/10.1016/j.sajb.2019.07.031.
7. Ahmed, S.; Khan, S.T.; Zargaham, M.K.; Khan, A.U.; Khan, S.; Hussain, A.; Uddin, J.; Khan, A.; Al-Harrasi, A. Potential therapeutic natural products against Alzheimer's disease with Reference of Acetylcholinesterase. *Biomed. Pharmacother* **2021**, *139*, 111609, https://doi.org/10.1016/j.biopha.2021.111609.
8. Karakaya, S.; Bingol, Z.; Koca, M.; Dagoglu, S.; Pınar, N.M.; Demirci, B.; Gulcin, İ.; Brestic, M.; Sytar, O. Identification of non-alkaloid natural compounds of Angelica purpurascens (Avé-Lall.) Gilli. (Apiaceae) with cholinesterase and carbonic anhydrase inhibition potential. *Saudi Pharmaceutical Journal* **2020**, *28*, 1-14, https://doi.org/10.1016/j.jsps.2019.11.001.
9. Honorio, P.; Sainimnuan, S.; Hannongbua, S.; Saparpakorn, P. Binding interaction of protoberberine alkaloids against acetylcholinesterase (AChE) using molecular dynamics simulations and QM/MM calculations. *Chemico-Biological Interactions* **2021**, *344*, 109523, https://doi.org/10.1016/j.cbi.2021.109523.
10. Kim, S.W.; Kang, J.; Park, I.K. Fumigant toxicity of Apiaceae essential oils and their constituents against Sitophilus oryzae and their acetylcholinesterase inhibitory activity. *J. Asia. Pac. Entomol* **2013**, *16*, 443–448, https://doi.org/10.1016/j.aspen.2013.07.002.
11. Marrelli, M.; Amodeo, V.; Perri, M.R.; Conforti, F.; Statti, G. Essential oils and bioactive components against arthritis: A novel perspective on their therapeutic potential. *Plants* **2020**, *9*, 1–17, https://doi.org/10.3390/plants9101252.
12. de Albuquerque Lima, T.; de Queiroz Baptista, N.M.; de Oliveira, A.P.S.; da Silva, P.A.; de Gusmão, N.B.; dos Santos Correia, M.T.; Napoleão, T.H.; da Silva, M.V.; Paiva, P.M.G. Insecticidal activity of a chemotype VI essential oil from Lippia alba leaves collected at Caatinga and the major compound (1,8-cineole) against Nasutitermes corniger and Sitophilus zeamais. *Pestic. Biochem. Physiol* **2021**, *177*, 104901, https://doi.org/10.1016/j.pestbp.2021.104901.
13. Karakaya, S.; Bingol, Z.; Koca, M.; Dagoglu, S.; Pınar, N.M.; Demirci, B.; Gulcin, İ.; Brestic, M.; Sytar, O. Identification of non-alkaloid natural compounds of Angelica purpurascens (Avé-Lall.) Gilli. (Apiaceae) with cholinesterase and carbonic anhydrase inhibition potential. *Saudi Pharm. J* **2020**, *28*, 1–14, https://doi.org/10.1016/j.jsps.2019.11.001.
14. Alzandi, A.A.; Taher, E.A.; Al-Sagheer, N.A.; Al-Khulaidi, A.W.; Azizi, M.; Naguib, D.M. Phytochemical components, antioxidant and anticancer activity of 18 major medicinal plants in Albaha region, Saudi Arabia. *Biocatal. Agric. Biotechnol* **2021**, *34*, 102020, https://doi.org/10.1016/j.bcab.2021.102020.
15. Pateiro, M.; Munekata, P.E.S.; Sant'Ana, A.S.; Domínguez, R.; Rodríguez-Lázaro, D.; Lorenzo, J.M. Application of essential oils as antimicrobial agents against spoilage and pathogenic microorganisms in meat products. *International journal of food microbiology* **2021**, *337*, 108966, https://doi.org/10.1016/j.ijfoodmicro.2020.108966.

16. Benali, T.; Bouyahya, A.; Habbadi, K.; Zengin, G.; Khabbach, A.; Achbani, E.H.; Hammani, K. Chemical composition and antibacterial activity of the essential oil and extracts of Cistus ladaniferus subsp. ladanifer and Mentha suaveolens against phytopathogenic bacteria and their ecofriendly management of phytopathogenic bacteria. *Biocatal. Agric. Biotechnol* **2020**, *28*, 101696, https://doi.org/10.1016/j.bcab.2020.101696.
17. Ali, S.; Khan, M.R.; Iqbal, J.; Batool, R.; Naz, I.; Yaseen, T.; Abbasi, B.A.; Nasir, J.A.; El-Serehy, H.A. Chemical composition and pharmacological bio-efficacy of Parrotiopsis jacquemontiana (Decne) Rehder for anticancer activity. *Saudi J. Biol. Sci* **2021**, *28*, 4969–4986, https://doi.org/10.1016/j.sjbs.2021.07.072.
18. Lima, L.R.; Andrade, F.K.; Alves, D.R.; de Morais, S.M.; Vieira, R.S. Anti-acetylcholinesterase and toxicity against Artemia salina of chitosan microparticles loaded with essential oils of Cymbopogon flexuosus, Pelargonium x ssp and Copaifera officinalis. *Int. J. Biol. Macromol* **2021**, *167*, 1361–1370, https://doi.org/10.1016/j.ijbiomac.2020.11.090.
19. Kang, J.S.; Kim, E.; Lee, S.H.; Park, I.K. Inhibition of acetylcholinesterases of the pinewood nematode, Bursaphelenchus xylophilus, by phytochemicals from plant essential oils. *Pestic. Biochem. Physiol* **2013**, *105*, 50–56, https://doi.org/10.1016/j.pestbp.2012.11.007.
20. Sayed-Ahmad, B.; Talou, T.; Saad, Z.; Hijazi, A.; Merah, O. The Apiaceae: Ethnomedicinal family as source for industrial uses. *Ind. Crops Prod* **2017**, *109*, 661–671, https://doi.org/10.1016/j.indcrop.2017.09.027.
21. Li, M.; Feng, K.; Hou, X.; Jiang, Q.; Xu, Z.; Wang, G.; Liu, J.; Wang, F. The genome sequence of celery (Apium graveolens L .), an important leaf vegetable crop rich in apigenin in the Apiaceae family. *Horticulture Research* **2020**, *7*, 1-10, https://doi.org/10.1038/s41438-019-0235-2.
22. Graça, V.C.; Calhelha, R.C.; Nunes, F.M.; Berthet, J.; Ferreira, I.C.F.R.; Santos, P.F. Isolation of secondary metabolites from Geranium molle L. with anticancer potential. *Industrial Crops and Products* **2019**, *142*, 111859, https://doi.org/10.1016/j.indcrop.2019.111859.
23. Muhaidat, R.; Al-qudah, M.A.; Samir, O.; Jacob, J.H.; Hussein, E.; Al-tarawneh, I.N.; Bsoul, E.; Abu, S.T. Phytochemical investigation and in vitro antibacterial activity of essential oils from Cleome droserifolia (Forssk .) Delile and C . trinervia Fresen . (Cleomaceae). *South African J. Bot* **2015**, *99*, 21–28, https://doi.org/10.1016/j.sajb.2015.03.184.
24. Lal, M.; Borah, A.; Pandey, S.K. Identification of a New High Geraniol Rich Variety "Jor Lab L-15" of Lemongrass [Cymbopogon khasianus (Hack) Stapf (ex Bor)]. *Journal of Essential Oil Bearing Plants* **2019**, *22*, 972-978, https://doi.org/10.1080/0972060X.2019.1661797.
25. El Khatabi, K.; Aanouz, I.; El-Mernissi, R.; Khaldan, A.; Ajana, M.A.; Bouachrine, M.; Lakhlifi, T. 3D-Qsar and Molecular Docking Studies of P-Aminobenzoic Acid Derivatives To Explore the Features Requirements of Alzheimer Inhibitors. *Orbital* **2020**, *12*, 172–181, https://doi.org/10.17807/orbital.v12i4.1467.
26. Systèmes, Dassault. Biovia, Discovery studio modeling environment. *Dassault Systèmes Biovia: San Diego, CA, USA* **2016,** https://www.3ds.com/products-services/biovia/products/molecular-modeling-simulation/biovia-discovery-studio/.
27. DeLano, W. L.; Pymol: An open-source molecular graphics tool. *CCP4 Newsletter on protein crystallography* **2002,** *40.1*, 82–92, https://www.scienceopen.com/document?vid=4362f9a2-0b29-433f-aa65-51db01f4962f.
28. Trott, O.; Olson, A.J. AutoDock Vina : Improving the Speed and Accuracy of Docking with a New Scoring Function , Efficient Optimization , and Multithreading. *Journal of computational* **2010**, *31*, 455-461, https://doi.org/10.1002/jcc.21334.
29. Benabdallah, A.; Boumendjel, M.; Aissi, O.; Rahmoune, C.; Boussaid, M.; Messaoud, C. Chemical composition, antioxidant activity and acetylcholinesterase inhibitory of wild Mentha species from northeastern Algeria. *South African J. Bot.*, **2018**, *116*, 131–139, https://doi.org/10.1016/j.sajb.2018.03.002.