



Essential oils from *Salvia marashica* and *Salvia multicaulis* as natural ingredients: phytochemical composition, antioxidant activity, enzyme inhibition, and molecular docking studies

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Abstract

The increasing prevalence of neurodegenerative and metabolic disorders underscores the need for safe, natural, and multifunctional bioactive agents capable of modulating oxidative stress and key metabolic enzymes. In this study, the chemical composition and in vitro biological activities of essential oils obtained from the aerial parts of *Salvia marashica* and *S. multicaulis* were investigated. The essential oils were extracted by hydrodistillation and characterized using GC–MS analysis. Eucalyptol (20.68%) and α -terpineol (11.16%) were identified as the major constituents of *S. marashica*, whereas *S. multicaulis* was rich in camphor (16.04%) and eucalyptol (13.34%). Antioxidant activities were evaluated using DPPH, ABTS, FRAP, and CUPRAC assays, revealing that *S. marashica* essential oil exhibited higher antioxidant potential in most assays. Enzyme inhibition studies showed that *S. marashica* essential oil exerted stronger inhibitory effects against acetylcholinesterase and butyrylcholinesterase ($IC_{50} = 114.579$ and $138.028 \mu\text{g/mL}$, respectively), indicating potential relevance for Alzheimer’s disease–related enzyme modulation. In contrast, *S. multicaulis* essential oil demonstrated more potent α -glucosidase inhibition ($IC_{50} = 77.270 \mu\text{g/mL}$), suggesting promising antidiabetic potential. To support the experimental findings, molecular docking studies were performed on 52 identified constituents against α -amylase, α -glucosidase, acetylcholinesterase, butyrylcholinesterase, and tyrosinase. Oxygenated sesquiterpenes, particularly β -eudesmol, cubedol, and caryophyllene oxide, showed the strongest binding affinities, providing a molecular rationale for the observed activities. This study presents the first report on the chemical composition and biological activities of *S. marashica* essential oil and the first evidence of the antidiabetic potential of *S. multicaulis* essential oil, highlighting their potential as natural multifunctional bioactive agents.

Keywords Alzheimer’s disease · Antioxidant · Diabetes · GC/MS · Lamiaceae

Introduction

Essential oils from natural sources have attracted considerable attention for their wide range of pharmacological and biological activities. Their antioxidant effects, largely due to phenolic compounds and terpenoids, may help protect cells from oxidative stress and lower the risk of chronic diseases such as cancer, diabetes, cardiovascular, and neurodegenerative disorders [1–4]. Beyond their antioxidant capacity, several essential oils have demonstrated neuroprotective and antidiabetic effects by modulating key metabolic enzymes, enhancing insulin secretion, improving glucose uptake, and regulating cholinergic neurotransmission [5, 6]. Owing to this multifunctional bioactivity profile, essential

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oils are increasingly regarded as promising natural therapeutic agents. Furthermore, their strong antioxidant and enzyme-inhibitory properties have promoted their use in the food industry as natural preservatives that delay lipid oxidation, inhibit spoilage-related enzymes, and improve food stability [7, 8].

In this context, the genus *Salvia* L. (Lamiaceae) is among the most chemically and pharmacologically diverse genera of medicinal plants. Comprising nearly 1000 species worldwide, *Salvia* species are widely distributed in temperate and subtropical regions and have a long history of use in traditional medicine for the treatment of various ailments, including inflammatory disorders, infections, metabolic diseases, and cognitive impairment [9].

Previous studies on *Salvia* species have reported diverse biological properties, including antioxidant, antidiabetic, neuroprotective, and dermatological effects [10]. For instance, essential oils from *S. officinalis*, *S. dominica*, *S. tomentosa* exhibited notable α -amylase, α -glucosidase and tyrosinase inhibition and antioxidant activity [11–14], while *S. officinalis*, *S. aristata* and *S. lanigera* demonstrated cholinesterase inhibitory activity relevant to Alzheimer's disease [15–17]. Phytochemical investigations of *Salvia* essential oils have revealed a rich composition, dominated by monoterpenes and sesquiterpenes, including 1,8-cineole, camphor, α - and β -thujone, borneol, and caryophyllene derivatives, which have been closely associated with antioxidant, antidiabetic, neuroprotective, and enzyme-inhibitory activities [18–20]. These findings underscore the therapeutic versatility of *Salvia* essential oils and support their continued investigation as sources of bioactive natural compounds.

Despite extensive research on well-known *Salvia* species, several taxa remain poorly explored, particularly endemic and regionally distributed species. *S. marashica* İlçim, Celep & Doğan is a perennial suffrutescent with a woody rootstock stem, lower parts covered with long villous and dense retrorsely pilose hairs. Leaves pinnatisect with linear-oblong or obovate-elliptic segments. Inflorescences racemose, exceeding leaves with 3–10 (rarely to 12) verticillasters with black-headed glandular pilose. Calyx infundibular, bilabiate, 12–16 mm. Corolla 20–28 mm, pink, upper lip straight. Nuts ovoid-globose with slightly tuberculate, 3.4–3.6 × 2.7–3 mm. *S. marashica* is endemic and distributed in Kahramanmaraş (Fig. 1 (A)). The Turkish name for the plant is “Maraş adaçayı”. *S. marashica* is morphologically close to *S. rosifolia* Sm, differing primarily from the plant sessile glands (not plant pubescent); lower leaves terminal segment 1.2–7 × 0.3–1.8 mm (not flowers 2–4 × 0.4–1.5 mm); pedicel long 2–4 mm (not 4–7 mm long); corolla colour pink (not lilac-pink to violet) [21, 22].

Similarly, *S. multicaulis* Vahl is a perennial herb, mat-forming, with a predominantly glandular pilose stem, rarely glabrous or dendroid hairs (Fig. 1 (B)). Leaves are simple, rarely with 1–2 pairs of basal lobes. Verticillasters 4–10 flowered. Bracts 10–15 mm, ovate. Calyx campanulate, 15–17 mm. Corolla 18 mm, mostly purplish violet, tube generally straight. Nutlets rounded-trigonous. *S. multicaulis* is morphologically close to *S. absconditiflora* (Montbret & Aucher ex Benth.) Greuter & Burdet, differing primarily from the plant with basal lobes (without basal lobes); corolla color mostly purplish violet (not white or pink) [21].

Given the growing demand for natural enzyme inhibitors and antioxidants in both pharmaceutical and health-related research, there is a clear need to investigate underexplored *Salvia* species to identify novel bioactive essential oils and elucidate their mechanisms of action. Therefore, the antidiabetic effects of essential oils from the aerial parts of *S. marashica* and *S. multicaulis* were evaluated using α -amylase and α -glucosidase assays, and the efficacy against Alzheimer's disease was assessed by inhibiting acetylcholinesterase and butyrylcholinesterase enzymes. In addition to the antioxidant effects (as assessed by DPPH, ABTS, FRAP and CUPRAC tests), the anti-melanogenic activity of the essential oils was evaluated by inhibiting tyrosinase activity. GC-MS revealed the chemical composition of essential oils. This is the first report about the biological activity of *S. marashica* essential oil and the antidiabetic activity of essential oil from *S. multicaulis* based on chemical composition.

To further support and rationalize the observed biological activities, molecular docking was performed to predict binding interactions between the identified constituents and the relevant target enzymes. By integrating experimental and computational approaches, this study provides the first report on the biological activities of *S. marashica* essential oil and, to the best of our knowledge, the first detailed evaluation of the antidiabetic activity of *S. multicaulis* essential oil in relation to its chemical composition. These findings help fill existing research gaps and highlight the potential of these *Salvia* species as valuable sources of natural bioactive agents.

Materials and methods

Plant material

The aerial parts of *S. marashica* and *S. multicaulis* were collected from Sarıçukur, Kahramanmaraş province, Türkiye (37°40'42" N, 36°54'38" E; 37°40'59" N, 36°53'12" E, respectively) in June by Prof. Dr. Osman TUGAY (O.Tugay 21.408; O.Tugay 21.406). The plant materials were collected from their natural habitats and were not subjected to

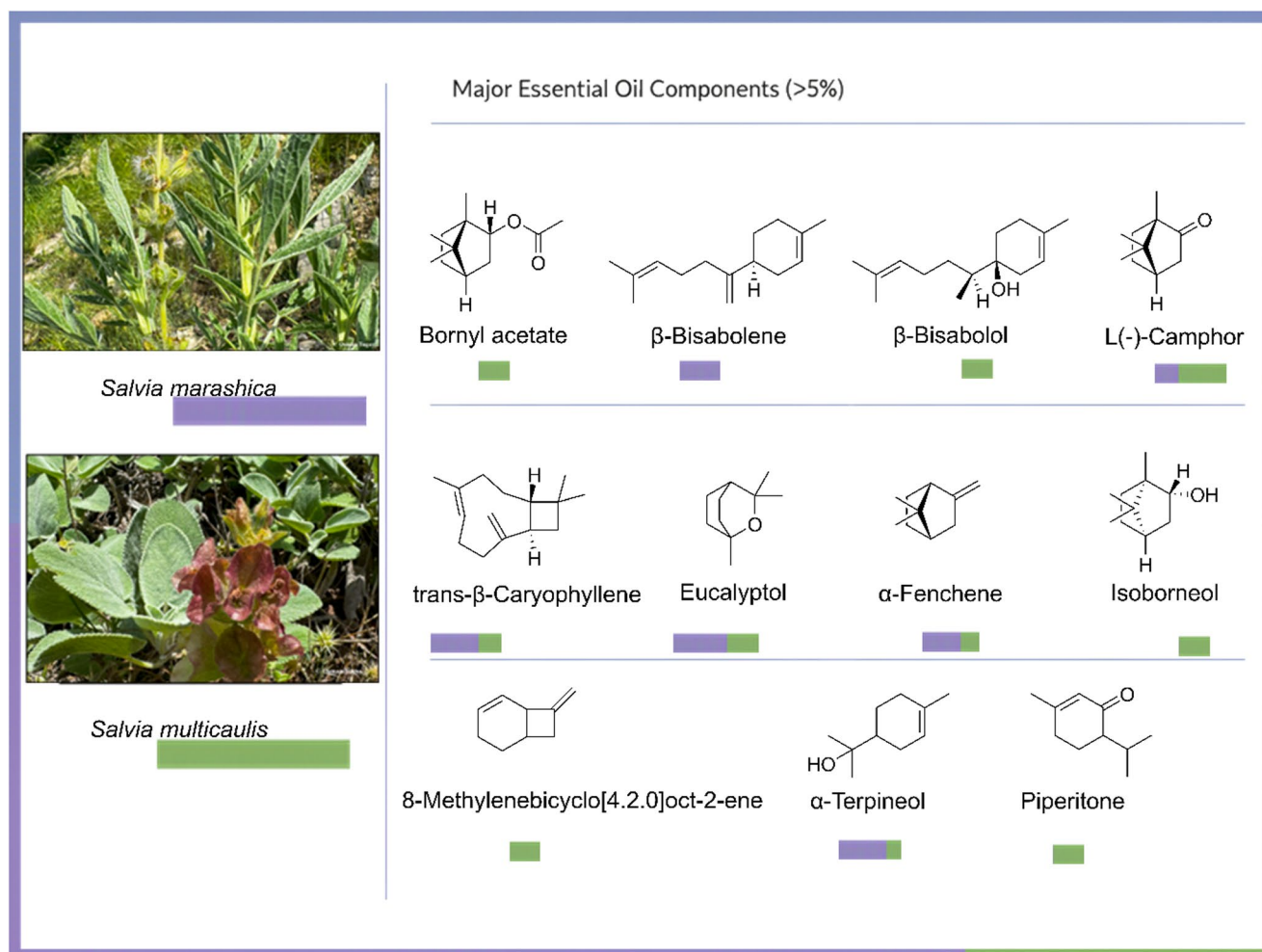


Fig. 1 Habit in the type locality and major essential oil constituents of *Salvia marashica* and *Salvia multicaulis* (plant photographs taken by Prof. Dr. Osman Tugay)

any agronomical practices such as irrigation, fertilization, or pesticide application. The aerial parts were harvested at the flowering stage. The collected samples were taxonomically identified and preserved at the Department of Pharmaceutical Botany, Faculty of Pharmacy, Selçuk University (Konya, Türkiye), and voucher specimens were deposited in the herbarium under the numbers KNYA Herb. No: 30.216 and KNYA Herb. No: 30.215.

Extraction of essential oil

The essential oils from *S. marashica* (SMEO) and *S. multicaulis* (SMTEO) were obtained by hydrodistillation using a Clevenger-type apparatus, as described in the European Pharmacopeia 11.0. Fresh plant material was finely ground and distilled with distilled water for 3–4 h to ensure complete extraction of essential oils. The distillate was separated, and the essential oil was collected, dried over anhydrous sodium sulfate, and stored in sealed amber vials

at 4 °C until analysis. The essential oils were diluted with hexane (10%, v/v) and analyzed by gas chromatography-mass spectrometry (GC-MS) to determine their composition and major bioactive constituents.

Moisture content and essential oil yields The moisture content of the fresh aerial parts was determined to be 25% for *S. marashica* and 35% for *S. multicaulis* using the distillation method with an apparatus described in the European Pharmacopeia 11.0. Essential oil yields were calculated based on the dry weights of the plant materials [23, 24]. The fresh aerial parts of *S. marashica* yielded 0.40% (v/w, dry weight basis), whereas those of *S. multicaulis* yielded 0.30% (v/w, dry weight basis).

Gas chromatography-mass spectrometry (GC/MS) analyses

The phytochemical composition of the essential oils was determined by gas chromatography-mass spectrometry

(GC–MS) using a Shimadzu GC–MS QP2010 Ultra (Japan). Before analysis, the essential oil sample was dissolved in ethyl acetate (10% v/v) and 1 μL was injected into the GC–MS system via an autosampler. Separation was performed on a Restek Rtx-5MS capillary column (30 m $\times$ 0.25 mm i.d., 0.25 μm film thickness) with helium as carrier gas (2 mL/min). The injector temperature was maintained at 285 $^{\circ}\text{C}$ in splitless mode. The GC oven temperature program was set from 40 to 100 $^{\circ}\text{C}$ at 2 $^{\circ}\text{C min}^{-1}$, with a 1 min hold, followed by an increase to 270 $^{\circ}\text{C}$ at 2 $^{\circ}\text{C min}^{-1}$ and a 5 min hold. The total run time was 121 min. Mass spectra were recorded in full-scan electron ionization (EI) mode over an m/z range of 45–650 at an ionization energy of 70 eV. The ion source temperature was set to 300 $^{\circ}\text{C}$ [25]. Compounds were identified by comparing retention times and mass spectra with those in the WILEY 09 and NIST 11 mass spectral databases and by comparing their relative retention indices (RRIs) with those of a n-alkane series.

In vitro evaluation of the antihyperglycemic activity

The antihyperglycemic potential of the tested samples was assessed through in vitro α -amylase and α -glucosidase enzyme inhibition assays, using acarbose as the positive control [26]. In the α -glucosidase inhibition assay, 20 μL of enzyme solution (2 U/mL) and 20 μL of the samples were incubated at 37 $^{\circ}\text{C}$ for 10 min. The reaction was initiated by adding 20 μL of 5 mM p-nitrophenyl- α -D-glucopyranoside (PNPG), followed by an additional incubation at 37 $^{\circ}\text{C}$ for 20 min. Enzymatic activity was terminated with 20 μL of 0.2 mM sodium carbonate solution, and the release of p-nitrophenol—a product of substrate hydrolysis—was quantified spectrophotometrically at 400 nm. For the α -amylase assay, porcine pancreatic α -amylase was prepared at a final concentration of 4 U/mL in ice-cold distilled water. The reaction mixture consisted of 40 μL of test extract, 80 μL of phosphate buffer, and 40 μL of enzyme solution, and was incubated at 25 $^{\circ}\text{C}$ for 5 min. After adding 40 μL of dinitrosalicylic acid (DNS) reagent, the samples were heated at 85 $^{\circ}\text{C}$ for 15 min to develop color. The mixture was then diluted with 100 μL of deionized water, and absorbance was measured at 540 nm.

These assays provided a comprehensive evaluation of the extracts' inhibitory capacity against two key carbohydrate-hydrolyzing enzymes, offering insight into their potential role in managing postprandial hyperglycemia.

In vitro cholinesterase inhibition assays

Inhibitory activities of the test samples against acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) enzymes were evaluated following the spectrophotometric

method described by Kararenk et al. [27]. The AChE assay was carried out using an enzyme solution prepared at a concentration of 0.22 U/mL, while the substrate acetylthiocholine iodide (0.71 mM) and the chromogenic reagent 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB, 0.5 mM) were employed to detect enzymatic activity. Briefly, 20 μL of the enzyme solution and test sample were mixed with 120 μL of phosphate buffer and incubated at room temperature for 30 min. Following this pre-incubation, 10 μL of DTNB was added, and the enzymatic reaction was initiated by adding 10 μL of acetylthiocholine iodide. The hydrolysis of the substrate was monitored by measuring absorbance at 412 nm, corresponding to the formation of a yellow-colored 5-thio-2-nitrobenzoate anion from the reaction between DTNB and the thiocholine product. Donepezil was used as the positive control in the assay. The BChE inhibition assay followed the same procedural steps as the AChE assay, with the only modifications being the use of butyrylthiocholine iodide as the substrate and butyrylcholinesterase (0.1 U/mL) derived from horse serum as the enzyme source.

These assays provided a reliable means of assessing the cholinesterase-inhibitory potential of the tested samples and contributed to the evaluation of their possible relevance for neurodegenerative conditions such as Alzheimer's disease.

Tyrosinase enzyme inhibition assay

The tyrosinase inhibitory potential of the samples was evaluated using a microplate-based enzymatic assay, as described by Paşayeva et al. (2025). The reaction mixture was prepared in a 96-well plate using 0.1 M phosphate buffer (pH 6.8), mushroom tyrosinase (250 U/mL), and L-tyrosine (3 mM) as the substrate. Kojic acid was used as a positive control. Briefly, 20 μL of the test sample and enzyme solution were mixed with 100 μL of buffer and incubated at room temperature for 10 min. After preincubation, 20 μL of the L-tyrosine solution was added to initiate the enzymatic reaction, which was carried out at 25 $^{\circ}\text{C}$ for 30 min. The extent of tyrosinase activity was determined by measuring the absorbance at 492 nm using a microplate reader. This assay assessed the samples' inhibitory effects on tyrosinase, an enzyme relevant to melanin biosynthesis and hyperpigmentation-related conditions.

Antioxidant activity assessment

The antioxidant potential of the essential oils was evaluated using several well-established colorimetric assays.

The DPPH radical scavenging assay, a widely accepted method for assessing free radical neutralization, was conducted according to the protocol of Kararenk et al. (2024). This assay is based on the reduction of the deep-violet

DPPH radical by antioxidants, resulting in a measurable decrease in absorbance.

Similarly, the ABTS^{•+} assay, adapted from Thaipong et al. (2006), was used to assess the ability of the essential oil to quench the ABTS radical cation, which exhibits an absorbance peak at 734 nm. This method is particularly advantageous because it applies to both hydrophilic and lipophilic systems [28].

To evaluate the cupric ion reducing antioxidant capacity (CUPRAC), a reaction mixture was prepared by combining 1 mL each of CuCl₂ solution, neocuproine (2,9-dimethyl-1,10-phenanthroline), and ammonium acetate buffer (pH 7.0), followed by the addition of 0.5 mL of the essential oil or standard solution. After 30 min of incubation in the dark, absorbance was recorded at 450 nm. Various concentrations (500, 250, 100, 50, and 25 µg/mL) were prepared in methanol, and calibration curves were constructed to interpret the results [29].

The ferric reducing antioxidant power (FRAP) assay, which measures the reduction of ferric (Fe³⁺) to ferrous (Fe²⁺) ions in the presence of antioxidants, was performed according to the method of Paşayeva et al. (2025). Together with the radical scavenging assays, this method provides a comprehensive evaluation of antioxidant capacity by assessing the reducing power of the samples.

Molecular docking protocol

The crystal structures of the target enzymes α -amylase (PDB ID: 1B2Y) [30], α -glucosidase (PDB ID: 3TOP) [31], AChE (PDB ID: 7E3H) [32], BChE (PDB ID: 4BDS) [33], and tyrosinase (PDB ID: 5M8M) [34] were retrieved from the Protein Data Bank (PDB). Protein preparation was performed using the Protein Preparation Wizard in Schrödinger v2024-2 Maestro, including assignment of bond orders, addition of hydrogen atoms, optimization of protonation states, and energy minimization with the OPLS4 force field. The hydrogen bonding network was optimized, and protonation states of ionizable residues were predicted using PROPKA at pH 7.4 to ensure chemically accurate states. Crystallographic water molecules beyond 5 Å from the active site were removed.

A total of 52 identified constituents from the essential oils of *S. marashica* and *S. multicaulis* were docked against the selected target enzymes. Their 3D structures were retrieved from PubChem in SDF format and prepared using the LigPrep module of the Schrödinger Suite to generate low-energy conformations with appropriate stereochemistry and protonation states at pH 7.4. The complete Glide Gscore dataset for all docked constituents is provided in Table S1. At the same time, the compounds highlighted in the main text and Fig. 2 were selected as representative examples

based on their more favorable docking scores and more informative binding interactions.

Docking validation was performed by re-docking the co-crystallized ligands of each enzyme into their respective binding sites using the same Glide protocol. The resulting poses were compared to the original crystallographic conformations to confirm the accuracy of the docking procedure. Validation was considered successful when the root mean square deviation (RMSD) between the docked and crystallographic ligand positions was <2.0 Å. In this study, the redocking RMSD values obtained were 0.45 Å for α -amylase (PDB ID: 1B2Y), 0.18 Å for α -glucosidase (PDB ID: 3TOP), 0.03 Å for BChE (PDB ID: 4BDS), 0.51 Å for AChE (PDB ID: 7E3H), and 0.52 Å for tyrosinase (PDB ID: 5M8M), confirming the reliability of the docking protocol.

After validation, molecular docking of the 52 prepared ligands was carried out using the Glide module in Standard Precision (SP) mode [35]. The receptor grid was generated around the active site defined by the position of the co-crystallized ligand. For each ligand, multiple poses were generated, and the pose with the lowest Glide Gscore was selected for further analysis.

Docking results were analyzed based on the Glide Gscore and the type of interactions formed (hydrogen bonding, hydrophobic, π - π stacking, and metal coordination). The most favorable poses were visualized using BIOVIA Discovery Studio Visualizer v2024.

Statistical analysis

Statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc., La Jolla, CA, USA). Data normality and homogeneity of variances were assessed before analysis. Comparisons among groups were carried out using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. Results are expressed as mean $\pm$ standard deviation (SD), where $n = 3$ represents independent technical replicates. Differences were considered statistically significant at $p < 0.05$. In tables, different lowercase letters indicate statistically significant differences between groups based on Tukey's multiple comparisons test [36].

Results and discussion

Gas chromatography results

The chemical composition and molecular structures of essential oils from *S. marashica* and *S. multicaulis* were presented in Table 1 and Table S1. According to the results, in the SMEO essential oil, eucalyptol (20.68%) and α -terpineol (11.16%) were detected as major compounds. However,

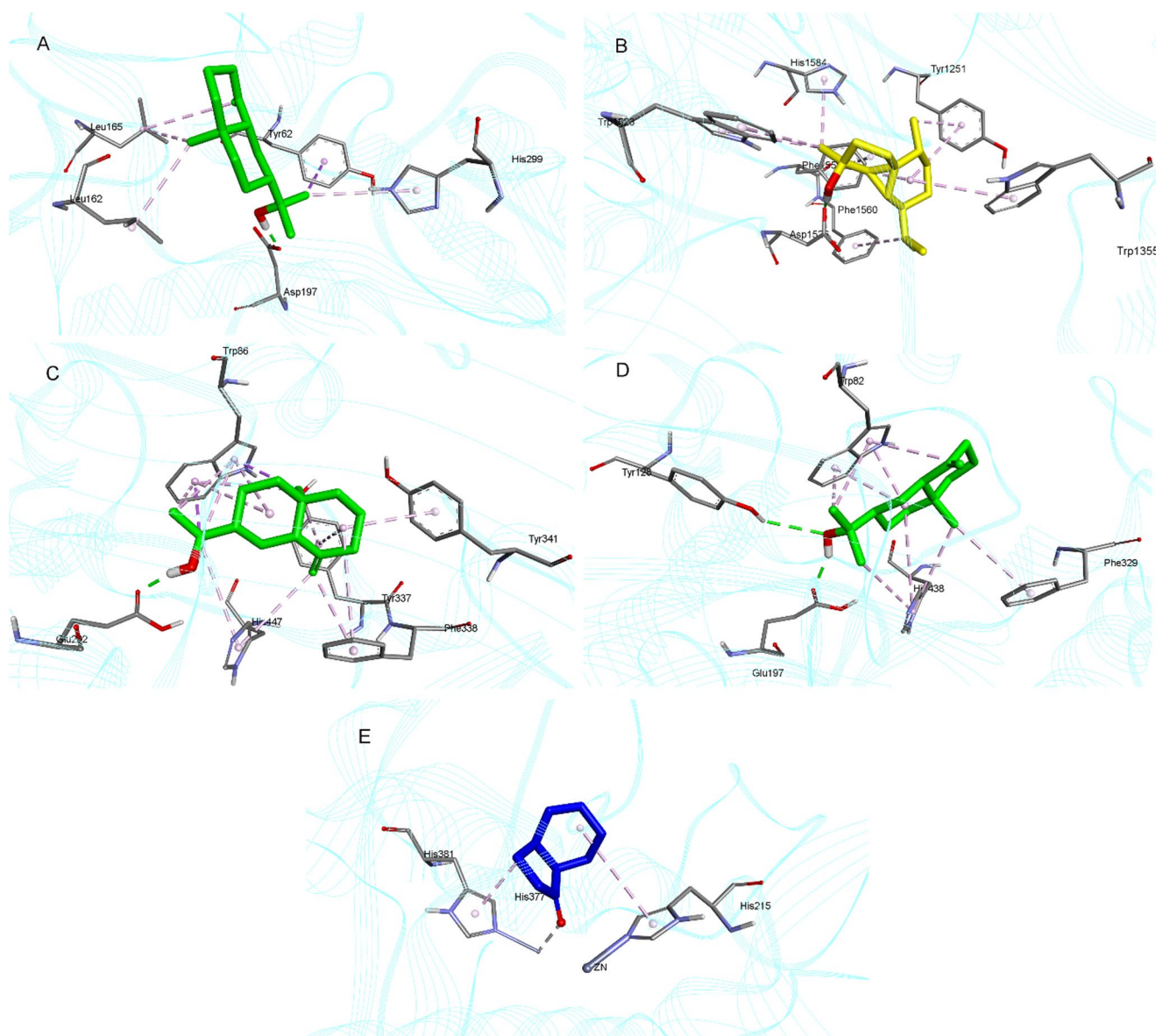


Fig. 2 Binding poses of the selected essential oil constituents, chosen based on their interaction energies and types, in the active sites of target enzymes: **(A)** β -eudesmol with α -amylase (PDB ID: 1B2Y), **(B)**

cubedol with α -glucosidase (PDB ID: 3TOP), **(C)** β -eudesmol with AChE (PDB ID: 7E3H), **(D)** β -eudesmol with BChE (PDB ID: 4BDS), and **(E)** octahydroindene-1-one with tyrosinase (PDB ID: 5M8M)

L-(–)-camphor (16.04%) and eucalyptol (13.34%) were found at higher levels in SMTEO. Eucalyptol, also known as 1,8-cineole, is a monoterpene and a cyclic ether with the molecular formula $C_{10}H_{18}O$. It is a major component of essential oils from *Eucalyptus* species and other aromatic plants [37]. In the literature, eucalyptol has been reported to exhibit antihyperglycemic effects through mechanisms such as enhancing insulin sensitivity, modulating glucose metabolism, and protecting pancreatic β -cells [38, 39]. It may also inhibit key carbohydrate-hydrolyzing enzymes, such as α -amylase and α -glucosidase, thus reducing postprandial hyperglycemia [14, 40, 41]. Eucalyptol has demonstrated neuroprotective properties in various experimental models.

Its ability to inhibit acetylcholinesterase (AChE) may help enhance cholinergic neurotransmission, which is impaired in Alzheimer's disease. Additionally, its anti-inflammatory and antioxidant properties reduce neuroinflammation and oxidative stress, which are implicated in the pathogenesis of neurodegenerative disorders [42].

α -Terpineol is a naturally occurring monoterpene alcohol in several isomeric forms, with ($\pm$)- α -terpineol being the most commonly studied. Structurally, it comprises a cyclohexene ring bearing a tertiary hydroxyl group, which contributes to its moderate polarity and biological activity [43]. Recent studies have highlighted α -terpineol's anti-diabetic potential, primarily through its ability to enhance

Table 1 Phytochemical composition of the essential oils from *S. marashica* and *S. multicaulis*

S.No	RT (min)	RI ^a	Compound name	Content* (%)	
				SMEO	SMTEO
1	10.261	1015	2-(2-methylpropyl) pyrazine	2.63	-
2	10.909	910	8-Methylenebicyclo [4.2.0] oct-2-ene	-	9.78
3	10.330	1068	Phenyl propyl carbonate	0.36	-
4	11.225	1025	7-Propylidene-bicyclo [4.1.0] heptane	1.44	-
5	12.933	943	α -Fenchene	7.44	4.38
6	13.779	958	β -Myrcene	4.41	1.94
7	15.225	969	Amyl vinyl carbinol	0.71	0.42
8	16.781	1059	Eucalyptol	20.68	13.34
9	17.684	976	β -Ocimene	1.15	0.45
10	18.261	998	γ -Terpinene	1.43	0.32
11	18.830	1182	2-methyl-2-(4-methylpent-3-enyl)cyclopropane-1-carbaldehyde	-	0.12
12	19.270	1158	cis- β -Terpineol	0.63	-
13	19.873	1052	α -Terpinolene	1.39	-
14	22.080	1109	1-Octen-3-yl-acetate	-	0.95
15	22.932	1082	Linalool	4.44	-
16	24.695	1121	L-(-)-Camphor	9.65	16.04
17	27.196	1137	Terpinen-4-ol	3.98	-
18	27.654	1198	Isoborneol	-	7.42
19	29.619	1143	α -Terpineol	11.16	2.21
20	31.140	1174	Citral	0.04	-
21	33.009	1158	Piperitone	-	6.85
22	34.510	1277	Bornyl acetate	-	5.89
23	36.618	1314	Myrtenyl acetate	-	0.13
24	38.398	1333	α -Terpnyl acetate	-	0.39
25	38.548	1384	Perillyl acetate	0.35	-
26	39.570	1270	Lavandulyl acetate	0.30	-
27	39.581	1352	Geranyl acetate	-	0.80
28	40.303	1339	β -Bourbonene	0.44	-
29	40.905	1352	Neryl acetate	0.36	1.34
30	43.604	1494	trans- β -Caryophyllene	10.08	3.35
31	45.321	1579	Humulene	-	1.92
32	45.816	1510	β -Bisabolene	5.71	-
33	46.680	1221	α -Copaene	0.43	-
34	47.416	1524	α -Curcumene	-	1.54
35	47.611	1276	trans-Chrysanthenyl acetate	0.40	-
36	47.846	1499	Isocaryophyllene	-	0.50
37	48.322	1555	6-epi-Shyobunol	0.46	-
38	49.128	1480	β -Curcumene	-	1.04
39	49.812	1484	Cubedol	1.29	-
40	49.881	1469	(+)- γ -Cadinene	-	0.92
41	52.205	1523	7-epi-cis-sesquisabinene hydrate	-	0.31
42	53.914	1507	Caryophyllene oxide	3.82	0.99
43	55.210	1153	Octahydroinden-1-one	-	0.34
44	55.386	1592	Humulene epoxide II	1.02	-
45	56.445	1403	(-)- α -Cedrene	0.43	-
46	56.535	1243	trans-syn-trans-Tricyclo[7.3.0.0(2,6)]dodecane	-	1.39
47	58.367	1593	β -Eudesmol	1.26	-
48	59.598	1619	β -Bisabolol	-	6.81
49	59.676	1531	trans-Z- α -Bisabolene epoxide	0.37	-
50	60.636	1625	α -Bisabolol	-	1.30
51	80.150	2072	Cembrene	0.63	-
52	84.749	1789	Kaur-16-ene	0.53	-
Monoterpene hydrocarbons (S. No. 2, 4, 5, 6, 9, 10, 13)				17.26	16.87
Oxygenated monoterpenes (S. No. 7, 8, 11, 12, 14–27, 29, 35)				52.19	55.90

Table 1 (continued)

S.No	RT (min)	RI ^a	Compound name	Content* (%)	
				SMEO	SMTEO
Sesquiterpene hydrocarbons (S. No. 30–34, 36, 38, 40, 45, 51)				17.72	9.27
Oxygenated sesquiterpenes (S. No. 37, 39, 41, 42, 44, 47–50)				8.22	9.41
Phenyl propanoides and phenolic acid derivatives (S. No. 3)				0.36	-
Miscellaneous (S. No. 1, 43, 46, 52)				3.16	1.73
Total identified compounds				98.91	93.18

RI-Relative Retention Index for polar column (C₇-C₄₀ carbon series); * ≥ 0.5%

insulin sensitivity and modulate key enzymes involved in glucose metabolism, such as α -amylase and α -glucosidase. It may help reduce postprandial hyperglycemia, suggesting a possible role in the management of type 2 diabetes [44, 45]. In the context of Alzheimer's disease, α -terpineol has shown neuroprotective and anti-inflammatory effects. It may inhibit acetylcholinesterase (AChE) activity, thereby enhancing cholinergic neurotransmission [46, 47]. Furthermore, α -terpineol demonstrates significant antioxidant activity, acting as a free radical scavenger and reducing lipid peroxidation. These properties help mitigate oxidative stress, which is implicated in the pathogenesis of diabetes and neurodegenerative diseases [47, 48].

Several studies have investigated the phytochemical composition of *S. multicaulis* essential oil; however, the chemical composition of *S. marashica* essential oil is reported here for the first time. According to the literature data, it was described that the major compounds of *S. multicaulis* essential oil were α -pinene (21.9%), eucalyptol (20.1%), camphor (11.0%), camphene (7.8%) and borneol (7.3%) [49, 50]; 1,8-cineole (33.05%) and D-limonene (21.18%) in natural specimen of species, 1,8-cineole (42.35%) and α -pinene (15.74%) in the cultivated sample of *S. multicaulis* [51]; eucalyptol (13.88, 18.39%; 14.89, 21.33%; 19.57, 23.29%), α -pinene (11.60, 10.02%; 13.72, 11.00%; 11.64, 11.69%), and camphor (10.87, 7.43%; 16.02, 6.18%; 16.41, 4.70%) in essential oils of the *S. multicaulis* collected from two different location in Malatya (Türkiye) in May, June, and July [52]; α -copaene (6.6%), α -pinene (5.5%), myrtenol (4.6%), sabinyl acetate (4.6%), 1,8-cineole (3.1%), β -caryophyllene (4.4%) and aromadendrene (3.9%) in the essential oil from *S. multicaulis* var. *simplicifolia* [53]; α -pinene (16.3%) and eucalyptol (16.2%), in essential oil of aerial parts of *S. multicaulis* from Zahlé region and trans-nerolidol (12.3%) from Bechwet region of Lebanese [53]; bornyl acetate (18.1%), β -caryophyllene (16.5%), α -pinene (15.6%), 1,8-cineole (8.3%), limonene (8.3%) [54] and camphor (11.0%), 1,8-cineole (10.7%), borneol (8.6%) and α -pinene (7.5%) in *S. multicaulis* essential oil from Iran [55]; α -pinene (1.4 to 43.2%) and β -pinene (1.1 to 32.3%) in all essential oils from flowers, stems and roots of *S. multicaulis* [56]; trans-sabinyl acetate (23.0%), trans-sabinol (14.7%), α -pinene (37.7%), α -pinene (36.9%) in essential oil from *S. multicaulis* dry

leaf, fresh leaf, pre-flowering and flowering stage, respectively [57]; α -pinene (15.4%), 1,8-cineole (10.2%), camphene (8.1%), β -pinene (3.9%), camphor (6.6%), borneol (8.8%), bornyl acetate (10.3%) and (E)- β -caryophyllene (9.9%) in the essential oils of *S. multicaulis* obtained by hydro distillation and α -pinene (41.2%), camphene (19.3%), 1,8-cineole (11.1%), β -pinene (5.0%), myrcene (2.3%), limonene (4.1%) and camphor (3.6%) by headspace extraction method [58].

These findings suggest that eucalyptol may contribute substantially to the biological activity of both essential oils because it occurs at relatively high levels in both samples. However, the fact that SMEO essential oil was found to be more active in the experiments reveals that the effect may be due not only to this compound but also to its combined contributions with α -terpineol and other constituents. Although eucalyptol and camphor were among the major constituents of the investigated essential oils, the marked differences in enzyme inhibitory activity between the two species suggest that these effects cannot be attributed to a single dominant compound alone, but rather to the combined contribution of multiple constituents within the oils.

Consistent with the findings from the present study, several studies on different *Salvia* species have highlighted the biological activities of essential oils rich in eucalyptol (1,8-cineole) and α -terpineol. For instance, essential oils of *S. officinalis* collected at different phenological stages were shown to contain 1,8-cineole as one of the major components, alongside camphor and α -thujone, with the oil from the full flowering stage exhibiting the strongest antioxidant, antidiabetic, lipase, and lipoxygenase inhibitory activities, as well as pronounced antibacterial properties (IC₅₀ values ranging from 9.24 to 69.23 μ g/mL) [11]. Similarly, the essential oil of *S. lanigera*, characterized by 1,8-cineole (27.28%), camphor (25.82%), α -pinene (7.71%), and α -terpineol (7.67%), demonstrated remarkable radical scavenging potential and significant inhibition of acetylcholinesterase and α -glucosidase enzymes, thereby supporting its potential use in diabetes and neurodegenerative disorders [15]. In another study, *S. aristata* essential oil, although dominated by sesquiterpene hydrocarbons, also showed notable cholinesterase inhibition and neuroprotective effects in oxidative stress models, confirming the relevance of its

constituents in modulating CNS-related pathways [16]. Moreover, the essential oils of *S. dominica*, which contained considerable amounts of oxygenated monoterpenes such as linalool, 1,8-cineole, and α -terpineol, exhibited strong antioxidant activity and moderate antibacterial, anticancer, and enzyme-inhibitory effects [12].

Overall, these studies support the hypothesis that eucalyptol plays an important role in the biological activities of *Salvia* essential oils. In contrast, combined contributions of multiple constituents with other components, particularly α -terpineol, may further enhance their pharmacological properties.

The results of the Antihyperglycemic Activity

Regarding the antihyperglycemic activity of both essential oils, SMEO exhibited higher inhibitory activity than SMTEO in the α -amylase assay (Table 2). Under the applied assay conditions, SMEO showed an IC_{50} value (170.167 μ g/mL) within a comparable range to that of the reference inhibitor, acarbose (IC_{50} = 160.628 μ g/mL). In the α -glucosidase assay, SMTEO demonstrated stronger inhibitory activity than SMEO, yielding an IC_{50} value (77.270 μ g/mL) within a similar range to that of acarbose (IC_{50} = 74.633 μ g/mL). Statistical analysis confirmed that the inhibitory effects of SMEO in the α -amylase assay and SMTEO in the α -glucosidase assay were significantly different from the standard inhibitor acarbose ($p < 0.05$).

Values are expressed as mean $\pm$ SD ($n = 3$). Values with the different letters within each column are significantly different ($p < 0.05$). “-” indicates not calculated. SMEO: essential oil from *S. marashica* aerial parts; SMTEO: essential oil from *S. multicaulis* aerial parts.

These findings indicate that SMEO and SMTEO exhibit selective inhibitory activity against key digestive enzymes involved in carbohydrate metabolism. The potent α -amylase inhibition by SMEO and α -glucosidase inhibition by SMTEO highlight their potential as complementary natural agents in managing postprandial hyperglycemia.

The literature review indicated that, although there were antidiabetic studies on the extracts of *S. multicaulis*, no previous studies have evaluated the antidiabetic activity of the essential oils of either of the investigated *Salvia* species. Therefore, this study provides the first report on the antidiabetic activity of both essential oils.

Recent studies have highlighted the antidiabetic potential of essential oils derived from various *Salvia* species. In particular, the essential oils of *S. dominica*, *S. officinalis*, *S. tomentosa* and *S. lanigera* have been reported to exhibit inhibitory effects on α -amylase and α -glucosidase enzymes [11, 12, 15, 59]. In *S. officinalis*, essential oils collected at different phenological stages exhibited notable inhibitory effects on α -amylase and α -glucosidase, especially at the full flowering stage, where low IC_{50} values were reported for both enzymes. These findings were attributed to variations in the relative abundance of major constituents, including camphor, 1,8-cineole, and α -thujone. However, other reports have described markedly weaker or even negligible α -amylase inhibition for related species, with some studies suggesting enzyme activation rather than inhibition. Such discrepancies emphasize that the antidiabetic efficacy of *Salvia* essential oils cannot be generalized and is highly dependent on chemical composition. In particular, essential oils from different *Salvia* taxa have shown highly variable inhibitory effects on carbohydrate-hydrolyzing enzymes, indicating a pronounced species- and chemotype-dependent antidiabetic potential.

The results of the anticholinesterase activity

Based on the anticholinesterase activity results, the essential oil of *S. marashica* (SMEO) exhibited higher inhibitory activity against both acetylcholinesterase (IC_{50} = 114.579 μ g/mL) and butyrylcholinesterase (IC_{50} = 138.028 μ g/mL) compared to the other tested essential oils, as shown in Table 2. Donepezil was used as the reference inhibitor in these assays. Under the applied assay conditions, the IC_{50} values obtained for SMEO were within a similar range to those of the standard inhibitor.

Conversely, the SMTEO demonstrated moderate inhibitory activity, with IC_{50} values of 165.180 μ g/mL for acetylcholinesterase and 252.794 μ g/mL for butyrylcholinesterase. These values were also within a comparable range to those of donepezil (IC_{50} = 154.099 μ g/mL and 173.794 μ g/mL, respectively) under the same experimental conditions. Statistical analysis revealed significant differences ($p < 0.05$) in anticholinesterase activity between SMEO, the other essential oil, and the standard inhibitor.

Several studies on the inhibitory activities of *Salvia* species against acetylcholinesterase and butyrylcholinesterase

Table 2 Enzyme inhibition results for essential oils from *S. marashica* and *S. multicaulis*

Samples	α -amylase IC_{50} (μ g/mL)	α -glucosidase IC_{50} (μ g/mL)	AChE IC_{50} (μ g/mL)	BChE IC_{50} (μ g/mL)	Tyrosinase IC_{50} (μ g/mL)
SMEO	170.167 $\pm$ 1.089 ^a	391.684 $\pm$ 1.501 ^{a, c}	114.579 $\pm$ 4.079 ^a	138.028 $\pm$ 1.991 ^a	584.163 $\pm$ 0.832 ^a
SMTEO	456.862 $\pm$ 1.520 ^b	77.270 $\pm$ 1.797 ^b	165.180 $\pm$ 3.706 ^{b, c}	252.707 $\pm$ 2.032 ^b	563.259 $\pm$ 1.969 ^b
Acarbose	160.628 $\pm$ 0.827 ^c	74.633 $\pm$ 2.593 ^c	-	-	-
Donepezil	-	-	154.099 $\pm$ 0.241 ^c	173.794 $\pm$ 4.208 ^c	-
Kojic acid	-	-	-	-	267.508 $\pm$ 1.391 ^c

Table 3 Antioxidant capacity results for essential oils from *S. marashica* and *S. multicaulis*

Samples	DPPHIC ₅₀ (μg/mL)	ABTS(μmol Trolox eq./g _{extract})	FRAP(μmol Fe ²⁺ /g _{extract})	CUPRAC(μmol Trolox eq./g _{extract})
SMEO	365.168±2.389 ^a	542.001±3.003 ^{a, b}	2327.708±1.883 ^a	137.348±1.402 ^a
SMTEO	246.349±2.778^b	547.185±1.000 ^b	1582.240±2.142 ^b	79.967±2.447 ^b
Trolox		-	7917.908±1.878 ^c	-
BHA	103.057±3.428 ^c	596.241±4.012 ^c	-	920.767±4.676 ^c

Values are expressed as mean±SD ($n=3$). Different superscript lowercase letters within the same column indicate statistically significant differences among samples ($p < 0.05$). The same superscript letters indicate no statistically significant difference “-” indicates not calculated. SMEO: essential oil from *S. marashica* aerial parts; SMTEO: essential oil from *S. multicaulis* aerial parts

support the findings of the present study [15–17, 60]. In a study, the essential oils from natural and cultivated *S. multicaulis* species exhibited weak acetylcholinesterase inhibitory activity ($25.60 \pm 0.68\%$ and $32.48 \pm 1.02\%$ inhibition at $100 \mu\text{g/mL}$, respectively). Still, they demonstrated potent inhibition against butyrylcholinesterase ($71.20 \pm 0.87\%$ and $83.89 \pm 1.93\%$ inhibition at $100 \mu\text{g/mL}$, respectively) (Akdeniz et al., 2021). However, there are no published reports on the anticholinesterase activity of the essential oil of *S. marashica* [51]. The moderate anticholinesterase activity observed for *S. multicaulis* essential oil is consistent with previous reports, which described weak acetylcholinesterase inhibition but relatively stronger butyrylcholinesterase inhibition for this species. This selective inhibition pattern has been suggested to be associated with the specific terpenoid composition of the essential oil. In contrast, the strong dual inhibition exhibited by SMEO suggests a broader spectrum of cholinesterase modulation, arising from the combined contributions of its major and minor constituents.

The results of the antityrosinase activity

The antityrosinase activities of the essential oils are presented in Table 2. The IC₅₀ values indicate that both essential oils exhibited similar inhibitory effects under the assay conditions used. Specifically, the IC₅₀ values for SMEO and SMTEO were $584.163 \mu\text{g/mL}$ and $563.259 \mu\text{g/mL}$, respectively.

When evaluated alongside the reference inhibitor, both essential oils showed moderate antityrosinase activity, yielding IC₅₀ values higher than that of kojic acid (IC₅₀ = $267.508 \mu\text{g/mL}$) under the same experimental conditions. Statistical analysis revealed significant differences ($p < 0.05$) in inhibitory activity between the essential oils and kojic acid.

The findings of this study are partially supported by previous literature, particularly studies focusing on *S. multicaulis* essential oils. Akdeniz et al. (2021) reported that essential oils obtained from both natural and cultivated samples moderate inhibitory effects on tyrosinase [51]. However, to our knowledge, no prior data are available concerning the tyrosinase inhibitory activity of *S. marashica* essential oil. The alignment with findings on *S. multicaulis* supports the genus-level consistency in enzyme inhibition potential. At

the same time, the lack of prior data on *S. marashica* emphasizes the novelty and contribution of the present study.

The results of antioxidant Activity

The antioxidant activities of both essential oils are presented in Table 3. Based on the obtained results, SMEO exhibited higher antioxidant responses than SMTEO in the ABTS ($542.001 \mu\text{mol Trolox eq./g}_{\text{extract}}$), FRAP ($2327.708 \mu\text{mol Fe}^{2+}/\text{g}$), and CUPRAC ($137.348 \mu\text{mol Trolox eq./g}_{\text{extract}}$) assays under the applied experimental conditions. In contrast, in the DPPH assay, SMTEO showed higher radical-scavenging activity, with an IC₅₀ of $246 \mu\text{g/mL}$. When evaluated alongside the reference antioxidant, both essential oils exhibited measurable antioxidant responses in the ABTS assay, yielding values within a comparable range to that of BHA under the same assay conditions.

Although several studies have reported the antioxidant properties of *S. multicaulis* essential oil, data on *S. marashica* are limited. According to the literature, the essential oils of *S. cryptantha* and *S. multicaulis* exhibited strong antioxidant activity in the DPPH assay, with IC₅₀ values of $3.9 \mu\text{g/mL}$ and $2.4 \mu\text{g/mL}$, respectively [49]. In contrast, a more recent study by Akdeniz et al. (2021) reported weak antioxidant activity (IC₅₀ > $1000 \mu\text{g/mL}$) for both cultivated and wild *S. multicaulis* essential oils, as assessed by DPPH, ABTS, and CUPRAC assays. The present study's findings align with previously published data on *Salvia* species and suggest that these essential oils may serve as promising natural sources of antioxidant agents. These results, which support the antioxidant literature data of both *Salvia* essential oils, indicate that these plant materials can be a good source of antioxidants. The variability in DPPH results among different *Salvia* species in the literature also underscores the influence of species, origin, and assay type on antioxidant outcomes.

In silico docking evaluation of essential oil constituents

The essential oils obtained from *Salvia marashica* and *Salvia multicaulis* have demonstrated remarkable biological

activities, including inhibitory effects against α -amylase, α -glucosidase, AChE, BChE, and tyrosinase. To understand the molecular basis of these effects, docking studies were carried out using the crystal structures of the target enzymes (PDB IDs: 1B2Y, 3TOP, 7E3H, 4BDS, and 5M8M). Glide Gscore values were used to evaluate the binding affinities, with more negative scores indicating stronger interactions. Key catalytic residues for each enzyme include Asp197, Glu233, and Asp300 in α -amylase; Asp1526 and Arg1510 in α -glucosidase; the Ser203–His447–Glu334 triad in AChE; the Ser198–His438–Glu325 triad in BChE; and the copper-coordinating histidines (His61, His85, His259, His263) in tyrosinase, all of which govern ligand recognition and enzymatic activity.

The docking results (Table S1 in the Supporting Information) revealed clear trends that correlate with the experimental enzyme inhibition data. β -Eudesmol consistently emerged as the most potent inhibitor across multiple targets, with Gscores of -7.99 kcal/mol for AChE, -6.81 kcal/mol for BChE, and -4.89 kcal/mol for α -amylase. Interaction analysis confirmed its strong binding, characterized by multiple conventional hydrogen bonds (e.g., Asp197 in α -amylase, Glu202 in AChE, and Glu197 in BChE) and extensive π -alkyl contacts with hydrophobic and aromatic residues such as Trp86, Tyr337, Phe338, Tyr341, and His447 (Fig. 2A–C–D). These interactions provide a stable ligand orientation within the enzyme active sites, explaining its superior inhibitory activity observed in vitro.

Other oxygenated sesquiterpenes, such as caryophyllene oxide and cubedol, also showed favorable docking profiles. Caryophyllene oxide exhibited strong binding to BChE (-6.07 kcal/mol) and tyrosinase (-4.03 kcal/mol), while cubedol demonstrated potent inhibition of α -glucosidase (-5.56 kcal/mol) through a hydrogen bond with Asp1526 (1.59 Å) and hydrophobic contacts involving Tyr1251, Trp1355, Phe1559, and Phe1560 (Fig. 2B).

Octahydroinden-1-one stood out for its dual inhibitory potential, forming stabilizing hydrogen bonds with His1584 in α -glucosidase and coordinating with the catalytic Zn^{2+} ion in tyrosinase (2.16 Å) (Fig. 2D). This metal coordination, combined with π -alkyl interactions with His215 and His381, enhances its predicted tyrosinase inhibitory activity. These findings align with its strong binding energies (-5.63 kcal/mol for BChE and -4.82 kcal/mol for tyrosinase).

In the case of AChE, apart from β -eudesmol, compounds such as kaur-16-ene, piperitone, and phenyl propyl carbonate showed excellent docking energies (-7.60 , -7.39 , and -7.39 kcal/mol, respectively). Kaur-16-ene relied mainly on hydrophobic interactions with residues of the catalytic

anionic site (Trp86, Tyr337, Phe338, and Tyr341), while piperitone and phenyl propyl carbonate demonstrated mixed hydrophobic and weak polar interactions. These features suggest their potential as cholinesterase inhibitors.

For BChE, β -eudesmol again displayed the most favorable interaction profile, forming two strong hydrogen bonds with Tyr128 (2.99 Å) and Glu197 (1.99 Å), along with hydrophobic contacts involving Trp82, Phe329, and His438. In contrast, cembrene engaged only in hydrophobic and π -alkyl interactions, indicating weaker binding compared to β -eudesmol.

When analyzing tyrosinase, L-(–)-camphor formed a key hydrogen bond with Thr391 (1.86 Å) and hydrophobic interactions with Leu382, whereas octahydroinden-1-one exhibited a superior interaction network by coordinating with Zn^{2+} and forming additional hydrophobic bonds, highlighting its enhanced inhibitory potential.

Compounds with weak docking scores, such as β -myrcene and amyl vinyl carbinol (G-scores ranging from -3.0 to -1.2 kcal/mol), showed only limited hydrophobic interactions and lacked hydrogen bonding, suggesting that they contribute minimally to the biological activity of the oils.

The data from Table S1 in the Supporting Information show that compounds with G-scores below -7.0 kcal/mol (e.g., β -eudesmol, kaur-16-ene, piperitone, phenyl propyl carbonate) are potent inhibitors in vitro. Similarly, compounds with scores around -6.0 to -5.5 kcal/mol (e.g., cubedol, octahydroinden-1-one, caryophyllene oxide) demonstrate strong but slightly less potent inhibition. Conversely, molecules with scores higher than -4.0 kcal/mol (e.g., β -myrcene, citral, amyl vinyl carbinol) exhibit weak predicted binding and low enzymatic inhibition.

The integrated analysis of in vitro enzyme inhibition and in silico docking results confirms that the inhibitory potential of the essential oils of *S. marashica* and *S. multicaulis* is primarily due to oxygenated sesquiterpenes and hydrophobic bicyclic terpenoids. Notably, β -eudesmol consistently formed strong hydrogen bonds with catalytic residues across all tested enzymes, confirming its pivotal role as a multifunctional inhibitor. Kaur-16-ene, cubedol, octahydroinden-1-one, and caryophyllene oxide also showed significant interactions, reinforcing their pharmacological relevance.

These findings provide a molecular rationale for the therapeutic potential of these *Salvia* species and identify β -eudesmol, kaur-16-ene, cubedol, and octahydroinden-1-one as promising lead molecules for further drug development and pharmacological investigations.

Conclusions

This study demonstrated that the essential oils of *S. marashica* and *S. multicaulis* exhibit distinct yet complementary biological activities. *S. marashica* essential oil showed stronger antioxidant capacity and more pronounced inhibition of acetylcholinesterase and butyrylcholinesterase, whereas *S. multicaulis* essential oil displayed notable α -glucosidase inhibitory activity. Both oils exerted moderate tyrosinase inhibition, suggesting a broader modulation of the enzyme. The observed bioactivities are consistent with their chemical compositions, particularly the presence of eucalyptol, α -terpineol, and oxygenated sesquiterpenes. Molecular docking analyses supported the in vitro findings by revealing strong binding affinities of oxygenated sesquiterpenes, including β -eudesmol, cubedol, and caryophyllene oxide, toward the active sites of the target enzymes through hydrogen bonding and hydrophobic interactions. These results suggest that the biological effects of the essential oils are likely mediated by the combined actions of multiple constituents rather than a single dominant compound.

Future studies should focus on in vivo validation of these enzyme-inhibitory effects and antioxidant properties, together with detailed toxicity and pharmacokinetic evaluations. Additionally, the acquisition and independent evaluation of key constituents identified in the essential oils may help clarify structure–activity relationships and further support the development of these essential oils or their components as natural agents for managing metabolic, neurodegenerative, and oxidative stress–related conditions.

Abbreviations

SMEO	<i>S. marashica</i> essential oil
SMTEO	<i>S. multicaulis</i> essential oil
CUPRAC	cupric ion reducing antioxidant capacity

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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