Food Analytical Methods (2025) 18:2258–2276
https://doi.org/10.1007/s12161-025-02863-2

RESEARCH

Salvia lanigera Poiret Extracts: Study of the Phytochemical Profiling via GC–MS and HPLC–DAD and Bioactivity with ADME Analysis

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Received: 14 February 2025 / Accepted: 1 July 2025 / Published online: 22 July 2025
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Abstract

This investigation evaluated the chemical composition and the biological activities of the ethanol and petroleum ether extracts of *Salvia lanigera* Poiret from the M'sila region, Algeria. Phytochemical analysis identified 17 compounds in the ethanol extract (HPLC–DAD), with cynarin, ellagic acid, and rutin as major components. Petroleum ether extract (GC–MS) revealed 16 compounds, predominantly palmitic acid and stearic acid. Antioxidant activity was assessed using four assays: the ethanol extract showed significant activity in the phenanthroline assay (1.94 ± 0.18 µg/mL), and SNP assay (124.78 ± 0.59 µg/mL), compared to the BHA standard. Both extracts demonstrated antibacterial and antifungal effects, with inhibition zones of 10–13 mm and MIC values ranging from 0.78 to 3.125 mg/mL against tested strains. Enzymatic assays revealed α-glucosidase inhibition by the ethanol extract (IC_{50} = 27.07 ± 0.78 µg/mL), while α-amylase inhibition was lower (ethanol: 429.85 ± 1.43 µg/mL; petroleum ether: 520.31 ± 1.63 µg/mL). Acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) inhibition were minimal (IC_{50} > 200 µg/mL for AChE; ethanol: 365.84 ± 5.48 µg/mL, petroleum ether: 636.13 ± 4.49 µg/mL for BChE). Urease inhibition was notable for the ethanol extract (54.88%) and comparable for the petroleum ether extract (52.00%). These findings highlight the potential of *S. lanigera* extracts as sources of bioactive compounds with antioxidant, antimicrobial, and enzymatic inhibitory properties, warranting further exploration for therapeutic applications.

Keywords *Salvia lanigera* Poiret · HPLC–DAD · GC–MS · Antibacterial activity · Antifungal activity · Antioxidant activity · Enzymatic inhibitory activity

Introduction

The *Salvia* genus, recognized as one of the largest within the *Lamiaceae* family, comprises nearly one thousand formally identified species renowned for their ornamental, medicinal, and hallucinogenic attributes (Lu 2019; Ortiz-Mendoza et al. 2022). Medicinal plants have constituted a cornerstone of global healthcare systems, serving as the foundation for both traditional medicine and modern pharmacotherapy (Abdallah 2011; Aouzal et al. 2024; Lamari et al. 2025; Paşayeva et al. 2025). Among these, Salvia species hold particular pharmacological significance due to their well-documented therapeutic applications across diverse medical traditions.

A distinguishing feature of the genus is the unique modification of its stamens, which form a lever-like apparatus. This morphological feature, in conjunction with the distinct morphology of the calyx and corolla, has been crucial for the taxonomic differentiation of *Salvia* from other genera (Shahraki et al. 2024). Geographically, the genus demonstrates the greatest diversity in Europe, its primary area of distribution, with notable additional concentrations in the Old World, where approximately 350 species have been documented (Karalija et al. 2022). Furthermore, North Africa represents a significant region of *Salvia* diversity, with 27 taxa recorded across Morocco, Algeria, Tunisia, Libya, and Egypt (Euro-Med Checklist 2024).

A notable species within the *Salvia* genus is *Salvia lanigera Poiret* (also referenced as *Salvia verbenaca subsp. clandestina* (L.) Pugsley; *Salvia controversa* Ten), classified under the section *Pleiosphace.* This species is prevalent in Algeria, primarily thriving in desert or dry shrubland ecosystems. *Salvia lanigera* is easily identified by its distinctive morphology, characterized by pinnatipartite leaves with linear segments and dark purple flowers, complemented by a calyx adorned with sparse, visible green hairs (Quezel and Santa 1963; POWO 2024).

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Moreover, *S. lanigera* is recognized for its widespread medicinal significance across the Mediterranean region. This perennial herb is frequently employed in traditional herbal medicine, where it is administered orally for respiratory and genitourinary conditions (Li et al. 2013), and topically for dermatological ailments (Rahaman et al. 2023). The aerial parts of the plant are commonly prepared as an infusion or decoction for managing conditions such as diabetes (Paşayeva et al. 2020), while the dried leaves are utilized topically for treating wounds, burns, and abscesses (Douira & Zidane 2015).

Morphologically, *S. lanigera* grows between 10 and 50 cm in height, characterized by its hairy, odorous upper parts with glandular tips. The leaves are oval, measuring 2–3 cm in width, featuring scalloped or cut-edge designs. Its small flowers, which are pale blue or whitish, grow in close clusters (Canzoneri et al. 2011). This species is notable for its rich composition of secondary metabolites, including flavonoids, terpenoids, alkaloids, and phenolic acids, which exhibit antioxidative properties that mitigate free radical damage and reduce intracellular reactive oxygen species (ROS) (Mamache et al. 2020; Fatullayev et al. 2023).

Ethnobotanical research highlights *Salvia lanigera* as a medicinally valuable species within the Lamiaceae family, though its therapeutic mechanisms remain understudied compared to well-characterized relatives like *S. officinalis*. While existing studies (Boufadı et al. 2021; Tepe et al. 2008) confirm the antioxidant potential of *Salvia* species generally, specific phytochemical profiles and bioactivities require further investigation, particularly for *S. lanigera* distributed across Mediterranean ecosystems (Afzal-Rafii 1979).

This study provides a comprehensive analysis of Algerian *S. lanigera* extracts (ethanol and petroleum ether), characterizing their chemical composition and evaluating their antioxidant, antimicrobial, and anti-enzymatic activities.

Materials and Methods

Plant Material

Aerial parts of *S. lanigera* were collected during flowering in March 2023 from M'sila, Algeria (35° 11′ 03″ N, 4° 08′ 27″ E; 745 m altitude). Voucher specimen KR0014 was authenticated by Prof. Errol Vela (University of Montpellier) and deposited at M'sila University Herbarium. The cleaned plant material was dried, powdered, and stored in darkness until analysis.

Preparation of Extracts

For extraction, 20 g of *S. lanigera* dried powder was macerated in 200 mL of ethanol or petroleum ether (25 °C, 48 h). Filtered extracts were concentrated under reduced pressure (Ameur et al. 2024) to yield crude residues.

High-Performance Liquid Chromatography (HPLC-DAD)

Phenolic components in the ethanol extract of *S. lanigera* were analyzed using a Shimadzu HPLC system (LC-20AT pump, SPD-M20A DAD) with the LC-solution software. Separation was performed on an Inertsil ODS-3 column (4 µm, 4.0 × 150 mm) with a guard column at 40 °C. The extract (8 mg/mL in 80% methanol) was filtered (0.45 µm) and injected (20 µL). Standards from Tokul-Ölmez et al. (2020) were used for identification. The mobile phase for the analysis was composed of 0.1% acetic acid (Merck, Sternheim, Germany) in water (Phase A) and 0.1% acetic acid in methanol (Phase B, Merck, Sternheim, Germany), employing a programmed gradient elution over 40 min as follows: 0–0.01 min (0–20% B); 0.01–2 min (20–60% B); 2–15 min (60–80% B); 15–30 min (100% B); 30–35 min (100–10% B); and 35–40 min (10–0% B). The flow rate was consistently maintained at 1.5 mL/min.

The identification of phenolic compounds was conducted using the diode array detector over a wavelength range of 230–350 nm, correlating with the UV data and retention times of each commercial standard: theobromine (≥ 98.0%), (+)-catechin hydrate (≥ 98.0%), *p*-hydroxybenzoic acid (≥ 99.0%), *p*-hydroxybenzaldehyde (98.0%), vanillic acid (≥ 97.0%), epicatechin (≥ 90%), caffeic acid (≥ 98.0%), vanillin (≥ 99.0%), cynarine (phyproof® Reference Substance), *p*-coumaric acid (≥ 98.0%), ferulic acid (≥ 99.0%), rutin hydrate (≥ 94.0%), ellagic acid (≥ 99.0%), myricetin (≥ 96.0%), naringenin (≥ 98.0%), luteolin (≥ 98% (TLC)), apigenin (≥ 95.0%), all of which were purchased from Sigma-Aldrich-GmbH (Sternheim, Germany). Each analytical measurement was conducted in triplicate, and the identified phenolic compounds were characterized based on their retention times. The resulting data were quantified and expressed in mg/g of dry weight of the extract.

Pharmacokinetic Properties and Bioavailability Characteristics

The bioavailability of compounds identified in *S. lanigera* ethanol extract via HPLC–DAD was assessed using the SwissADME web tool, evaluating key physicochemical properties such as molecular size, lipophilicity, polarity,

and solubility (Mhadhbi et al. 2023). The druggability and pharmacokinetic profiles of these phytochemicals were also analyzed, with a focus on their absorption, distribution, metabolism, and excretion (ADME) properties (Derbak et al. 2024). SwissADME provided detailed insights into these characteristics, helping assess their potential as therapeutic agents.

Fatty Acid Analysis by Gas Chromatography-Mass Spectrometry (GC-MS)

In a 25-mL flask, 25 mg of S. lanigera petroleum ether extract was mixed with 2 mL of 0.5 N NaOH, sealed, and heated in a boiling water bath for 5 min. After cooling, 2 mL of BF3–MeOH was added, and the mixture was reheated at 80 °C for 3 min. Following another cooling step, 5 mL of saturated NaCl was added, and the solution was shaken and extracted twice with n-hexane (20 mL each). For analysis, a Shimadzu GC17 AAF system with a DB-1 column (0.25 mm ID, 0.25 µm film, 30 m length) was used, with helium as the carrier gas (1.2–1.3 mL/min). The injector and detector temperatures were set at 250 °C and 270 °C, respectively. The oven temperature began at 100 °C (5 min), increased to 238 °C (3 °C/min), and was held for 9 min. Fatty acid methyl esters (FAMEs) were quantified via GC-FID using the GC Solution/CLASS GC10 software. Further confirmation was performed using a Varian Saturn 2100 T GC–MS (EI, 70 eV), with detector, injector, and transfer line temperatures at 240 °C, 220 °C, and 290 °C, respectively. FAMEs were identified by comparing retention times with Supelco™ 37 FAME standards and matching spectra in the NIST/Wiley library (Crupi et al. 2018; Tel et al. 2013; Tokul-Ölmez et al. 2020).

Antioxidant Activity

All antioxidant assays were conducted in triplicate (n = 3). Positive controls (BHA, ascorbic acid, quercetin, α-tocopherol, BHT, or trolox) and negative controls (assay solvent without extract) were included in each experiment.

2,2-Diphenyl-1-Picrylhydrazyl (DPPH) Assay

The DPPH assay was evaluated and BHA, ascorbic acid, quercetin, α-tocopherol, and BHT were used as positive controls for comparison of the obtained results.

2,2′-Azinobis-(3-Ethylbenzothiazoline-6-Sulfonic Acid) (ABTS) Radical Scavenging Assay

The $ABTS^{\bullet+}$ activity was evaluated and the results were given as IC_{50}. BHA, ascorbic acid, quercetin, α-tocopherol, and BHT were used as positive controls for the comparison of the obtained results.

Phenanthroline Assay

The activity was determined by the phenanthroline method and the results were given as $A_{0.50}$ (µg/mL). BHA, ascorbic acid, quercetin, α-tocopherol, and BHT were used as positive contols for the comparison of the obtained results.

Silver Nanoparticle Assay

The SNP activity was evaluated according to the method described by Ozyürek et al. (2012), and the results were given as $A_{0.50}$ (µg/mL). BHA, ascorbic acid, quercetin, α-tocopherol, and BHT were used as positive contols for the comparison of the obtained results.

Enzyme Inhibition Activity

All enzyme inhibition assays were performed in triplicate ($n = 3$). Each assay included a standard inhibitor (galantamine for AChE/BChE, acarbose for α-amylase and α-glucosidase, thiourea for urease) as a positive control, and buffer-only reactions as negative controls.

Anticholinesterase Activity

The inhibition of AChE and BChE activity was determined according to Ellman et al. (1961) and Topal (2020). Galanthamine was used as a positive control.

α-Amylase/α-Glucosidase Inhibitory Activity

The inhibitory activity of *S. lanigera* on α-amylase and α-glucosidase enzymes was assessed using the SpectraMax 340PC384 microplate reader (Molecular Devices, USA) and spectrophotometric methods (Kim et al. 2010; Van Quan et al. 2019). Bioactivity data were analyzed using the Softmax PRO v5.2 software (Molecular Devices). Acarbose was used as a positive control.

Urease Inhibition Activity

Urease inhibitory activity was assessed using the indophenol method as described by Weatherburn (1967). Thiourea was used as a positive control.

Antimicrobial Activity

Antimicrobial tests, including disk diffusion and MIC determination, were performed in triplicate ($n=3$). Standard antibiotic discs and solvent blanks were used as positive and negative controls, respectively.

Isolation and Identification of Bacterial and Fungal Strains

The study evaluated four clinical *Escherichia coli* isolates and five fungal strains (two *Candida albicans*, three *Aspergillus niger*), along with reference strains *E. coli* ATCC 25922 and *C. albicans* ATCC 10231. Clinical isolates from Algerian diagnostic laboratories were identified using standard methods: API 20E system for bacteria and morphological analysis with serum filamentation testing (Mackenzie 1962) for *C. albicans* confirmation.

Evaluation of the Antibacterial and Antifungal Activity

Antimicrobial activity was evaluated using disk diffusion assays (Kirby-Bauer method) with Mueller–Hinton agar for *E. coli* and *C. albicans*, and Sabouraud-chloramphenicol agar for *A. niger* (Hajji 2016). Minimum inhibitory concentrations (MICs) were determined by broth microdilution in 96-well plates (CASFM 2023). DMSO was used as a negative control. Results were interpreted using established criteria: Ponce et al. (2003) for bacteria and yeast, and Abd-Ellatif et al. (2011) for mold inhibition.

Statistical Examinations

All experiments were conducted in triplicate ($n=3$), and the results are presented as mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was applied to assess differences between treatment groups, with the tested extracts considered as fixed factors. When statistically significant differences were observed ($p<0.05$), Tukey's multiple range test was used for post hoc comparisons. The IC_{50} (50% inhibition concentration) and $A_{0.5}$ (concentration corresponding to 0.5 absorbance) values were calculated using linear regression analysis performed in Microsoft Excel. These statistical analyses were conducted to ensure the reliability and reproducibility of the results.

Results and Discussion

Contents of Polyphenolic Compounds

The data resulted from HPLC–DAD analysis of *S. lanigera* ethanol extract are presented in Table 1 and Fig. 1. The analysis indicates that the compounds identified from *S. lanigera* can be categorized into two phenolic classes, specifically, seven phenolic acids (cynarin, vanillic acid, ferulic acid, p-hydroxybenzoic acid, p-coumaric acid, caffeic acid, and ellagic acid), and seven flavonoids (luteolin, epicatechin, rutin, apigenin, naringenin, catechin, and myricetin). One alkaloid (theobromine), and two aldehydes (p-hydroxy benzaldehyde and vanillin) were also identified. Cynarin was found in the highest concentration among the identified phenolic compounds in the analyzed ethanolic extract of *S. lanigera*, measuring 5.90 mg/g. This was followed by ellagic acid at 3.83 mg/g and rutin at 1.27 mg/g. Additionally, it is noteworthy that p-coumaric acid, p-hydroxybenzoic acid, caffeic acid, luteolin, ferulic acid, and apigenin have previously been isolated from *S. verbenaca* samples collected in Turkey Egypt, and Spain (Adzet et al. 1988; Khalil et al. 2007; Tepe 2008).

Luteolin, naringenin, p-hydroxy benzaldehyde, and myricetin were present in the lowest amounts (0.27 mg/g, 0.24 mg/g, 0.12 mg/g, and 0.02 mg/g, respectively). The rest of the compounds were noticed in trace amounts.

GC–MS analysis of *S. lanigera* petroleum ether extract has identified 16 compounds, as shown in Table 2 and Fig. 2. The primary constituents included palmitic acid (72.05%), stearic acid (7.42%), 3-hydroxypalmitic acid (7.42%), oleic acid (6.8%), and linoleic acid (6.18%). Palmitic acid is commonly identified as a major compound in various *Salvia* species (Kara et al. 2010; Bakoglu et al. 2016). The other constituents found in low amounts were the following: (z)−2-decenal, octanoic acid, glycerol, dodecanoic acid, azelaic acid, tetradecanoic acid, heptadcanoic acid, pentacosane, heptacosane, nonacosane, and B-Sitosterol.

The bioactive metabolites found in *Salvia* species exhibit significant antioxidant and antimicrobial properties, making them important for pharmacological applications. Notably, phenolic acids like ferulic acid, ellagic acid, and caffeic acid are acknowledged for their strong antioxidant capabilities, attributed to their function in scavenging free radicals and inhibiting lipid peroxidation (Ríos et al. 2018; Zeb 2020). Furthermore, flavonoids, including rutin, luteolin, and apigenin, are recognized for their robust antioxidant activities, which enhance their protective roles against oxidative stress (Muscolo et al. 2024). In addition, numerous compounds such as p-coumaric acid, catechin, and myricetin demonstrate antimicrobial properties against a variety of pathogens, including bacteria and fungi, by disrupting microbial cell membranes and inhibiting enzymatic pathways (Álvarez-Martínez et al. 2020). The fatty acids identified, particularly oleic and linoleic acids, are also linked to moderate antimicrobial effects and are essential in preserving cell integrity (Obukhova & Murzina 2024). Collectively, these findings underscore the substantial therapeutic potential of *S. lanigera* and related *Salvia* species as sources of

Table 1 Phenolic composition of the ethanol extract of *S. lanigera* by HPLC–DAD (mg/g extract)

Peak N^{o}	Phenolic compounds	RT[a]	Calib. eq	R^{2}[b]	Linear range (µg/mL)	λmax, nm	LOD [c] (µg/mL)[c]	LOQ [c] (µg/mL) [c]	Recovery (%)[d]	RSD [d] within day ($n=7$)	mg/g
1	**Theobromine**	25.967	$y=3942.7x+81{,}451$	0.9983	4.00–128	254	2.50	8.25	97.63 ± 5.01	3.12	*tr*
2	**Catechin**	30.274	$y=14456x+37{,}858$	0.9999	3.9–500	280	0.95	2.86	101.25 ± 2.16	4.00	*tr*
3	***p*-Hydroxy-benzoic acid**	30.867	$y=123758x+75{,}779$	0.9997	1.56–50.0	254	1.58	4.79	100.82 ± 3.89	4.00	*tr*
4	***p*-Hydroxy benzaldehyde**	33.367	$y=34376x+4239.6$	0.9996	1.25–50	280	1.33	4.44	99.01 ± 3.01	4.76	0.12
5	**Vanillic acid**	34.758	$y=74653x-9634.1$	0.9998	1.56–100	254	1.56	4.68	103.58 ± 4.43	5.06	*tr*
6	**Epicatechin**	35.278	$y=2097.6x+7998.2$	0.998	3.9–500	254	0.95	2.86	101.25 ± 3.66	4.00	*tr*
7	**Caffeic acid**	35.280	$y=49533x+213{,}471$	0.9957	3.00–30.0	254	4.54	13.75	102.67 ± 4.92	4.01	*tr*
8	**Vanillin**	36.915	$y=45495x+313{,}074$	0.9920	3.13–100	254	1.21	3.67	100.59 ± 4.84	1.76	*tr*
9	***p*–Coumaric acid**	40.874	$y=18300x+6153.3$	0.9998	6.25–400	254	5.46	16.56	101.60 ± 2.36	3.14	*tr*
10	**Ferulic acid**	42.564	$y=42245x+110{,}701$	0.9992	2.34–300	254	3.96	11.99	100.99 ± 3.54	3.20	*tr*
11	**Cynarin**	44.497	$y=42559x-2{,}000{,}000$	0.9959	4.00–128	254	2.50	8.25	97.63 ± 5.01	3.12	5.90
12	**Rutin**	47.527	$y=47899x+56{,}096$	0.9997	3.13–200	254	2.49	7.56	101.99 ± 3.45	3.01	1.27
13	**Ellagic acid**	50.005	$y=165729x-3{,}000{,}000$	0.9880	12.5–100	254	2.68	8.13	100.70 ± 5.43	7.34	3.83
14	**Myricetin**	50.368	$y=136859x+71{,}185$	0.995	0.35–22.5	254	0.35	1.07	97.41 ± 3.04	3.16	0.02
15	**Naringenin**	55.518	$y=72633x+837{,}946$	0.9996	4.84–155	280	5.01	15.03	100.58 ± 4.12	1.87	0.24
16	**Luteolin**	57.872	$y=89569x-62{,}198$	0.9995	3.01–220	254	2.41	7.16	100.99 ± 3.45	3.21	0.27
17	**Apigenin**	64.071	$y=71990x+62{,}472$	0.9996	0.66–170	254	0.65	1.96	98.80	1.36	*tr*

RT [a] retention time, *tr* trace amounts; percentage values −0.1%, [b] *R2*, linearity of the calibration graph, [c] *LOD,* limit of detection in µg/m land *LOQ*, limit of quantification in µg/mL, [d] *RSD,* percentage relative standard deviation

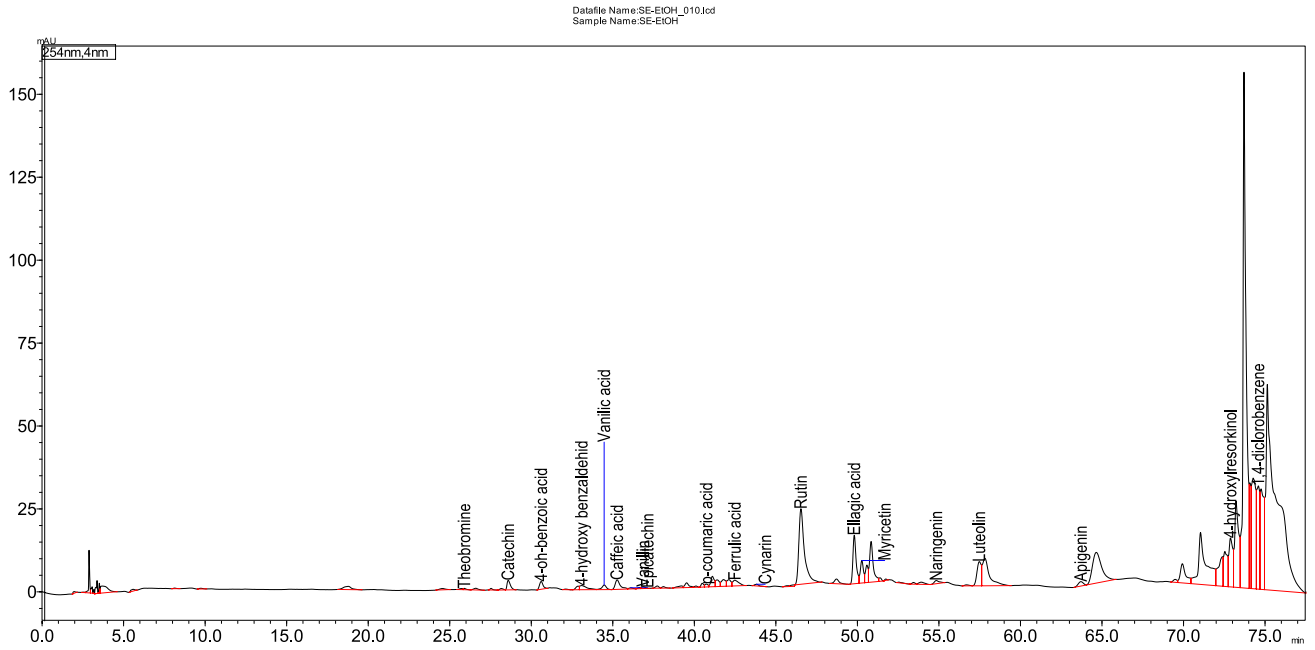


Fig. 1 *HPLC–DAD* chromatogram of *S. lanigera* ethanol extract

Table 2 Fatty acid composition determined by GC/MS in *S. lanigera* petroleum ether extract

Peak N°	RT	Compound name	Formula	MW (g/mol)	RI	Area	%
1.	9.061	(Z)−2-Decenal	$C_{10}H_{18}O$	154.25	1251	1000	0.012364
2.	9.22	Octanoic acid	$C_8H_{16}O_2$	144.21	1256	1000	0.012364
3.	9.888	Glycerol	$C_3H_8O_3$	92.09	1282	1000	0.012364
4.	19.766	Dodecanoic acid	$C_{12}H_24O_2$	200.32	1657	1000	0.012364
5.	23.227	Azelaic acid	$C_9H_{16}O_4$	188.22	1801	1000	0.012364
6.	24.225	Tetradecanoic acid	$C_{14}H_{28}O_2$	228.37	1850	1000	0.012364
7.	28.354	Palmitic acid	$C_{16}H_{32}O_2$	256.42	2045	5.83E+06	72.045
8.	29.404	Heptadcanoic acid	$C_{17}H_{34}O_2$	270.45	2100	1000	0.012364
9.	31.496	Linoleic acid	$C_{18}H_{32}O_2$	280.45	2200	5.00E+05	6.181998
10.	31.617	Oleic acid	$C_{18}H_{34}O_2$	282.47	2208	5.50E+05	6.800198
11.	31.807	3-Hydroxypalmitic acid	$C_{16}H_{32}O_3$	272.42	2216	6.00E+05	7.418398
12.	32.091	Stearic acid	$C_{18}H_{36}O_2$	284.48	2240	6.00E+05	7.418398
13.	36.59	Pentacosane	$C_{25}H_{52}$	352.69	2500	1000	0.012364
14.	39.639	Heptacosane	$C_{27}H_{56}$	380.74	2700	1000	0.012364
15.	42.665	Nonacosane	$C_{29}H_{60}$	404.80	2900	1.00E+03	0.012364
16.	50.171	B-Sitosterol	$C_{29}H_{50}O$	414.72	3380	1.00E+03	0.012364
Total							99.999996

MW molecular weight, *RT* retention time, *RI* retention index

bioactive compounds with dual antioxidant and antimicrobial effectiveness.

Pharmacokinetic Properties and Bioavailability Characteristics

The result of the ADME (absorption, distribution, metabolism, and excretion) analysis of the compounds identified in the ethanol extract of *S. lanigera* are presented in Table 3, Table S1 and Fig. 3. The physicochemical properties of the compounds, including molecular weight, lipophilicity (Log P), and topological polar surface area (TPSA), are critical determinants of their bioavailability and absorption (Agarwal et al. 2022). Most compounds, such as theobromine, catechin, and ellagic acid, exhibit molecular weights below 500 g/mol, aligning with Lipinski's rule of five and

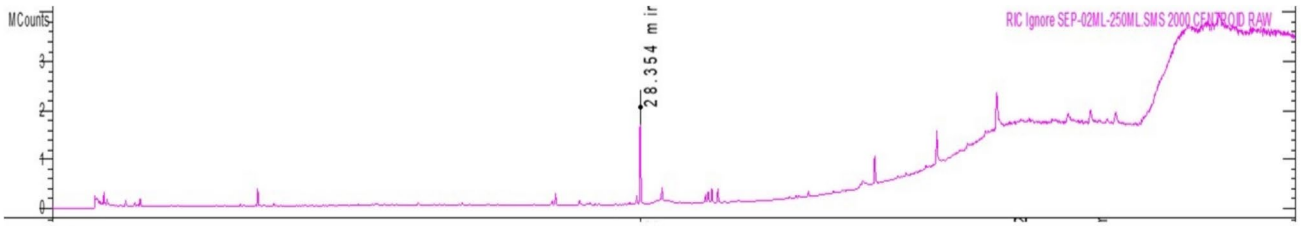


Fig. 2 GC–MS chromatogram of *S. lanigera* petroleum ether extract. Peaks correspond to fatty acid methyl esters (FAMEs) identified by comparison with the NIST/Wiley library and Supelco™ 37 standards

Table 3 ADME properties of compounds detected and quantified by HPLC–DAD in the ethanol Extract of *Salvia lanigera* Poiret

Compound	Theobromine	Catechin	Cynarin	Rutin	Ellagic acid	Apigenin
Molecular weight	180.16	290.27	516.45	610.52	302.19	270.24
TPSA (Å^2)	72.68	110.38	211.28	269.43	141.34	90.9
Consensus Log $P_{o/w}$	− 0.12	0.83	0.8	− 1.51	1	2.11
GI absorption	High	High	Low	Low	High	High
BBB permeant	No	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	Yes	Yes
CYP3A4 inhibitor	No	No	No	No	No	Yes
log Kp (cm/s)	− 7.95	− 7.82	− 8.37	− 10.26	− 7.36	−5.8
Bioavailability score	0.55	0.55	0.11	0.17	0.55	0.55

TPSA topological polar surface area, *Log P* lipophilicity, *GI* gastrointestinal, *BBB* blood-brain barrier, *log Kp* skin permeability

indicating favorable drug likeness (Ogunyemi et al. 2025). However, rutin and cynarin have higher molecular weights (610.52 and 516.45 g/mol, respectively), which may limit their absorption and bioavailability, as evidenced by their low gastrointestinal absorption scores. Log P values range from − 1.51 (rutin) to 2.11 (apigenin), with compounds like ellagic acid have a Log P value equal to 1 demonstrating moderate lipophilicity, which is optimal for membrane permeability and absorption. In contrast, rutin and cynarin exhibit low lipophilicity (− 1.51 and 0.8, respectively), limiting their permeability across cellular membranes, consistent with their poor GI absorption. TPSA values, which influence permeability and solubility, range from 37.3 Å^2 (p-hydroxy benzaldehyde) to 269.43 Å^2 (rutin). Compounds with TPSA values below 140 Å^2, such as theobromine (72.68 Å^2) and caffeic acid (77.76 Å^2), are more likely to exhibit good membrane permeability, while rutin and cynarin (269.43 Å^2 and 211.28 Å^2, respectively) have high TPSA values, further explaining their low absorption (da Silva et al. 2023). The GI absorption results indicate that most compounds, including theobromine, catechin, p-hydroxybenzoic acid, and ellagic acid, exhibit high GI absorption, suggesting their potential for oral bioavailability. In contrast, rutin and cynarin presented low GI absorption due to their high molecular weight, high TPSA, and low Log P values, necessitating advanced formulation strategies such as nanoparticles, liposomes, or prodrugs to enhance their therapeutic efficacy (Ashfaq et al. 2023). Bioavailability scores further support these observations, with compounds like p-hydroxy-benzoic acid, vanillic acid, and ferulic acid scoring 0.85, indicating high bioavailability, while rutin (0.17) and cynarin (0.11) score poorly, consistent with their limited absorption. Blood–brain barrier (BBB) permeability is another critical factor, particularly for neuroactive applications. Compounds such as p-hydroxy-benzoic acid, p-hydroxy benzaldehyde, vanillin, and ferulic acid are predicted to be BBB permeant, suggesting their potential for targeting the central nervous system. However, the majority of the compounds, including theobromine, catechin, and ellagic acid, are non-BBB permeant, limiting their use in treating neurological disorders (Razavi et al. 2025). Drug metabolism and enzyme interactions are also significant considerations. Compounds such as ellagic acid, myricetin, naringenin, luteolin, and apigenin inhibit CYP1A2, while myricetin, naringenin, luteolin, and apigenin inhibit CYP3A4, luteolin and apigenin specifically inhibit CYP2D6. These enzymes are integral to drug metabolism, and their inhibition may lead to altered pharmacokinetics or adverse effects when co-administered with other drugs metabolized by these pathways (Deodhar et al. 2020). Skin permeability (log Kp) values range from − 10.26 cm/s (rutin) to − 5.8 cm/s (apigenin). Compounds with higher log

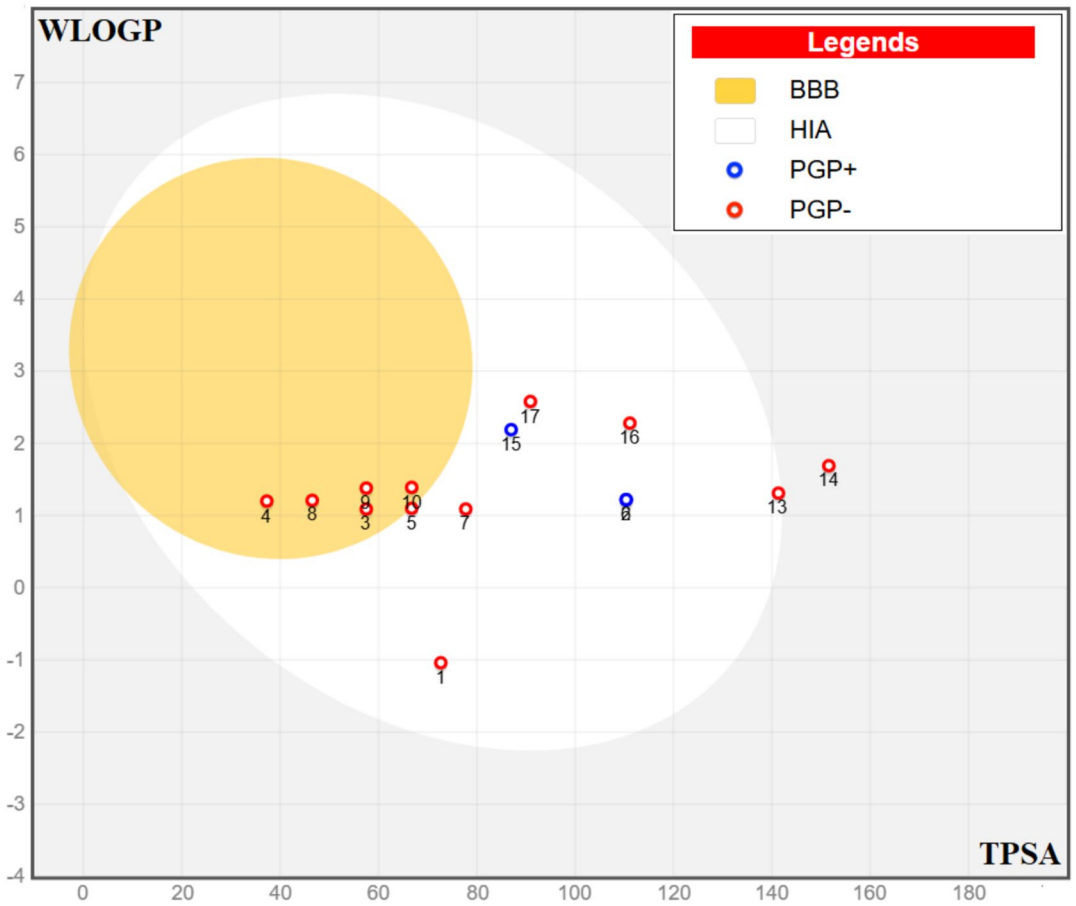


Fig. 3 Boiled-Egg model predicting gastrointestinal absorption and blood–brain barrier permeability of compounds identified and quantified by HPLC–DAD analysis in the ethanolic extract of *Salvia lanigera* Poiret. 1—Theobromine, 2—catechin, 3—p-hydroxy-benzoic acid, 4—p-hydroxy benzaldehyde, 5—vanillic acid, 6—epicatechin, 7—caffeic acid, 8—vanillin, 9—p-coumaric acid, 10—ferulic acid, 11—cynarin, 12—rutin, 13—ellagic acid, 14—myricetin, 15—naringenin, 16—luteolin, 17—apigenin

Kp values, such as apigenin and naringenin (− 6.17 cm/s), exhibit better skin permeability, suggesting their potential for topical applications. In contrast, rutin and cynarin have very low log Kp values, indicating poor skin absorption (Scheler et al. 2014). Synthetic accessibility scores range from 1 (p-hydroxy-benzoic acid) to 6.52 (rutin), indicating that some compounds, such as p-hydroxy-benzoic acid and p-hydroxy benzaldehyde, are easier to synthesize, while rutin and cynarin are more complex and challenging to produce (Ertl and Schuffenhauer 2009). These ADME predictions were interpreted according to established pharmacokinetic criteria. Compounds were considered to have favorable oral bioavailability if they complied with Lipinski's Rule of Five and showed high gastrointestinal absorption scores. BBB permeability was evaluated using the Boiled-Egg predictive model in SwissADME. Key physicochemical parameters, such as TPSA, Log P, and the number of hydrogen bond donors and acceptors, were analyzed to assess membrane permeability and solubility. Compounds with TPSA values below 140 $Å^2$ and molecular weights under 500 g/mol were considered more likely to exhibit good absorption and distribution properties. In addition, bioavailability scores and synthetic accessibility indices provided further insights into the compounds' potential for development as therapeutic agents, particularly regarding formulation strategies and synthetic feasibility (Derbak et al. 2025). These findings provide critical insights into the potential development of the identified compounds as therapeutic agents, emphasizing their pharmacokinetic profiles, challenges related to bioavailability, and the necessity for advanced delivery strategies to optimize their efficacy.

The Antioxidant Potential

In line with its ethnomedicinal applications across North Africa and the Mediterranean (Mamache et al. 2020), our phytochemical analysis reveals *S. lanigera*'s high phenolic content, particularly cynarin and ellagic acid, which correlates with its traditional use for oxidative stress-related conditions. This supports regional practices of employing leaf

decoctions (oral) for inflammatory disorders and poultices (topical) for dermatological ailments (Belmekki & Bendimerad 2012).

In vitro antioxidant potential of natural molecules can be assessed using various analytical methods that facilitate the characterization of the antioxidant properties of plant extracts. Due to the diversity in phytochemical compositions and oxidative mechanisms, it is essential to use multiple evaluation techniques (Bouzana et al. 2023). For example, crude extracts obtained from the aerial parts of *S. lanigera* were evaluated using four test-systems—DPPH, ABTS, phenanthroline, and SNP assays—and exhibited considerable antioxidant activity, which enhanced proportionally with increasing extract concentrations.

The DPPH and ABTS assays are widely recognized standard methods employed in the evaluation of antioxidant activity, offering a quick way to evaluate the radical-scavenging potential of spesific compounds or extracts (Munteanu & Apetrei 2021). The findings indicated that the radical scavenging activity of the ethanol extract of *S. lanigera* exhibited an increase in efficacy with escalating concentrations of the extract, reaching a plateau beyond which activity remained stable. Based on the determined IC_{50} values (Fig. 4), the ethanol extract demonstrated moderate antioxidant activity in the DPPH assay ($IC_{50} = 99.58 \pm 0.22$ µg/mL) and weaker scavenging efficacy in the ABTS assay ($IC_{50} = 232.14 \pm 0.38$ µg/mL), in comparison to standard references. This scavenging activity can be attributed to the

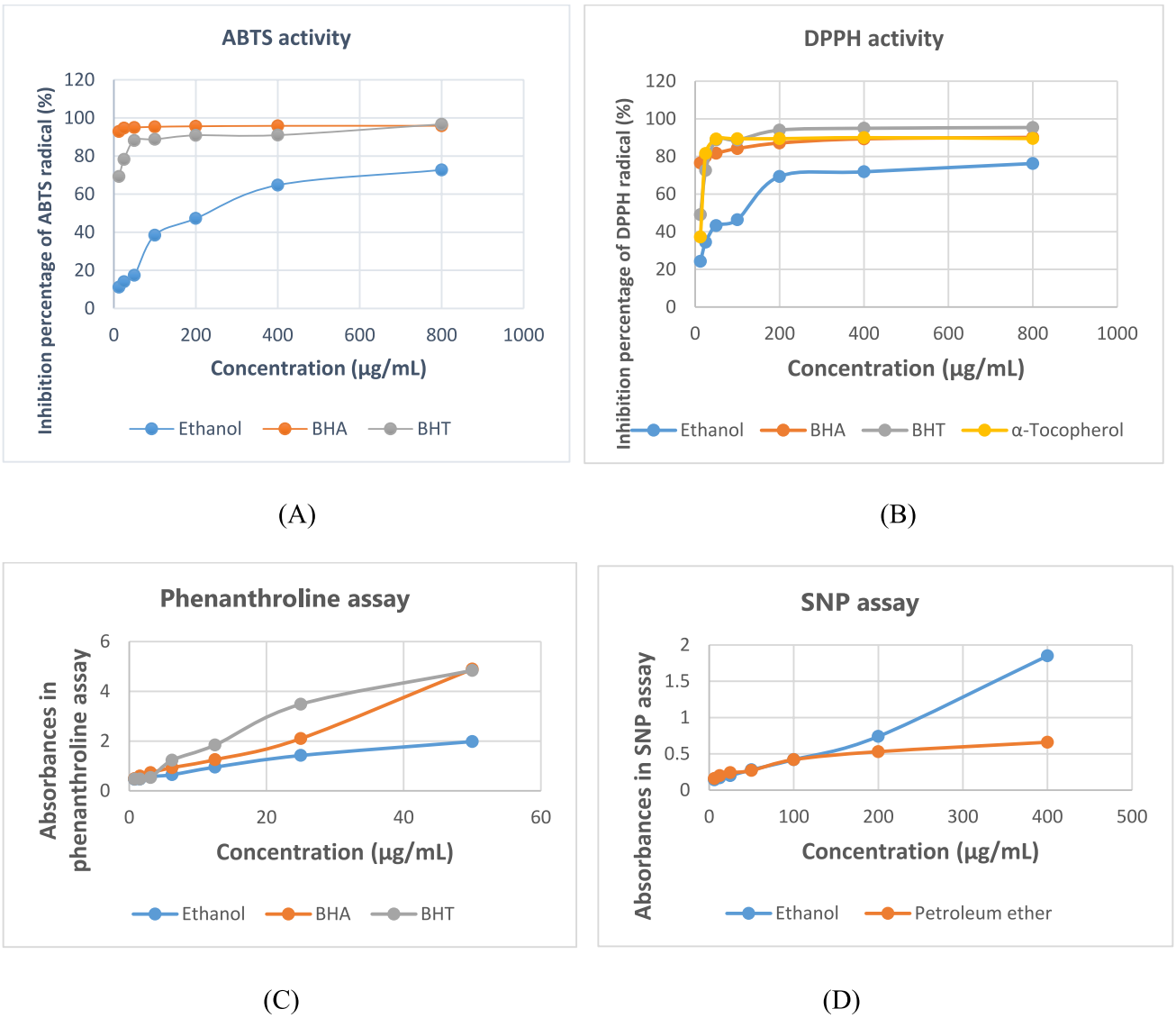


Fig. 4 Antioxidant capacity of *S. lanigera* extracts ABTS **A**, DPPH **B**, phenanthroline assay **C**, SNP assay **D**

presence of polyphenols and flavonoids within the extracts (Baliyan et al. 2022).

The ability of *S. lanigera* to reduce the Fe^{3+} ions as measured by the phenanthroline method is shown in Table 4. The ethanol extract demonstrated strong chelation ability ($A_{0.5} = 1.94 \pm 0.18$ µg/mL), compared to the standard BHT ($A_{0.5} = 2.24 \pm 0.17$ µg/mL).

The antioxidant scavenging effects of the evaluated extracts and standards against SNP were assessed through their $A_{0.5}$ values. The ethanol extract exhibited moderate antioxidant activity, with an $A_{0.5}$ value of 124.78 ± 0.59 µg/mL, making it approximately 4 times less effective than trolox and 2 times less effective than BHA. Conversely, the petroleum ether extract displayed the lowest scavenging activity, with an $A_{0.5}$ value of 241.64 ± 1.69 µg/mL, necessitating considerably higher concentrations to achieve 50% radical scavenging. Although the natural extracts are not as effective as synthetic standards, the ethanol extract's antioxidant potential is still relatively promising compared to the petroleum ether extract. The statistical analysis confirmed these differences in antioxidant activity. One-way ANOVA followed by Tukey's post hoc test ($p < 0.05$) showed that the ethanol extract's $A_{0.5}$ value in the phenanthroline assay (1.94 ± 0.18 µg/mL^b) was significantly lower than that of BHT (2.24 ± 0.17 µg/mL^a), indicating stronger reducing capacity. Similarly, in the SNP assay, the ethanol extract (124.78 ± 0.59 µg/mL^b) was significantly more effective than the petroleum ether extract (241.64 ± 1.69 µg/mL^a). These differences are statistically significant and highlighted with superscript letters in Table 4.

Investigations on the Libyan *S. lanigera* using various antioxidant assays indicated that its water extract demonstrated the most significant activity across the majority of tests. However, the DPPH activity of these extracts was notably lower, ranging from 205.45 to 614.23 µg/mL. Significantly, both water and methanol extracts exhibited ABTS activity that surpassed 1 mg AAE/g (Duletić-Laušević et al. 2018). In studies related to the Egyptian *S. lanigera*, Shaheen et al. (2011) discovered that acetone extracts possessed the highest antioxidant activity, comparable to that of α-tocopherol and surpassing that of BHT. Their findings revealed that flavonoid contents, determined by *HPLC*, were more strongly correlated with antioxidant activity across various assays than those assessed through spectrophotometry. Additionally, the DPPH assay exhibited weak to moderate correlations with phenolic components, while the ABTS assay showed a robust correlation with luteolin, genkwanin, and their glycosides (Mamache et al. 2020). Belkhiri et al. (2017) investigated methanol extracts of *S. lanigera* using the DPPH method, metal chelating activity assays, and reducing power tests, revealing strong antioxidant activity across all extracts (Mamache et al. 2020). Additionally, research on the essential oils of *S. lanigera* from Cyprus showed that they exhibited superior DPPH radical-scavenging activity when compared to standard compounds. This enhanced activity is likely attributed to phenolic compounds such as carvacrol and thymol, which serve as powerful free radical scavengers through their hydrogen-donating capabilities (Hou et al. 2022). Research on *S. officinalis* from Soliman demonstrated remarkable free radical scavenging activity, with DPPH yielding an IC_{50} of 3.37 µg/mL and ABTS showing 766.30 µM TE/mg (Farhat et al. 2019). Another study indicated IC_{50} values of 830 and 800 µg/mL for DPPH and ABTS radicals, respectively, in *S. officinalis* extracts (Baharara et al. 2017). Our plant extract showed weaker ABTS scavenging activity compared to DPPH, which is consistent with observations in other Tunisian *Salvia* species (Farhat et al. 2019).

Previous reseach have studied the Fe^{3+} reducing capacity the *S. verbenaca* extracts by phenanthroline assay, and confirmed thier strong antioxidant abilities, with the methanolic extract demonstrating the highest activity (Nassar et al. 2021). The Tunisian *S. verbenaca* also exhibited notable antioxidant potential, with methanol extracts from the aerial parts presenting an IC_{50} of 86.9 µg/mL in the DPPH assay, lower than trolox ($IC_{50} = 23.12$ µg/mL) (Salah et al. 2006). Notably,

Table 4 Antioxidant activity of *S. lanigera* by DPPH, $ABTS^+$, SNP, and O-phenanthroline assays

Extracts	DPPH assay IC_{50} (µg/mL)	$ABTS^+$ assay	SNP assay $A_{0,5}$ (µg/mL)	Phenanthroline
Ethanol	99.58 ± 0.22^a	232.14 ± 0.38^a	124.78 ± 0.59^b	1.94 ± 0.18^b
Petrolium ether	NT	NT	241.64 ± 1.69^a	NT
BHA	6.14 ± 0.41^c	1.29 ± 0.30^b	73.47 ± 0.88^c	0.93 ± 0.07^c
BHT	12.99 ± 0.41^b	1.81 ± 0.10^b	NT	2.24 ± 0.17^a
α-Tocopherol	13.02 ± 1.17^b	NT	NT	NT
Ascorbic acid	NT	NT	> 200	NT
Trolox	NT	NT	34.17 ± 1.23^d	NT

BHA butylated hydroxyanisole; *BHT* butylated hydroxyltoluene, *NT* not tested, The values with different superscripts (a,. b,. c,. or d) in the same columns are significantly different ($p < p < 0.05$, Tukey's test). IC50 and A0.5 represent the means ± S.D of three parallel measurements, calculated by linear regression analysis

the ABTS assay demonstrated increasing antioxidant capacity but remained four times less potent than trolox. Moreover, Farhat et al. (2019) concluded that the antioxidant capacity, as measured by ABTS and DPPH assays, was greatly affected by the collection site, and total phenolic content exhibited a strong correlation with antioxidant activity. Overall, antioxidant activity of various *Salvia* species has been well documented (Mervić et al. 2022; Moshari-Nasirkandi et al. 2024). The findings of these studies, along with our current investigation, confirm the presence of moderate to robust antioxidant properties in the extracts derived from *Salvia* species.

Antimicrobial Activity of S. lanigera

The antimicrobial properties of *S. lanigera* extracts exhibited significant efficacy against selected microbial strains, notably E. *coli*, *C. albicans*, and *A. niger*, which are associated with respiratory, gastrointestinal, skin, and urinary disorders and are prevalent foodborne pathogens. All tested bacterial strains were sensitive to both petroleum ether and ethanol extracts with inhibition zone diameters in the range 10–13 mm and MIC values varying between 0.78 and 3.125 mg/mL (Table 5 and Fig. 5).

There are limited studies on the antimicrobial activity of *S. lanigera* extracts, although other members of the *Salvia* genus have been extensively studied (Nasr et al. 2023; Anagnostou et al. 2025).

Research on the antibacterial activity of S. Fruticosa grown in Lybya revealed that its ethanol extract exhibited moderate inhibitory effects against *E. coli* Gonaid et al. (2012). The essential oil of the same plant showed pronounced activity against *E. coli*, with an MIC of 50 µg/mL

Table 5 Antimicrobial activity of *S. lanigera* extracts

Extracts microbial strains	Petroleum ether extract		Ethanol extract	
	IZ (mm)	MIC (mg/mL)	IZ (mm)	MIC (mg/mL)
E. coli ATCC 25922	10 ± 0.10	3.125	11 ± 0.8	1.56
E. coli 01	13 ± 0.35	3.125	13 ± 0.12	1.56
E. coli 02	12 ± 0.29	1.56	12 ± 0.81	0.78
E. coli 03	10 ± 0.12	3.125	10 ± 0.37	1.56
E. coli 04	12 ± 1.02	3.125	11 ± 0.34	1.56
C. albicans ATCC 10231	10 ± 0.72	3.125	11 ± 0.84	1.56
C. albicans 01	12 ± 0.58	12.5	R	R
C. albicans 02	12 ± 0.29	12.5	12 ± 2.01	12.5
Growth inhibition percentage (%)				
	Concentration (mg/mL)	**% inhibition**	**Concentration (mg/mL)**	**% inhibition**
A. niger 01	NA	NA	12.5	10
A. niger 02	NA	NA	50	5
A. niger 03	50	50°°	25	10

R resistant; (09 < Ø < 14 mm): sensitive; *NA* no activity; °°: 50 to 60%: moderate activity

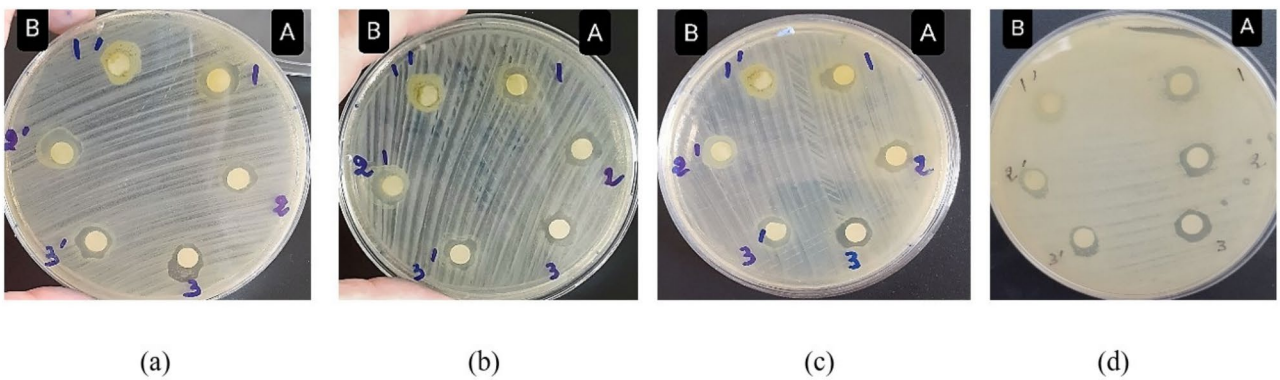


Fig. 5 Antimicrobial activity of *S. lanigera* extracts against *Escherichia coli* strains and *Candida albicans*. (A) Petroleum ether extract; (B) ethanol extract. Tested concentrations: 1 (50 mg/mL), 2 (25 mg/mL), 3 (12.5 mg/mL). Microorganisms: **a** *E. coli* strain 1, **b** *E. coli* strain 2, **c** *E. coli* strain 4, **d** *C. albicans* strain 2

(Tenore et al. 2011). In contrast, earlier studies on various extracts and essential oils of *S. verbenaca* were observed predominantly against Gram positive bacteria (Canzoneri et al. 2011). For Gram-negative bacteria (*E. coli*), *S. verbenaca* have indicated weaker activity against *E. coli*, with acetone extract exhibiting activity at 128 mg/mL (Kabouche and Kabouche 2008) and methanolic extract displaying MIC values of 8 mg/mL (Kamatou et al. 2007). The reduced susceptibility of Gram-bacteria may be attributed to their structural characteristics, including an additional outer membrane that acts as a penetration barrier (Kozłowska et al. 2022).

The antibacterial activity of *S. lanigera* is mostly enhanced by its flavonoid content, particularly naringenin, which inhibits biofilm formation and reduces fatty acid secretion, destabilizing bacterial resistance mechanisms (Wang et al. 2017; Donadio et al. 2021).

In addition to its antibacterial properties, the antifungal activity of *S. lanigera* was also evaluated. The majority of *C. albicans* strains displayed sensitivity to both petroleum ether and ethanol extracts, with inhibition zone diameters in the range 10 to 12 mm and MIC values between 1.56 and 12.5 mg/mL. Notably, one strain, *C. albicans* 1, exhibited resistance to the ethanol extract. Compared to previous studies, the essential oils of *S. lanigera* from Cyprus (Tenore et al. 2011), and from Saudi Arabia (Al-Howiriny 2003) were effective against *Candida* species. The antifungal activity of our extracts was found to be inferior to that of *S. lanigera* essential oils (MIC: 2.0 mg/mL), and the methanolic extract with an MIC > 1000 µg/mL according to Salah et al. (2006). Additionally, the petroleum ether extract exhibited moderate activity against *A. niger*, achieving 50% growth inhibition for *A. niger* 3 (Fig. 6).

The ethanol extract of the Libyan *S. lanigera* inhibited the growth of *C. albicans*, with MIC values ranging from 16 to 64 mg/mL, whereas the water extract exhibited no inhibitory effect against this species (Duletić-Laušević et al. 2018). The essential oil derived from S. *lanigera* grown in Cyprus demonstrated a higher susceptibility to *C. albicans* (MIC of 50 µg/mL), in comparison to *A. niger*, which showed reduced sensitivity with MIC values exceeding 100 µg/mL.

The antimicrobial properties of *S. lanigera* could be attributed to phenolic compounds and flavonoids such as cynarin (Laghezza Masci et al. 2024), ellagic acid (Li ZJ et al. 2015), rutin (Stojković et al. 2013) and luteolin (Kahrizi & Mohammadi 2023), prevalent in its ethanol extract, as well as fatty acids, including octanoic acid, dodecanoic acid, and oleic and linoleic acids, found in the petroleum ether extract (Obukhova & Murzina 2024). These compounds disrupt microbial cell membranes, inhibit growth, and induce cell lysis (Zhang et al. 2013; Yoon et al. 2018). Furthermore, the Libyan *S. lanigera* demonstrated antifungal activity against various *Aspergillus* species, including *A. glaucus*, with MIC/minimum fungicidal concentration (MFC) values ranging from 8 to 64 mg/mL, indicating potential efficacy against *A. niger* (Duletić-Laušević et al. 2018).

The antimicrobial efficacy of *S. lanigera* is increasingly documented, with variations in results depending on the type of assay, tested strains and the solvent used which influences the spectrum and intensity of activity. Bioactive compounds, such as polyphenols, flavonoids, and terpenes, may function alone or together to suppress microbial growth (Singh et al. 2025). Although the antimicrobial properties of a plant extract are often attributed to its predominant components, recent studies emphasize that minor components may also contribute significantly through synergistic or antagonistic interactions (Renda et al. 2024). Further research is needed to elucidate the exact mechanisms and optimize extraction methods to maximize antimicrobial efficacy.

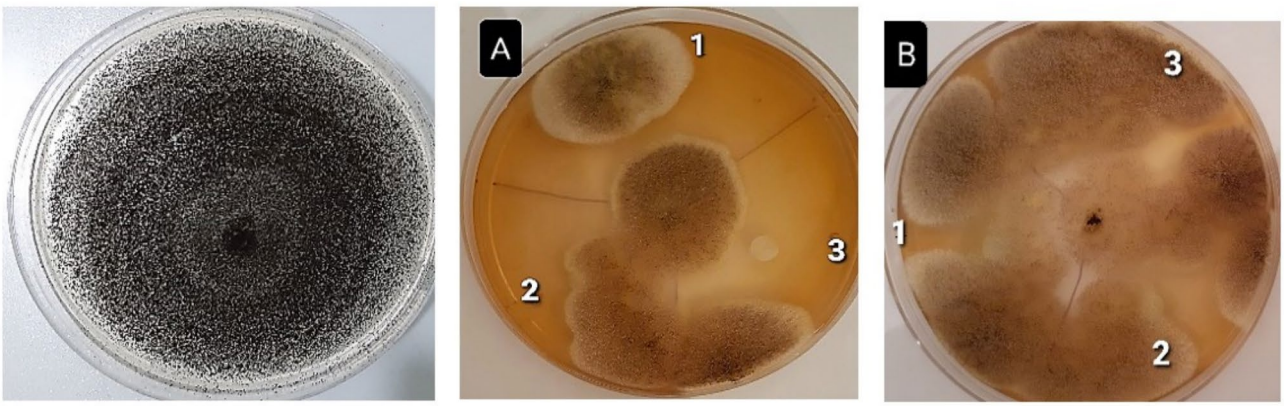


Fig. 6 Antifungal activity of *S. lanigera* extracts against *Aspergillus niger* strain 3. **A** Petroleum ether extract; **B** Ethanol extract. Test concentrations: 1 (50 mg/mL), 2 (25 mg/mL), 3 (12.5 mg/mL)

Enzyme Inhibition Activity

Urease Activity

Urease is commonly present in various bacteria such as *Helicobacter pylori*, an enzyme that triggers the breakdown of urea into ammonia and carbamate. This reaction leads to the rapid production of ammonia, increasing the pH and potentially causing harmful effect in human health, such as gastric and duodenal ulcers (Graham & Miftahussurur 2018). Focusing on urease as a treatment for illnesses caused by urease-producing bacteria has received significant interest in recent times (Kumar et al. 2022). In this context, the urease activity of *S. lanigera* extracts was examined for the first time and compared to the standard drug, thiourea, with the findings showed in Fig. 7 and Table 6. The obtained findings demonstrated that *S. lanigera* extracts had a moderate level of urease inhibitory activity. At the concentration of 200 µg.mL^{-1}, the inhibition of thiourea (98.9%) was the highest, followed by the ethanol extract (54.88%) and then the petroleum ether extract (52.00%). The values of IC_{50} in Table 6 validated these results, with the ethanol extract proving to be more effective enzyme inhibitor than the petroleum ether extract with an IC_{50} of 30.72 µg/mL. Statistical analysis using one-way ANOVA and Tukey's multiple range test ($p < 0.05$) confirmed significant differences between all groups. The ethanol extract demonstrated significantly higher urease inhibition than the petroleum ether extract, while thiourea exhibited the strongest effect. These differences are clearly reflected in the table using superscript letters. This activity may be attributed to its high content of phenolic compounds, which are known to inhibit urease by interacting with the enzyme's nickel active sites or by disrupting protein structure (Carlini and Ligabue-Braun 2016; Al-Rooqi et al. 2023).

Therefore, *S. lanigera*, which is rich in phenolics, holds potential as an effective urease inhibitor.

Anticholinesterase Activity

Alzheimer's disease (AD) is characterized by the degeneration of cholinergic neurons and a reduction in acetylcholine levels within specific brain regions, resulting in impairments in memory and learning (Srief et al. 2023). The principal enzymes implicated in the pharmacotherapy for AD, including Rivastigimine, Donepezil, and Galantamine, are BChE

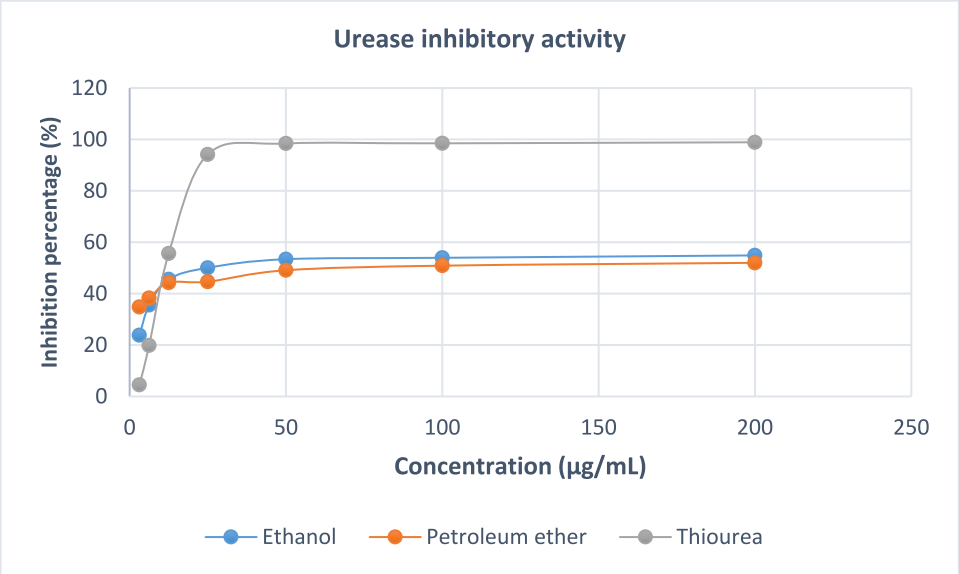


Fig. 7 Urease inhibitory activity of *S. lanigera* extracts compared to thiourea standard. Extracts tested: petroleum ether and ethanol. Concentration range: 3.125–200 µg/mL

Table 6 Urease inhibitory activity of *S. lanigera*

Extracts	% Inhibition							
	3.125 µg	6.25 µg	12.5 µg	25 µg	50 µg	100 µg	200 µg	IC_{50} µg/mL
Ethanol	23.85 ± 1.23	35.59 ± 0.03	45.60 ± 0.24	50.07 ± 0.26	53.40 ± 0.05	53.95 ± 0.11	54,0.8 ± 0.01	30.72 ± 0.69^{b}
Petroleum ether	34.83 ± 0.04	38.28 ± 0.07	44.27 ± 0.12	44.64 ± 0.06	49.10 ± 0.07	50.89 ± 0.10	52.00 ± 0.04	80.27 ± 0.61^{a}
Thiourea	4.49 ± 0.78	19.85 ± 2.74	55.64 ± 4.24	94.17 ± 0.15	98.42 ± 0.19	98.49 ± 0.41	98.90 ± 0.05	11.57 ± 0.68^{c}

Values in the same columns that have different superscripts (a, b, c) indicate significant differences ($p < 0.05$, Tukey's test). The IC_{50} values represent the means ± standard deviation (SD) of three parallel measurements, derived from linear regression analysis

Table 7 Anticholinesterase and anti-diabetic inhibitory activities of the extracts of *S. lanigera*

Extracts and compounds	Anticholinesterase activity IC_{50} (µg/mL)		Anti-diabetic inhibitory activity IC_{50} (µg/mL)		Urease inhibitory assay IC_{50} (µg/mL)
	AChE	BChE	α-Amylase	α-Glucosidase	
Cont. studied	25–200 µg/mL	25–200 µg/mL	50–400 µg/mL	25–200 µg/mL	3.125–200 µg/mL
Ethanol	> 200	365.84 ± 5.48^{b}	429.85 ± 1.43^{b}	27.07 ± 0.78^{b}	30.72 ± 0.69^{b}
Petroleum ether	*NA*	636.13 ± 4.49^{a}	520.31 ± 1.63^{c}	129.47 ± 1.22^{a}	80.27 ± 3.61^{c}
Galantamine	4.44 ± 1.57	30.79 ± 0.13^{c}	NT	NT	NT
Acarbose	NT	NT	36.74 ± 4.50^{c}	22.28 ± 2.03^{c}	NT
Thiourea	NT	NT	NT	NT	11.57 ± 0.68^{c}

*NT*Not tested. The values with different superscripts (a, b, c) in the same columns are significantly different ($p < 0.05$, Tukey's test). IC_{50} represent the means ± SD of three parallel measurements, calculated by linear regression analysis

and AChE (Sridhar et al. 2021). Galantamine, a cholinesterase inhibitor, is extensively utilized in the management of Alzheimer's disease and serves as a positive control for comparative analyses. The inhibitory effects of *S. lanigera* on BChE and AChE enzymes are quantified in terms of IC_{50} values, as shown in Table 7 and Fig. 4. The findings indicate that the plant extracts exhibited comparatively low inhibitory activity against both AChE and BChE enzymes when compared with galantamine. The ethanol and petroleum ether extracts displayed negligible activity toward AChE, with an IC_{50} higher than 200 µg/mL. Similarly, both extracts showed limited inhibitory action against the BChE enzyme, reflecting minimal BChE inhibition relative to the standard galantamine ($IC_{50} = 30.79 \pm 0.13$ µg/mL), with IC_{50} values recorded at 365.84 ± 5.48 µg/mL, and 636.13 ± 4.49 µg/mL, respectively. The enzymatic activities of AChE and BChE may be influenced by secondary metabolites present in ethanol and petroleum ether extracts. Numerous studies have demonstrated the capacity of various natural compounds, such as phenolic compounds, alkaloids, and terpenoids to inhibit BChE and AChE (Tamfu et al. 2021; Alves et al. 2022). The results of our investigation on cholinesterase inhibition align with those reported by (Mamache et al. 2020), which showed that the Turkish *S. verbenaca* exhibited low inhibitory activity against AChE compared to galantamine. Additionally, this plant significantly inhibited BChE activity at a concentration of 100 µg/mL, with an IC_{50} value of $71.60 \pm 4.33\%$.

The ethanol extract was twice more effective in inhibiting BChE than the petroleum ether extract, whereas, both extracts showed weak activity toward AChE. This aligns with other research indicating that *Salvia* species, at low concentrations, do not exhibit a significant inhibitory effect. This may be attributed to the lack of certain phenolic molecules that exert a stronger inhibitory effect on BChE compared to AChE, a phenomenon influenced by the quantity and arrangement of OH/OCH_3 groups on the phenolic rings (aromatic compounds) (Levaya et al 2025).

In the AChE inhibition assay performed by Duletić-Laušević et al. (2018), extracts of *S. lanigera*, particularly the ethanol extract, exhibited slightly reduced activity (16.28–32.42%) compared to the standard galantamine (42.38–57.11%). Additionally, Orhan et al. (2013) tested ethanol extracts from fourteen *Salvia* species at concentrations of 25, 50, and 100 µg/mL, observing AChE inhibition levels ranging from 1.00 to 27.95%.

Ferreira et al. (2006) reported that dichloromethane extracts from ten *Salvia* species exhibited the highest AChE inhibitory activity compared to ethanol extracts. Similarly, a study on the Turkish *Salvia* species assessing AChE activity using dichloromethane and ethyl acetate extracts found that only *S. fructicosa* demonstrated significant and promising inhibitory activity (Şenol et al. 2010). In contrast, some researchers have indicated that more polar extracts (methanol and ethyl acetate) showed a nonsignificant inhibitory effect when compared to petroleum ether and chloroform extracts (Lachkar et al. 2021; Mukherjee et al. 2024).

Anti-diabetic Activity

In vitro enzymatic assays conducted to investigate potential anti-diabetic properties revealed that *S. lanigera* demonstrated low to moderate inhibitory activity against the α-amylase enzyme. The calculated IC_{50} values for the ethanol and petroleum ether extracts were 429.85 ± 1.43 µg/mL and 520.31 ± 1.63 µg/mL, respectively. In comparison, the standard reference drug acarbose exhibited significantly greater inhibitory potency, with an IC_{50} value of 36.74 ± 4.50 µg/mL. Furthermore, both extracts of *S. lanigera* also inhibited the α-glucosidase enzyme, with the ethanol extract exhibiting the most potent activity ($IC_{50} = 27.07 \pm 0.78$ µg/mL), which is close to the acarbose value ($IC_{50} = 22.28 \pm 2.03$ µg/mL). Conversely, the petroleum ether extract demonstrated weaker inhibition of α-glucosidase, with an IC_{50} of 129.47 ± 1.22 µg/mL (Table 7).

Carbohydrate hydrolase inhibitors are recognized as promising therapeutic strategies for the management of obesity, diabetes, and associated complications (Akter et al. 2022). The results of this study indicate that the ethanol extract of *S. lanigera* is significantly more effective against the α-glucosidase enzyme, exhibiting potentials approximately five times greater than that of the petroleum ether extract. The statistical analysis confirmed the significance of these observations. One-way ANOVA and Tukey's post hoc test ($p < 0.05$) showed that the ethanol extract ($IC_{50} = 27.07 \pm 0.78$ µg/mL^{b}) was significantly more effective than the petroleum ether extract ($IC_{50} = 129.47 \pm 1.22$ µg/mL^{a}), and its activity was comparable to the standard acarbose ($IC_{50} = 22.28 \pm 2.03$ µg/mL^{c}). These statistical differences are indicated in Table 7. This finding is consistent with the work of Adımcılar et al. (2019), who reported that methanol extracts derived from various Anatolian *Salvia* species effectively inhibited the α-glucosidase enzyme at lower concentrations. Conversely, Kasabri et al. (2014) observed that water extracts from certain *Salvia* species demonstrated inhibitory effects only at elevated concentrations.

Several studies have demonstrated the significant antidiabetic potential of various *Salvia* species extracts and their bioactive compounds (Bahadori et al. 2017; Ben Khedher et al. 2018; Mocan et al. 2018; Adımcılar et al. 2019). Notably, Loizzo et al. (2008) reported that *S. acetabulosa* methanol extract exhibited the strong inhibitory activity against the α-amylase enzyme compared to chloroform or hexane extracts. Likewise, Kocak et al. (2016) demonstrated that *S. cadmica* methanol extract strongly inhibited the α-amylase enzyme, with subsequent effects observed for water and ethyl acetate extracts, although these latter extracts displayed considerably weaker inhibition of the enzyme α-glucosidase.

Extracts from *Salvia* species, including *S. elegans*, *S. greggii*, and *S. officinalis*, have been studied for their inhibitory effects on carbohydrate metabolic enzymes. A proposed correlation exists between the phenolic components of these extracts and their capability to inhibit the α-glucosidase enzyme, likely linked to their high concentrations of caffeic acid and its derivatives (Pereira et al. 2018; Adımcılar et al. 2019). Additionally, virtual screening studies employing molecular docking techniques assessed the inhibitory potential of polyphenols against α-amylase and α-glucosidase. Notable compounds identified as significant inhibitors of these enzymes include hesperetin, caffeic acid, daidzein, pinoresinol, curcumin, cyanidin, naringenin, pelargonidin, quercetin, kaempferol, and silibinin (Rasouli et al. 2017). This information suggests that the inhibitory effect of the ethanol extract of *S. lanigera* may be attributed to its polyphenolic content known for their bioactive properties, including the inhibition of carbohydrate metabolic enzymes (Shahidi & Danielski 2024). The presence of these compounds can enhance the extract's capacity to inhibit enzymes such as α-amylase and α-glucosidase, thereby contributing to its potential anti-diabetic effects.

Conclusion

This study highlights *S. lanigera*, a healing plant in traditional medicine for the treatment of various illnesses, as a promising source of bioactive compounds, including phenolic acids, flavonoids, and terpenoids. The ethanol and petroleum ether extracts exhibited significant antioxidant and antimicrobial activities, along with targeted enzymatic inhibition, notably against α-glucosidase ($IC_{50} = 27.07 \pm 0.78$ µg/mL) and urease (54.88% inhibition), supporting their potential in managing oxidative stress, infections, and metabolic disorders like diabetes. The implications of these findings are substantial, indicating the plant's potential therapeutic applications in managing oxidative stress, microbial infections, and metabolic disorders. However, to translate these promising results into practical healthcare solutions, future research should prioritize the isolation and characterization of the specific bioactive compounds (such as cynarin for antioxidant properties and palmitic acid for antimicrobial effects) to identify potential lead molecules; and conducting mechanistic and in vivo studies to validate the observed anti-diabetic potential and anti-ulcer applications (urease modulation) in physiological systems. Understanding their mechanisms of action is crucial, alongside conducting thorough toxicological studies to evaluate safety across various dosages and administration methods. These steps are vital for the effective development of therapeutics derived from *S. lanigera*, ensuring that they can be safely integrated into modern medicinal practices while maximizing their health benefits.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12161-025-02863-2.

Acknowledgements The authors aknowledgement the Deanship of Scientific Research at Imam Mohammad Ibn Saud Islamic University (IMSIU) (grant number IMSIU-DDRSP2501) for supporting this research.

Author Contributions "R. C., A. B. and L. D.: Writing – original draft; H. B. and M. Ö.: Conceptualization; M. A. M. A. and I. H.: Data Curation; M. A. M. A. and F. B.: Formal Analysis; M. Ö. and H. B.: Funding Acquisition; R. C., D. Ç. I. H. and L. D.: Investigation; C. B. and M. Ö.: Methodology; M. Ö. and H. B.: Project Administration; K. R.: Resources; M. Ö. and L. D.: Software; H. B. and S. G.: Supervision; M. Ö. and H. B.: Validation; S. G., M. Ö., F. B. and D. Ç.: Visualization; H. B., M. Ö. and S. G.: Writing – Review & Editing. All authors reviewed the manuscript."

Funding Open access funding provided by Università degli Studi di Roma La Sapienza within the CRUI-CARE Agreement. This work was supported and funded by the Deanship of Scientific Research at Imam Mohammad Ibn Saud Islamic University (IMSIU) (grant number IMSIU-DDRSP2501).

Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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